DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ONCOLOGY SUBCOMMITTEE OF THE ONCOLOGY DRUGS ADVISORY COMMITTEE

Tuesday, March 14, 2006

8:00 a.m.

Gaithersburg Hilton
Gaithersburg, Maryland

PARTICIPANTS

Gregory H. Reaman, M.D., Chair
Johanna Clifford, M.Sc., R.N, Executive Secretary

MEMBER

Pamela J. Haylock, R.N.

CONSULTANTS (VOTING)

Peter Adamson, M.D.
Barry Anderson, M.D., Ph.D.
(Sessions II and III)
Stacy Berg, M.D.
Gary Brittenham, M.D. (Session II)
(via telecom)
Susan Blaney, M.D.
Ralph D'Agostino, Ph.D.
Jerry Z. Finklestein, M.D.
Charles P. Reynolds, M.D.
(Sessions I and III)
George Schreiber, Sc.D.
(Sessions I and II)
Victor Santana, M.D
Malcolm Smith, Ph.D.

PATIENT REPRESENTATIVES

Marilyn S. Eichner
Cathy A. O'Connell
Susan Winner (Session II)

FDA

Richard Pazdur, M.D
Karen Weiss, M.D.
Ramzi Dagher, M.D. (Session I)
Mark Goldberger, M.D. (Session III)
Robert Justice, M.D. (Sessions I and III)
Patricia Keegan, M.D. (Session III)
Rafel Rieves, M.D., (Session II)
Kathy Robie-Suh, M.D., Ph.D. (Session III)
George Shashaty, M.D., MBAC (Session II)

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

Session I

Clinical Studies of Methotrexate and Daunomycin

to be Conducted under the

Best Pharmaceuticals for Children Act (BPCA)

Call to Order and Introduction of the Committee

DR. REAMAN: Good morning. This is the Pediatric Oncology Subcommittee of the Oncology Drugs Advisory Committee. I would like to welcome you all.

We will call this meeting to order. First, I would like to start by having people around the table introduce themselves, and we will start with Dr. Weiss and the representatives from the FDA, please.

DR. WEISS: Karen Weiss, Deputy Director, Office of Oncology Drug Products, CDER, FDA.

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

DR. DAGHER: Ramzi Dagher, Medical Team Leader, Division of Oncology Drug Products, FDA.

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

DR. D'AGOSTINO: Ralph D'Agostino, Boston University, statistician.

DR. FINKLESTEIN: Jerry Finklestein, pediatric hematologist/oncologist, UCLA.

MS. O'CONNELL: Cathy O'Connell, Patient Representative.

MS. CLIFFORD: Johanna Clifford, Executive Secretary to the ODAC and the Pediatric Oncology Subcommittee, FDA.

DR. REAMAN: Gregory Reaman, pediatric oncologist, Children's Hospital, Washington, D.C., George Washington University.

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

DR. BLANEY: Susan Blaney, pediatric oncologist, Baylor College of Medicine.

DR. BERG: Stacy Berg, pediatric oncologist, Baylor College of Medicine.

DR. ADAMSON: Peter Adamson, pediatric

oncologist, Children's Hospital of Philadelphia.

MS. HAYLOCK: Pamela Haylock, oncology nurse and Consumer Representative.

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

DR. SCHREIBER: George Schreiber, epidemiologist, WESTAT in Rockville, Maryland, and I was on the BPAC that evaluated the Exjade.

DR. REAMAN: Thank you. Ms. Clifford will read the Conflict of Interest Statement.

Conflict of Interest Statement

MS. CLIFFORD: Because this morning's session is involving the two products, I have two separate meeting statements, so bear with me.

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

Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug

Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. Section 208(b)(3), full waivers have been granted for the following participants:

Ralph D'Agostino for being a member of three competitors' advisory boards on unrelated matters. He receives less than $10,001 per year from two competitors, and from $10,001 to $50,000 per year from a competitor. Dr. D'Agostino is also a consultant for a competitor on an unrelated matter for which he receives from $10,001 to $50,000 per year.

In accordance with 18 U.S.C. 208(b)(3) and 21 U.S.C. 355(n)(4), full waivers have been granted for the following participants:

Pamela Haylock for stock ownership in two competing firms, one valued at less that $5,001, and the other valued from $25,001 to $50,000;

Peter Adamson for stock ownership in six competing firms, four valued at less than $5,001,

and two valued from $5,001 to $25,000.

Lastly, in accordance with 21 U.S.C. 355(n)(4), waivers have been granted to the following participants:

Dr. Victor Santana for ownership in competitor's stock valued from $5,001 to $25,000. This de minimis financial interest falls under 5 CFR Part 2640, which is covered by regulatory waiver under 18 U.S.C. 208(b)(2);

Dr. Stacy Berg for ownership in a competitor's stock valued from $5,001 to $25,000. This de minimis financial interest falls under 5 CFR Part 2640, which is covered by regulatory waiver under 18 U.S.C. 208(b)(2).

A copy of these waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

This announcement addresses the issue of daunomycin for conflict of interest and is made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. Section 208(b)(3), full waivers have been granted for the following participants:

Dr. Ralph D'Agostino for being a consultant for a competitor on an unregulated matter for which he receives from $10,001 to $50,000 per year.

In accordance with 21 U.S.C. 355(n), a waiver has been granted to the following participant:

Dr. Victor Santana for ownership in a competitor's stock valued from $5,001 to $25,000. This de minimis financial interest falls under 5 CFR Part 2640, which is covered by a regulatory waiver under 18 U.S.C. 208(b)(2).

A copy of these waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

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

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

Lastly, I would like to note that we do not have an acting industry rep today. We had an industry rep yesterday. He had to leave early. We did request the attendance of two additional industry reps, and they were not able to make it.

Thank you.

DR. REAMAN: Thank you.

Dr. Weiss.

Opening Remarks

DR. WEISS: I, first of all, want to welcome everybody to the Pediatric Subcommittee to ODAC, and just to introduce the first topic of the day. We have three somewhat separate topics to discuss during the day.

The first one is to discuss two older oncology drugs that have been added to the list for additional study as per the Best Pharmaceuticals for Children Act off-patent process. The two drugs are daunomycin and methotrexate.

I am very delighted that we have experts in the study of both of these drugs here to actually present proposed or ongoing studies that might address specific areas where there is need for obtaining additional information for these drugs.

So, the topic for the morning is to discuss these particular studies and to ask the committee's input on additional suggestions about those study designs that might optimize the type of

information that we obtain from them.

Thank you.

DR. REAMAN: So, I think we can begin then this first session with the discussion of one of these proposals related to investigation of daunomycin.

Dr. Berg.

Daunomycin Proposal

DR. BERG: Thanks very much for the invitation to speak this morning.

[Slide.]

What I would like to do is give some background that is probably familiar to many of you about what we know about anthracycline kinetics in general in children, because we actually don't know very much about daunomycin kinetics.

As you all know, anthracyclines are widely used in pediatric cancer. Doxorubicin is mostly used in solid tumors and daunomycin is mostly used in leukemias.

What you see here is the structure of daunomycin. Doxorubicin just differs where the red

arrow is in one substitution.

[Slide.]

Now, the reason that I at least think we should care about the kinetics of anthracyclines, even though we have been using them for a long time, is that for most anticancer drugs, we still do dosing based on body size, and we have an important concern when a patient deviates from what we consider a relatively normal or ideal body weight.

With anthracyclines, there is some adult data that suggests that doxorubicin clearance is decreased and the half-life is increased as a patient becomes percentages larger than ideal body weight.

We have very little data for children that addresses this question at all. In fact, we have very little anthracycline pharmacokinetic data in children at all.

[Slide.]

Now, for doxorubicin, there have been a small number of studies using single samples,

generally, one blood draw at the end of a 24-hour infusion to try to evaluate kinetics and look at relationships with body size.

These studies suggest that the clearance is about 400 ml/min/m2. There is wide variability in the clearance suggested by these studies, which is typical for anthracyclines in adults.

In those studies, there has not been a clear correlation between the clearance or the end of infusion concentrations with factors that, as pediatric oncologists, we care about, like age, or with body mass index, or weight.

Now, interestingly, in leukemia patients who were studied in induction, there is a difference in the maximum concentration depending on whether there is a very high or very low white count.

[Slide.]

What I would like to talk about this morning in terms of background is a study that I was involved with, with the Glaser Pediatric Research Foundation, that looked in a exploratory

fashion at doxorubicin pharmacokinetics as they relate to body composition in children, and then I would like to talk a little bit more about COG proposals to study daunomycin.

[Slide.]

The objectives of the Glaser study were to evaluate the relationship between obesity and doxorubicin kinetics, and particularly to correlate pharmacokinetic parameters with body mass index and body composition, and then to do more exploratory analyses of the relationship between the PK parameters and other patient characteristics like age, gender, ethnicity, and laboratory values.

[Slide.]

Eligibility, I will just skip through quickly in the interest of time, but the bottom line was it had to be children getting doxorubicin over one or two days, any dose and any schedule except not continuous infusion, and the reason for that is that it just got too labor intensive to design different sampling schedules if you added in the possibilities of continuous infusions.

These children also had to be receiving doxorubicin based on their true body weight, so if they were already getting some kind of dose manipulation because of their size, they weren't eligible.

[Slide.]

We collected height, weight, and body surface area information, the sort of typical laboratory parameters that you would expect, concomitant medication information, and then what we did was obtain body composition by DEXA scanning within seven days of the time that we got doxorubicin kinetics, and we did extensive pharmacokinetic sampling.

[Slide.]

This study was closed after 22 patients were accrued, which was a little bit lower than the planned target accrual. You see the demographics here. Two points that I want to make was that the median age tended to be young adolescents, which is not too uncommon in pharmacokinetic studies, and then the range of body fat and of BMI, as you can

see, was a pretty broad range.

Now, we had made the strategic decision that we didn't want to specifically try to accrue patients in groups of obese versus non-obese, because we thought it might be difficult to accrue large numbers of obese solid tumor patients, and I think that that was borne out. Although we had a nice range of BMI, it turned out to be better really to treat it as a continuous variable rather than to try to group patients.

[Slide.]

I will skip through the assay development except to say that it works nicely and although this was a study of doxorubicin, we used daunomycin as the internal standard, which is convenient to have for future daunomycin pharmacokinetic studies.

[Slide.]

We did pharmacokinetic modeling to determine doxorubicin and doxorubicin all pharmacokinetic behavior. Basically, what ended up being the best model for most patients was a three-compartment model for doxorubicin and then

irreversible conversion to doxorubicin, all which was then described by a two compartment model.

This let us describe both doxorubicin and doxorubicin all pharmacokinetics, and actually, it really worked, which was nice.

[Slide.]

What you see here is, in yellow, doxorubicin concentrations, and in white, doxorubicin all concentrations.

[Slide.]

This is a graph from a single patient who had a four-hour infusion, and the squares and dots are the actual measured concentrations, and the lines are the model predicted concentrations.

[Slide.]

The same thing works if you give a short infusion or a two-day schedule, and that is one of the advantages of the kind of modeling approach that I showed is that you can actually account for the dose and the infusion schedule in the model, so that it is not important to have everybody get the same dose or the same schedule, and you can still

derive the pharmacokinetic parameters, which makes your accrual potentially much easier.

[Slide.]

Now, from this model, what we have determined--and this is really hot off the press data that I have just finished in the last week or two, so it is also rather preliminary--the median clearance is about 400 ml/min/m2, which is in pretty good agreement with the meager pediatric data that we already had and also with the adult data.

There is a wide range of clearance as is expected with anthracyclines. The terminal half-life is close to 30 hours, and the doxorubicin, all terminal half-life is even longer. The practical implication for that is that you have to do sampling for a long time if you want to characterize the terminal half-life accurately. As I said, this is fairly similar to published data.

[Slide.]

When we get to what was really the major goal of this study, which was to look at PK

parameters versus parameters of body composition, and this is all just preliminary univariate analyses, it looks like there is a significant negative correlation between clearance and body mass index, so that as your body mass index gets bigger, your doxorubicin clearance decreases.

[Slide.]

Now, interestingly, it doesn't look like this relationship, at least with this number of patients, achieves statistical significance when you look at body fat as measured by DEXA instead of at body mass index even though those two things are actually pretty closely related, but I think that is something important to keep in mind, because you have to think a little bit about what parameters you really want to look at when you are looking for correlations.

[Slide.]

The doxorubicin half-life tended to change with the percent of body fat, but that didn't reach statistical significance, and importantly, over the range of patient ages that we had, which was 3 to

21, there was no evidence that clearance was affected by age.

[Slide.]

Other things that at least in preliminary analysis looked like they are not significantly correlated with doxorubicin PK parameters are body mass index, the Z score for body mass index or body fat, and volumes of distribution or really, any doxorubicin all parameters.

[Slide.]

So, where we are at the end of that study in terms of preliminary information with anthracycline is that doxorubicin clearance appears to decrease with increasing body mass index, and tends to decrease with increasing percent body fat. There is a lot of analysis, as I mentioned, still to do with this data. There is quite a lot of data, and so I think we have quite a bit to do.

[Slide.]

Now, this formed the basis for interest in a similar, but expanded study looking at daunomycin, and our proposed goals for the

daunomycin study are, first of all, to describe daunomycin pharmacokinetics in children, period, because I haven't been able to find any published data on that topic, and so even if we just do that, we will have contributed to what we know about daunomycin, but certainly from there, we have an opportunity to explore body mass index and body composition effect on pharmacokinetics, and if the obesity epidemic continues to grow the way it is predicted to, I think that this is likely to become a topic that we have more and more clinical concern about in terms of appropriate dosing.

We will also explore other correlations and very preliminarily, we will have the opportunity to explore the relationship between pharmacokinetics and adverse events and also pharmacokinetics and the organ function labs that we typically get when we are treating children with anticancer drugs.

[Slide.]

Our proposal is that this be a groupwide study with two years of accrual. The study that I

showed you before accrued 22 patients at three institutions in two years, so accrual groupwide should feasibly give us the opportunity to do a much larger study, and we can take advantage of things like building in reminders of this study into the study registration system when patients are enrolled on studies that call for daunomycin use.

Any children with any diagnosis will be eligible. There aren't any specific organ function criteria. Patients will already be selected because clinically, people will have determined that their organ function is adequate to receive daunomycin.

[Slide.]

We can use, as I showed, really any one- or two-day infusion as long as the duration is less than 24 hours, and in fact, the children do not have to be on a particular other COG study. They can just be patients getting daunomycin at COG institutions.

As I will mention a little bit in a

minute, we want to coordinate with some efforts that are particular to leukemia that are coming out of the cancer control group.

[Slide.]

So, our goals are to look at the impact of obesity on pharmacokinetics--I am sorry, this is the goal of the related cancer control AALL study--to look at the impact of obesity on the pharmacokinetics in high-risk ALL, to explore the relationship between the pharmacokinetics and event-free survivals, overall survivals, and remission rates.

They are planning to look at four drugs in induction, not just daunomycin. The study has a narrower eligibility than the daunomycin pharmacokinetic study that I am discussing with you this morning, but the important part is that we can actually share that data between the two studies, so we can do all the pharmacokinetics together and really leverage the amount of information that we get out of those patients.

One of the important differences is that

the high-risk ALL study will obtain pharmacokinetics on older children because that is who is eligible for that study.

[Slide.]

Now, the daunomycin pharmacokinetic study that I am proposing to you today, the plan is to obtain the height and weight of patients, the laboratory values that you see.

At participating institutions, we would like to get body composition information by DEXA, and that capability is available at many, but not all, institutions, so it will be important also to look just at body mass index correlations, and, in fact, that makes sense, because ultimately, to be clinically useful, it will be better if we can concentrate on easily obtained demographic information about patients rather than correlating only with something specialized and more labor intensive like DEXA.

We will do intensive PK sampling, so that we can fully characterize the pharmacokinetics. We will collect information about concomitant

medications in order to explore for whether there is any data that we can come up with on drug interactions.

That is not a topic that is widely discussed as a problem with anthracyclines, and I don't know if that is because there is no influence of concomitant medications or because we have never looked really at the data.

We will also collect adverse events for the cycle in which we do the pharmacokinetics, and that will be for exploratory reasons, as well.

[Slide.]

Our proposed sample size is 100 subjects, which should be feasible to accrue groupwide. This will detect relatively small correlations with relatively high power, and in terms of multivariate analysis, the real reason for going to such a high sample size is to be able to let us look closely at the effect of adding variables to the analysis.

Although our design does not have us accruing certain numbers of patients in particular age groups, I think an important part of the plan

is to track accrual real time, so that we can adjust and be sure that we are actually getting a good spread of age and particularly of younger patients who are always the harder kind of patients to accrue to this sort of study.

[Slide.]

The challenges for us, number one, accrual especially of younger children, will be a challenge. It is asking relatively a lot of people to have their kids volunteer for this sort of study, and for younger kids, that is always a bigger issue.

I don't think we will have too much of a problem with blood volume drawing because the assay is pretty sensitive and we can go to pretty small blood volumes if we need to.

There are also technical challenges. One is that at least in the doxorubicin study that I showed you the results of, we pretty well persuaded ourselves that we couldn't draw the samples through a central line that the doxorubicin was administered through, because we got contamination,

which is particularly important for the low concentrations that you see at late time points, but there is some work going on within COG by Dr. Adamson on ways to try to overcome this, because the studies become a lot easier to do if you can draw the blood through a central line.

Then, a minor, but real, technical challenge is that actually getting daunomycin all made in a fashion pure enough to be analytical grade is actually a little bit difficult, and one of the work-arounds for that, if we really can't do it, would be just to look at daunomycin and daunomycin equivalents, which is feasible.

[Slide.]

I think that doing a study like this will open a lot of opportunities, as well, for future science to be done.

One is that from this data we should be able to do quite a bit of population modeling that will guide us in terms of where we need to look further, but also, one of the important things is that we should be able to develop in the course of

this study and to test limited sampling models that could be used for future studies to make them much less labor intensive, and that would really open the door to be able to look at daunomycin pharmacokinetics in a much greater range of the studies.

Then, I think the kinds of questions that we would like to know the answer to are what should we do prospectively in terms of dose adjustments, should we try to dose patients, for example, based on ideal body weights, should we continue or discard the practice that we often do without a lot of data to support it, which is to say when people get really big, the size of the drug dose just makes us too nervous, so we arbitrarily cap people at doses equivalent, say, to 2m2 and that sort of thing.

So, I think that this study will give us a lot to build on for future work in anthracyclines in children.

That's all I have.

DR. REAMAN: Thank you.

I think maybe before moving on to the next subject, since they are so very different, we will entertain some questions, if there are any, for Dr. Berg.

Dr. D'Agostino.

DR. D'AGOSTINO: In the dox clearance in the BMI and the body fat, it looked like your relationships would have been probably destroyed because of a couple of outliers or a couple of individuals who are sitting in places that don't fit the line.

I am not at all familiar with what you do, but do you process to remove outliers, or do you keep everybody in them?

DR. BERG: Well, in this analysis, we included everybody. We certainly will look down the road at what happens if you take out a couple of the big kids--

DR. D'AGOSTINO: Well, these were the small ones it looked like.

DR. BERG: Or small kids. I think part of what we are eager to do is characterize what

happens in the outliers, because we are pretty comfortable with the people who fall in the middle, and what we really want to know is in the really small, frail kids, and in the really big kids, are they different.

DR. D'AGOSTINO: That is where my question was really going. I mean you can get a nice relationship if you remove them, but they may be the ones that you are really interested in.

DR. BERG: Exactly.

DR. REAMAN: Dr. Adamson.

DR. ADAMSON: I had a very similar question, but let me take it one step further. So, it looks like you had I think four extreme outliers, and for the children with very low clearance, my question would be were they at close to the limit of detection of the assay, or were there ADCs extrapolated to a much greater degree, and at the higher end, if it gets very hard to come up with a reason why you would estimate that other than did they get the right dose.

DR. BERG: Right. In terms of did they

get the right dose, we have the usual checks. We have the source documents for prescribed dose. We don't have a way to measure what actually went in the bag.

One of the nice things about anthracyclines is that the assays are sensitive and the concentrations are high, so you are really nowhere near the limit of detection of the assay. Even at 48 hours, you are still nowhere near, so that is not a problem.

Now, the data that I showed you especially for doxorubicin ALL, all that data is model dependent, so if your model is wrong, your parameters could be wrong. There is not much you can do easily that is model independent with the metabolite beyond, say, what the half-life is, so you get more data out of the model dependent kinetics.

In terms of the number of outliers, you know, it is true that they look like there are maybe four kids who are really different, but that is still 4 out of 22, so it is a small study and I

think you need to just look at everybody and say what do these people tell me, and then that sort of question will be better addressed in a bigger study, because if there are 4 out of 100, then, those really are outliers and maybe you don't care so much, but if there is 20 out of 100, then, they become an important subpopulation.

DR. REAMAN: Dr. Reynolds.

DR. REYNOLDS: Stacy, we have an ongoing COG study looking at 13-cis RA, both PK and pharmacogenomics, and one of the things we did in there was to ask people to send a red cell pellet that they collected the plasma in, that is enough to store DNA for the pharmacogenomics.

I wonder if you considered doing something like that and just storing that material, so that you could ask PG questions with this very nice dataset in the future once it became available.

DR. BERG: With the doxorubicin study that I showed you, we thought long and hard about that, and ultimately, we didn't do it because, first of all, anthracycline metabolism is really not very

well understood, and second of all, at least at the time, nobody really had any good idea about what genetic changes we would be looking for, or what polymorphisms we might ascertain.

Now, I think that that is a more important question within COG where we have better infrastructure and an easier way to do it, and storing DNA against the day that we develop the questions, I think would be a great idea.

I don't have the specific question right now to propose.

DR. REYNOLDS: Because you can do it off of the same blood sample that you get your PK from, I would encourage you to just store it because it might be useful in the future.

DR. REAMAN: Dr. Santana.

DR. SANTANA: Stacy, can you expand on some feasibility logistical issues? You commented that in your pilot study of 22 patients, the accrual was less than targeted.

Can you expand whether that was for logistical reasons or other reasons, and the

corollary to that is when you move then to a groupwide study in which a number of patients are going to get DEXA scanning, have you piloted or estimated the proportion of patients that are likely to get that study done in a groupwide setting, so that you can estimate, then, the feasibility of that kind of question?

DR. BERG: In terms of the first, the reason that accrual was less than expected in the Glaser network is because there were only five institutions, and two of them in this particular study for internal reasons weren't participants. So, we accrued in three institutions, so actually, I think that that is encouraging in terms of our ability to accrue COG groupwide.

In terms of DEXA, no, I don't have that information yet although we certainly should be able to obtain it.

DR. REAMAN: Dr. Dagher.

DR. DAGHER: A couple of questions. First, you talked briefly on the ALL high-risk study, which was looking at PK with a number of

agents, including daunomycin.

I guess this is a question, not just for you, for Dr. Smith and others, it wasn't clear from previous discussions whether submission of data from that study would also be part of potentially the proposal for submission of data on daunomycin would seem that would be something important to clarify. I guess we can get to that more in the questions, but if somebody can clarify that, that would be helpful.

The second question was in terms of the relationship between PK and adverse events on the proposed COG study, I assumed this might involve both, you know, sort of initial adverse events and also potentially also more long term. If you could elaborate on what adverse events that might include.

DR. BERG: Right. For the study that I have been speaking about, because the eligibility for the study includes basically anybody getting daunomycin, and the reason for that decision is surely just feasibility.

If we limit to one study or one dose or one schedule, I think will hurt accrual, and since the primary goal is really to do descriptive kinetics, I think it is an advantage to maximize or a chance to get patients.

The flip side of that is that people will be getting a lot of other concomitant chemotherapy, that we, in the ideal world, would do our kinetics during single drug administration, but there really isn't any single drug daunomycin administration, so that is just plain not feasible.

People will be getting kinetics with different diseases, at different phases of their disease, and so although we wanted to explore pharmacodynamics in the sense of adverse events, what we decided was going to be most feasible would be to look at acute adverse events in the cycle where we had the kinetic data.

So, we are collecting CTC Version 3, adverse event data, whatever those events are, and we will explore it. Now, one of the things that would be good to come out of this study would be

particularly some more feasible limited sampling, so that in the future, we can look at what are really I think more important toxicity questions like particularly cardiac toxicity.

So, I would view this as a stepping stone to be able to do that, but not something that we will directly do in this study.

DR. REAMAN: I think just to clarify your question about the adverse events that are specifically going to be evaluated in this COG study, they will be acute adverse events that occur during or after induction therapy.

Dr. Santana.

DR. SANTANA: Greg has indicated that we can ask you all our questions now and not later, so I will go ahead and try to see if you can clarify two other issues.

One is a little bit related to the question that we just discussed, and that is, a lot of these patients are going to be getting a lot of concomitant meds that potentially affect protein binding, but also fat and body composition like

steroids, asparaginase, and things like that.

So, how are you going to model that in your study, and in particular, when this drug is also used in another study in the myelogenous leukemia setting in which those patients don't have those other concomitant meds? Is there consideration that potentially, this study could be expanded to another population, so you could sort those things out? And I have a follow-up question, too.

DR. BERG: This study is open basically to all comers, so we will probably get some AML patients, probably mostly ALL patients if you look at where the drug is used, but it is not limited at all to disease type.

In terms of concomitant meds, we will collect that data, so we will be able to explore it, but really, that's all. We certainly won't be able to control for it, and what we will do to control for the effect, for example, of steroids on body composition, is we will use the BMI from the cycle that they are getting their daunomycin dose

in, and for the subset of patients who get DEXA, the DEXA will be within seven days before or after the PK.

So, that is not perfect, but it's feasible and pretty close.

DR. SANTANA: Another question has to do with PK. In the proposal that we were given as part of our package, there is pharmacokinetic sampling strategy. Coming from an institution that does a lot of PK and issues related to feasibility and burden both on patients and staff, I was struck by the number of early samples that you were requesting.

So, I wanted you to comment on how feasible it would be both in terms of burden to the patient and also burden to the staff to request all those very early time points and particularly when you addressed that the main issue, at least one of the main issues seems to be the terminal half-life, and those are probably critical samples.

One of the concerns I always have is that people then, to do a few samples, and they don't do

all samples, and then you would be really maybe missing the very important ones, so is there a way that you can modify this pharmacokinetic sampling strategy to make it less burdensome both to patients and staff, and is that critical to the study?

DR. BERG: Yes, it is clearly a burdensome approach to the pharmacokinetics, and the reason for taking a sampling intensive approach rather than a sparse approach is that in the study, we are looking potentially for smallish differences, and we have the potential to actually miss differences if we make assumptions that everybody is going to behave the same.

Now, we could, when I look carefully at that question, I think you could maybe take out one or two early time points which would help some. I think the honest truth is that the difficulty is the later sampling because patients are around anyway in the hospital or in the clinic in their immediate post-infusion period when most of the samples are.

What is hard is the 24-, 48-, and, you know, 72-hour sampling times, and, in fact, those are for a drug whose half-life is 30 hours, those are informative times, so we can approach that by logistical things like being able to send home health nurses to collect the samples, and that sort of thing, but those samples I don't think we can eliminate.

I also think this is a good opportunity to make a full court press on that kind of sampling, but, you know, for exactly the reason that you asked about, it will be important to take that opportunity to develop an easier and less burdensome sampling schedule that we can take into studies going forward.

DR. SANTANA: I guess from experience, I just know that the more samples you request, the less likely you are to get them, so I think you will have to consider that once the study is finalized and submitted for other review.

Then, one last question I promise. The issue of body composition is also related to gender

and age obviously. How are you going to control for that in your study, so that you wind up with a population that really reflects somehow the ultimate population in which this drug will be used, females, you know, pre-adolescent versus adolescent significantly have differences in BMI, so how are you planning to control that?

I ask that because I was struck in your pilot study by the disparity in racial groups, for example, that you saw, and obviously, that was a very limited institution pilot study, and knowing that you are from Texas, there is a lot of Hispanic population there, so that is not unique, but it doesn't really reflect the population at large in the U.S., so how are you going to control for gender and ethnicity in the study?

DR. BERG: The places where the previous study accrued were California and Texas, and so actually, I think we pretty well did reflect the population that was being treated at those sites, and that is one of the strengths of doing a COG groupwide approach is that to the extent that we

are ever reflecting a population, we ought to be able to do it with a groupwide study.

Now, in terms particularly of age, we plan to monitor as the study goes, and we can do that for gender, as well, and if we need to close or alter accrual to certain groups in order to try to get good heterogeneity, we can do that. We don't have that designed formally, because there is not a formal plan to compare PK parameters, for example, between different age groups or between different body composition groups.

DR. SANTANA: It was to look at different age groups.

DR. BERG: No, it's to look at age as a covariate, but not to compare between age groups, so I think that helps us a little bit as long as we are sure that we get a good spectrum of age.

Going back to your first question in terms of feasibility of accruing patients when you ask them to donate that many samples, the sampling schedule was the same in the Glaser study, so I think we have a suggestion from that study that

it's feasible, but certainly I expect a lot of potential subjects who get approached will say no thanks, and I think that is appropriate in this kind of study.

DR. SANTANA: Or they will say thanks and only give three samples rather than the X number that you requested, that's just as bad?

DR. BERG: Well, certainly we wouldn't want to have--if we find that half the patients are dropping out after 12 hours, then, I think we need to re-approach what we are asking, and we would still get some information, but not the information that we want.

That wasn't our experience in the Glaser study. The experience that we had was that people either said forget it, I am just not interested, or they said sure, I will do that, and then I think we only had one person who actually withdrew in the course of the study.

DR. REAMAN: Dr. Smith.

DR. SMITH: One question about the feasibility relates to whether you can draw samples

from the central catheter, and could you or Dr. Adamson say more about where you stand and being able to do that with daunomycin?

DR. BERG: I couldn't, but Dr. Adamson could.

DR. ADAMSON: We are looking right now, as you know, at vincristine and actinomycin-D for a single catheter procedure that would give great assurance that we don't have contamination.

I am hoping that within the next two months, those studies will be completed, and if successful, and I think there is a reasonably high likelihood that they will be, we, I think could work with Stacy to move quickly to validate it for daunomycin.

There is a reasonable likelihood it may be drug specific, so I wouldn't want to extrapolate from two drugs to a third without actual data, however, if we end up doing about half a dozen of these, and the approach is the same, then, I think we will be on firmer ground as we move forward with unknown agents.

So, hopefully, within about two months, we will have the data. Where we are right now is simultaneous draws from a peripheral and central catheter and head-to-head comparison of those for the two drugs.

DR. REAMAN: Any other questions?

I have a question for Dr. Weiss. In looking at the questions for the committee, I am wondering if it might make more sense to address the daunomycin specific questions now rather than going on and discussing a totally different topic with different issues.

DR. WEISS: That would be fine with us. I think that would probably be more feasible, plus I am not sure if our other speaker is actually here yet--oh, yes, great. That's fine.

DR. REAMAN: Maybe before we do that, we have a new member of the committee, if you could introduce yourself, please.

MS. EICHNER: Marilyn Eichner, Patient Representative.

Questions to the Subcommittee

DR. REAMAN: The questions that we have been asked to address by the FDA are actually in the back of your packets. Daunomycin and methotrexate are off-patent drugs that were referred to the NICHD by the Foundation for the NIH, reviewed by expert consultants, and recommended for further study in the setting of pediatric oncology.

Among the goals of the studies presented are to develop additional data that could result in health benefits for children with cancer.

With respect to daunomycin, please discuss the ability of the proposed study to meets its objective of determining the relationship between body composition and daunomycin pharmacokinetics.

Specifically, the study will correlate body composition, size, age, gender, and ethnic background with daunomycin PK. Please identify any other patient or disease-specific factors for which PK correlations should be made.

I think Dr. Reynolds certainly made an excellent suggestion about saving, storing DNA for

future potential pharmacogenetic studies, which I think is certainly a very good recommendation.

Any others? Dr. Finklestein.

DR. FINKLESTEIN: I think this, and I mentioned this at the last meeting, I think this is an important topic not only in terms of daunomycin, but every drug that we use in pediatrics in general, not only oncology, but hematology and just pediatrics in general, and I would like the FDA, with the cooperation of scientists who study this throughout the country to look at this in terms of pediatrics.

We have got a real problem with body mass index. We have a real problem with obesity. With daunomycin, your presentation was superb. You know, I am embarrassed to say that I have been around since daunomycin started, and we don't know very much about it, so that just in general, I think this is a topic for the FDA to really look at it as a full court press.

DR. REAMAN: Thank you.

DR. SANTANA: Stacy, I think you alluded

to this before and certainly for the FDA in terms of their questions, and it was the issue of the timing of when this medication is given in the context of other therapies, and I was struck by some of the preliminary data from another study in which white count was a relevant factor, and I personally could never understand why that would be, but certainly since the drug is going to be given and studied at different intervals, if I understood correctly, then, maybe you may need to put some variables in there like that variable and adjust for that potentially, because I didn't understand why white count would be important in the other study, but clearly, it is a red flag, and as a disease-specific factor, you may want to look at that in the context of your study.

DR. BERG: I agree, Victor, we will collect white count data that is part of the data being collected, and mostly in ALL studies, this drug is used fairly early, but that doesn't mean that we will get pharmacokinetics in the first dose of daunomycin, so I think we certainly had the

opportunity to explore this, and it's a very interesting route for future study, as well.

DR. REAMAN: Any other suggestions, recommendations? Dr. Weiss.

DR. WEISS: It just struck me, also, just something you said, Stacy, about cycle of therapy and whether or not, if you are going to be collecting that information, and whether or not there is any change in kinetics based on cycle of administration, if you have some type of up or down regulation, or some type of mechanisms.

DR. BERG: We will collect the information, so we will know what cycle we got the kinetics in. With this extensive sampling, I don't think it will be feasible to sample the same patient more than once.

There is some fairly old anthracycline data, and I can't remember whether it's daunomycin or doxorubicin. I think it's doxorubicin in adults where infusion schedules, different schedules were looked at in the same patients.

To my knowledge, there has never been a

suggestion either of dose dependent kinetics with daunomycin or doxorubicin, or of induction of metabolism that alters kinetics between cycles in the same patient, but I don't think that that is very well characterized, so again, a potential future work to come out of this study would be if we can develop an easier sampling strategy that really opens the door to all kinds of questions like that.

DR. REAMAN: Just to follow up on the white cell question, in your experience with the doxorubicin, were they ALL or AML patients? I mean is there the potential that there may be variability there also?

DR. BERG: They were primarily solid tumor in a few lymphoma patients, and I haven't looked at that data yet, but we have it, so I am kind of excited about that.

The one study that showed that, the difference was between white count greater than 50,000, and white count less than 10,000, so relative extremes, but potentially important for

that first induction dose.

DR. ADAMSON: A brief comment on the white count, I mean there may be a direct or an indirect effect, and I agree with Victor, one can't postulate for this drug how white count is a mechanism of clearance, but it may correlate with hepatomegaly. Certainly, we can capture that.

We have no good measure of how well livers can function early in therapy, and it may be an indirect effect of the leukemia burden on the liver as opposed to a direct effect of drug clearance.

But I would also agree with you, Stacy, that coming up with a limited sampling method is really going to be key, because we also need to look at the intrapatient variation, because if the intrapatient variation is high, we can then start focusing on things other than genetics, which don't change from cycle to cycle, and BMI may not change appreciably cycle to cycle also. We have a lot of drugs where we know the intrapatient variation is high, and looking for drug interactions, food interactions, and so forth, might be the avenue.

So, I would echo the goal to come up with a limited sampling methodology for additional study.

DR. REAMAN: So, we can maybe move on to (b). Should the study link the PK data in the study that was described by Dr. Berg as specifically related to the BPCA request, with clinical and/or laboratory outcomes?

If so, which outcomes would be most relevant? If linkage to such outcomes is not appropriate or feasible in this study, should another study be conducted in order to develop these correlations? If so, please comment on optimal study designs.

So, we actually have a bit of an answer to that question. There is another planned correlative study within COG. It is planned, so I think there would be certainly opportunity for recommendations to expand or improve the design of that study. If there are questions, issues?

DR. WEISS: Can you clarify, that is the study that you just briefly mentioned, that is the

ALL study, is that correct?

DR. REAMAN: That's correct.

DR. WEISS: Okay, because I think that would be very useful and very interesting information to have.

DR. REAMAN: Malcolm.

DR. SMITH: I think it will be challenging in the context of ALL studies to isolate a daunomycin effect since it is given primarily just during induction, and then a different anthracycline is used during reinduction, and there are so many other drugs that are given that are effective.

You may have better opportunity to find an association between clinical outcome and daunomycin PK with AML where there are fewer drugs that are used, and the anthracycline probably has a proportionately greater effect.

But that type of study would require the limited sampling in some future study.

DR. REAMAN: Even with the AML, there is still going to be the issue of confounding

additional drugs or concomitant drugs that are given with the anthracyclines.

Dr. Dagher.

DR. DAGHER: Just to expand a little bit, the issue here was that, you know, ideally, one would want not only PK data, but also some rather strong links to the clinical outcomes in the sense that you would probably want to have something like that if you were, for example, going to have labeling that proposes this approach to the dosing as opposed to the more traditional approaches with all the limitations that Dr. Berg outlined already.

So, I guess a separate question would be granted that we don't know much about the PK of daunomycin historically, I suppose one would not really be able to rely on previous studies that had, as their goal, mainly the clinical outcomes, and link that to the PK, because we don't have the PK, I suppose.

So, given that, you talked really at the end of your presentation on potentially this being a stepping stone to studies that might look at

adjusting for body composition as part of the primary question for the study.

I guess it's probably too early to discuss details of those designs, but I think that is where our concern was, that we would be at the end of the day here with very important PK data, but not being able from a practical standpoint to say okay, based on this data, what would we recommend in terms of a different approach to the dosing unless we had those future studies or some other information. That is part of the concern quite frankly.

DR. BERG: I think as with a lot of things we do in children, there is some tension between what the perfect study would be and what the doable study is, and, you know, a perfect study I would give single dose daunomycin to patients at the same phase of the same disease and make everything as homogeneous as possible, but, you know, I think it would take 30 years to do.

This study, it takes the opposite approach, which is to say that we will accept that we are looking at a heterogeneous population, and,

in fact, we will try to let that heterogeneity teach us as much as we can learn by describing the heterogeneity, as well as the pharmacokinetics, but I think that it is clear that there is considerable additional work that one would want to do beyond what is basically descriptive and exploratory in this study.

If this were a brand-new drug, I don't think we would expect to get all the data for its use forever out of one study either. It is just we have been using it for a long time and we are surprised by the kind of data that we don't have.

DR. WEISS: I think that it's a good lesson as far as new agents come along in terms of maybe how to try to optimize information before they start being used in multi-agent regimens where it becomes more difficult to tease out the effects. So, it's a lesson from what we can take away from the older drugs that we might want to not duplicate as new agents come along.

DR. SANTANA: But the study will look at adverse events, so you will have that data

obviously in the context of five other drugs, but we know that there may be some toxicities that are associated with anthracyclines acutely, like mucositis and GI, and things like that, or liver enzymes and things like that, so you will have some toxicity data.

You will have the outcome data in terms of remission rates although, you know, they are probably going to be good, so you are not going to be able to dissect that, but you will have that data.

Now, whether you are going to be able to correlate it with daunomycin exposure, that's a very different question, and I don't think you will know the answer to that maybe except in very small subsets of patients, and then Stacy is right, it will just be purely exploratory, but it could launch a complete different field of investigation if you find those data, but I think we can't ask the study to provide us all the outcome data like we would have in a clean study with a single agent for patients.

So, I think it is going to be a little bit, quote unquote "dirty," but that's the best we can do. So, you are going to have to take it for that.

DR. REAMAN: Despite the exploratory and descriptive nature of this, I think there will be important information with respect to how people use this drug. Some people use this drug in capping doses and adjusting doses based on ideal body weight. I mean despite protocols that give specific guidelines, there are people who don't follow those guidelines.

So, I think there will be some important information that could be added to the existing label despite not having all of the answers that, as Victor mentioned, will come from hopefully a series of successor studies.

DR. REAMAN: Malcolm.

DR. SMITH: I guess I would ask Stacy to comment on the issue. You know, Dr. Dagher raises a question of what do we do about the relationship between daunomycin, PK, and outcome, but we also

have the relationship between daunomycin, PK, and demographic, and variables like obesity, and how much information we can get from the latter, you know, that may inform us about dosing even when we don't get the clinical outcome data correlations.

DR. BERG: Well, I think there are a couple of approaches to that. One is that at least we will have some data, which will frankly be ahead of where we are right now.

The ALL cancer control study will take their piece of the daunomycin pharmacokinetic data and correlate it more directly with remission rate and event-free survival, so that will, from the point of view of my study, in effect be a subset analysis, but I think it will still be valuable, and it will probably be a pretty decent size subset.

Then, we are going to capture and look at relationships with things like ethnicity and obesity. One of the things that I think we actually don't know for sure is how many patients we expect to be obese in the future when they are

getting their first dose of daunomycin, and I guess at the rate things are going, it might turn out to be a pretty substantial proportion.

If we find that patients over, say, you know, a BMI of 30, or something like that, have a significantly lower clearance, and particularly if we think there is a hint of increased adverse events, that might inform the design of future studies at least as a scientific question, if not as an actual recommendation for dose modification.

I wouldn't want to predict right now whether we will come out with dose modification recommendations from this study, but I would be surprised if we didn't come out with questions about it.

DR. REAMAN: So, maybe we can move on to the third area here, related to how the varied infusion regimens, infusions of any duration less than 24 hours, might affect the interpretation of any exposure-response relationships for daunomycin.

So, any concerns, issues here? I understood, Stacy, that you have data with

doxorubicin, but nothing even preliminary with daunomycin, correct?

DR. BERG: No, but it's actually one of the nice things about this pharmacokinetic modeling approach in general, is that the infusion rate and the dose is just part of the model, and it's accounted for, and it's quite straightforward.

DR. SANTANA: I am sorry, I read this, and I missed it maybe. So, for the targeted leukemia studies, what are the infusion schedules that are going to be used? It wasn't clear to me.

DR. BERG: For most of the leukemia studies, the dose is usually at 25 mg/m2. I think there is a few where it's 45 mg/m2. For most of them, it is a short infusion.

DR. SANTANA: Short, less than an hour or less than 30 minutes?

DR. REAMAN: It's less than an hour.

DR. BERG: Yes.

DR. SANTANA: So, it would be fairly consistent. I guess the FDA question kind of surmised to me that maybe there were different

schedules or infusion times?

DR. BERG: Yes, there is actually I think more variability in the way people use doxorubicin, because there are some studies where people do prolonged infusions. I think that that is less common in daunomycin, and when I looked through the open COG studies, they are almost all some variation on short infusion, which simplifies things, but even a longer infusion, really the only reason I was kind of arbitrary in saying using less than a 24-hour infusion, because if you go much longer than that, then, you have to keep designing different sampling schedules, and it was just too hard, but that was just to make the study a little more straightforward, not because it affects the modeling.

DR. REAMAN: But actually to point out that this study is going to be done, not in patients who are on a specific COG leukemia study, so there will be some variability even more so than patients on the same study, but the other study that Dr. Berg mentioned in the high-risk patients,

I believe that our uniform guidelines for administration of daunomycin now say by short infusion defined as less than 30 minutes.

DR. DAGHER: Just to clarify that this was intended to ask about the proposed COG study that wasn't specifically targeted to ALL, certainly, the other study, as you point out, would have more specific regimens, and data from both would be very helpful obviously.

DR. WEISS: As Stacy said, the criteria said less than 24 hours, so we thought there might be a large range in variability of schedules that might be evaluated, but, you know, your presentation indicated that that would be taken into account in your modeling, so it was probably less of an issue.

DR. REAMAN: Dr. Smith, did you have a question?

DR. SMITH: I was just going to say that the high-risk protocols for ALL are IV push at 15 minutes, so it would be that. I think the AML studies in the past had longer infusions I think

that had to be continued about six hours for the daunomycin.

DR. WEISS: I just was wondering if I could ask, I was going to ask Anne Zajicek, who is here from the NIH, I don't mean to put you on the spot, but whether or not there are any other questions of clarification, because, you know, the NIH is a very active player in the off-patent process.

DR. ZAJICEK: Good morning. Again, just to recap, we had received these recommendations through the Children's Oncology Group to study these drugs as we had received recommendations of vincristine and actinomycin-D and we were interested in working with COG and the FDA and, you know, advancing these trials, but, you know, again the best way to do this is to make these as practical as possible. So, I think that addresses our questions. Thank you.

DR. WEISS: We have a number of clinical pharmacologists at the FDA staff, who have also been very involved in helping us in terms of

shaping the questions, so I would just like to just turn to my colleagues and ask if we have all of our questions addressed. Yes? Okay, great. Thank you very much.

DR. REAMAN: Thank you.

So, then, maybe we can move on to the next topic, which is methotrexate, and the use of high-dose methotrexate in the treatment of acute leukemia.

Dr. Malcolm Smith.

High-Dose Methotrexate: Safety and Toxicity

DR. SMITH: I am going to provide an overview of methotrexate clinical evaluations that will provide a background for the subsequent discussions of the proposed studies of methotrexate through the Best Pharmaceuticals for Children Act.

Please note that there are a few minor changes on the slides I will be presenting from what are in the handout.

[Slide.]

We have been in this business for a long time as oncology researchers. This slide reminds

you that we have 40 years of randomized trials evaluating methotrexate, you know, 41 years ago now, the Acute Leukemia Group B published a study that looked at patients who had achieved remission and compared a low oral dose of methotrexate to a higher dose given intravenously, and the higher dose intravenously was more effective.

Here we are, 40 years later, and we are still trying to learn the optimal way to use methotrexate for children and adults with acute lymphoblastic leukemia.

[Slide.]

In fairness to the researchers who have been doing this for 40 or more years, it is not easy studying methotrexate and particularly when you get into high-dose methotrexate and the number of variables that there are, any of which could affect the efficacy and the toxicity of the methotrexate.

When we think of high-dose methotrexate, we can think of 1 gm/m2 of methotrexate as POG studied for years, or 2 gm/m2 studied by Dutch

researchers, 5 gm/m2, which we have kind of standardized now in COG and which the BFM group has studied for years, or 8 gm/m2 from the Scandinavian group, and all the way up to 33 gm/m2, which was studied in the 1980s and 1990s.

It is not only the dose of methotrexate that we have to consider, it is the timing and dose of leucovorin rescue. It has ranged from 24 hours to 36 hours, 42 hours to 48 hours in various studies that have been reported.

The number of courses of high-dose methotrexate, ranging from 1 course of high-dose methotrexate all the way up to 12 courses of high-dose methotrexate, and that can have an enormous impact on both efficacy considerations, as well as toxicity.

Then, added to the mix we have another way of using methotrexate intensively, called the Capizzi escalating dose methotrexate, escalating to the highest tolerable dose without leucovorin rescue and using asparaginase rescue.

So, there are more variables than we can

study in probably a century.

[Slide.]

Let me briefly review some of the clinical experience relating to the efficacy of high-dose methotrexate.

There was a childhood ALL collaborative group that provided an overview of CNS-directed therapies, and one of their analyses looked at eight randomized trials that were asking a IV methotrexate question of therapy plus or minus IV methotrexate with methotrexate doses that ranged from 0.5 gm/m2 all the way up to 8 gm/m2.

This meta-analysis found that the addition of IV methotrexate to either long-term IT therapy or radiotherapy with IT therapy reduced the overall event rate by 17 percent, a modest difference.

Interestingly, the IV methotrexate reduced the non-CNS relapse rate. In this meta-analysis, no effect was found on the rate of CNS relapses.

The caveat to this is that the meta-analysis combined diverse backbone regimens and that the methotrexate doses weren't

standardized, the leucovorin rescue regimens weren't standardized, so all of the caveats associated with meta-analyses.

[Slide.]

But there was a difference, that event-free survival had a p-value of 0.003, a modest benefit for the use of IV methotrexate compared to its non-use.

[Slide.]

Now, there are several important studies conducted over the last decade in North America by POG and CCG, and I will describe several of these briefly.

One was a POG-9005 study for B-precursor ALL. This was a standard risk population, and it used the old POG method of what we call intermediate dose or high-dose methotrexate, 1 gm/m2, and it compared 12 courses of 1 gm/m2 methotrexate to an intensive oral methotrexate regimen in which 30 mg/m2 was given every 6 hours for 6 doses.

In this study, the continuous complete

remission rate was superior for the IV methotrexate compared to the oral methotrexate, so a benefit was identified, but the caveat here, the critics of this study will point to the fact that too much leucovorin rescue, in their mind, was used in the PO methotrexate arm, and that were a lower amount of leucovorin rescue provided in that arm, perhaps this difference wouldn't have been observed.

[Slide.]

We have another study from POG. This was a study for T-cell ALL and lymphoblastic lymphoma, and this study investigated the addition of IV methotrexate 5 gm/m2 to consolidation therapy, and this study observed a clear benefit in terms of EFS for the addition of high-dose methotrexate.

The EFS rates at 3 years were 86 percent for high-dose methotrexate versus 72 percent in the absence of high-dose methotrexate, and the study was closed early because it crossed a boundary for event-free survival.

Interestingly, in contrast to the overview that I described previously, the primary difference

in arms in this study was for CNS events, that there was a lower rate of CNS relapses in the high-dose methotrexate arm compared to the arm not receiving high-dose methotrexate.

There was a caveat to this study, as well, and critics of the study design will note that the radiation was delayed in the no high-dose methotrexate arm, and this may have resulted in an increased CNS event rate for the control patients compared to what might have been observed if radiation had been delivered earlier.

[Slide.]

The final two studies I will describe look at the Capizzi methotrexate, Capizzi methotrexate delivered during interim maintenance, approximately the third month of therapy, an 8-week treatment block.

Capizzi methotrexate involves administering methotrexate starting at a dose of 100 mg/m2, giving it every 10 days without leucovorin rescue, escalating the dose to tolerance. Asparaginase is given 24 hours after

each dose of methotrexate, and vincristine is given on the day of methotrexate administration.

Capizzi methotrexate was one component of the augmented BFM regimen that CCG studied in their 1882 study and in their 1961 study.

In the 1882 study, this was high-risk ALL patients with a slow early response, and the augmented BFM regimen, including the Capizzi methotrexate, had superior outcome compared to the standard regimen in which interim maintenance didn't include Capizzi methotrexate.

This same approach was applied then to rapid early responders in the CCG-1961 study, and in this study, an improved outcome for the augmented regimen was observed in this rapid early response population.

The caveat here in terms of attributing this to methotrexate is that the augmented BFM differs from standard COG BFM in multiple ways, additional doses of vincristine and asparaginase, and so the Capizzi methotrexate isn't the only difference between augmented BFM and the standard

BFM that CCG is studied.

[Slide.]

But this slide does show that there was a significant improvement in outcome. This is in the rapid early response population and the 5-year EFS rates from 80 percent at 5 years with the augmented BFM compared to 70 percent with the standard BFM.

[Slide.]

So the question of the day for the next 5 years or so, in 2006 and in the remainder of this decade: What is the best way to administer methotrexate during the post-remission, pre-maintenance phase of therapy for children with high-risk acute lymphoblastic leukemia?

I would note that all the studies that we are talking about are for the high-risk ALL population, either high risk because of B-precursor agent, white count, and other factors, or high risk because of T-cell disease.

[Slide.]

Now, this slide I show, whenever slides like this are showed, schemas like this are showed,

the medical oncologists in the audience cringe and wonder how you could possibly treat with protocols this complex.

There is actually an underlying simplicity behind this schema, that basically, what we are talking about are blocks of therapy, the induction followed by consolidation. Interim maintenance is what we are talking about here for isolating methotrexate treatment effects.

This is followed by delayed intensification, which is basically the induction and consolidation more or less repeated, and then maintenance therapy. So, it is not as complex as it looks.

The interim maintenance that we are talking about for these methotrexate questions of therapy are 8-week treatment blocks. The two approaches for using methotrexate that we are considering are the Capizzi methotrexate that I have described previously, and the high-dose methotrexate.

The high-dose methotrexate, we have now

kind of standardized on in COG clinical trials is basically the same that the BFM has studied in their studies in Europe, 5 gm/m2 given every two weeks for 4 doses. The leucovorin rescue is 15 mg/m2 beginning at Hour 42.

In this study, in the way Capizzi methotrexate and the high-dose methotrexate are given here, vincristine is administered on the day of methotrexate, and then in the case of Capizzi methotrexate, PEG-asparaginase is given. For the high-dose methotrexate, a low-dose of oral 6MP is administered daily.

[Slide.]

The two studies that are asking randomized questions of therapy related to methotrexate are the ALL0232 study for high-risk B-precursor ALL.

This study uses a 2 x 2 factorial design on an augmented intensity BFM backbone. It was activated in late 2003, will enroll approximately 2,000 patients.

The first randomization, the factorial is a question of dexamethasone versus prednisone

during induction therapy.

In the second randomization, the one we are interested in discussing today, is the one during interim maintenance and looking at the high-dose methotrexate that I described previously versus a Capizzi escalating methotrexate.

[Slide.]

The other study has a very similar design. This is the 0434 study for T-cell ALL. Also, we use a 2 x 2 factorial design on an augmented intensity BFM backbone. This study is planned for activation in the second quarter of 2006, and will enroll approximately 1,200 patients over 6 years.

Again, a factorial design. The first randomization here is a plus/minus nelarabine or Compound 506U78. The nelarabine is given to half of the patients during consolidation, delayed intensification and maintenance phases of therapy. It is given in 5-day treatment blocks that are intercalated between these phases of therapy.

The second randomization is the same as for the 0232 study, the high-dose methotrexate

during interim maintenance versus the Capizzi escalating methotrexate.

So, these are the two randomized studies that we are talking about for looking at efficacy comparisons for these two ways of administering high-dose methotrexate during interim maintenance, but also looking for comparisons of toxicity, and particularly neurological toxicity.

[Slide.]

Let me, before I turn the podium over to Dr. Armstrong to discuss neurological toxicity in detail, just say a few words about the neurological toxicity.

Fifteen to 20 years ago, neurological toxicity was clearly recognized as a sequelae of therapy for ALL, but it was ascribed almost completely to cranial irradiation, and there was a belief at that time that if we could just avoid cranial irradiation, that neurologic toxicity would be avoided.

So, a number of studies in the late eighties, in 1980s and 1990s, sought to get rid of

cranial irradiation and substitute other CNS-directed therapies, both more intensive intrathecal therapy, as well as CNS-directed therapies, like high-dose methotrexate.

What we have learned in the interim is that certainly methotrexate can have serious neurological toxicity. This is dependent upon how many courses are administered and all of the variables that I discussed about high-dose methotrexate. Intrathecal therapy, as well, can have CNS toxicities.

In retrospect and from where we sit today, it is clear there is biological, biochemical plausibility for the neurological toxicity of methotrexate.

This table is taken from a review from 2003, and listing some of the plausible mechanisms by which methotrexate may have neurotoxicity. The reduction in levels of S-adenosylmethionine can decrease the methylation capacity in the central nervous system, potentially leading to demyelination.

Increased levels of homocysteine could have toxic effects on the vascular endothelium. Increased levels of the sulphur-containing excitatory amino acids could produce increased neuronal excitability, producing seizures and other toxicities, increased level of adenosine also potentially producing neurotoxicity.

[Slide.]

So, where we sit today, we realize clearly that methotrexate can have neurological toxicity, both acute neurological toxicity, such as seizures that are observed with high-dose methotrexate occasionally, with intrathecal methotrexate, but it can also be observed with oral low-dose methotrexate, as was observed in the UT Southwestern experience described by Dr. Winick.

Of more concern than the acute neurological toxicities are the chronic neurological toxicity, and Dr. Armstrong will say much more about this. Depending on the way the methotrexate is administered, these may range from severe leukoencephalopathy to subtle findings on

neuropsychological testing.

What is proposed with the support from the Best Pharmaceuticals for Children Act funds is to evaluate neurological toxicity as an important secondary endpoint for both the 0232 study and the 0434 study.

[Slide.]

So, in summary, despite more than 50 years of evaluation and treatment refinements, there still remain important questions that need to be addressed about how best to use methotrexate for children with ALL.

Future use of methotrexate should be based on data from Phase III trials like the ones that I have described, that are looking both at efficacy for the different ways of administering methotrexate, and also at toxicity endpoints, and in particular, neuropsychological endpoints.

DR. REAMAN: Thanks, Malcolm.

Maybe we will have the other speaker and then do questions for both of you.

So, Dr. Armstrong on the Cognitive

Neurotoxicity Associated with Methotrexate Use.

DR. ARMSTRONG: Thank you.

Just as a correction, in your materials, I am listed as an M.D. I am actually a Ph.D. psychologist, but I think that speaks highly to where we are in terms of transdisciplinary research in this area.

[Slide.]

When we look at methotrexate toxicity, we have looked at this, and Dr. Smith has done a very nice job in giving the background of how the protocols have been developed.

Prior to 1986, we had CNA prophylaxis that primarily involved CRT with or without intrathecal methotrexate, and what we knew in terms of cognitive neurotoxicity as a long-term late effect was that we had learning disabilities.

In the early 1990s, a paper came out that actually consolidated in a review piece that the majority of these difficulties were in slower processing speed, in the ability to do visual-motor integration, sustained attention and concentration,

and memory, and with significant impact on mathematics abilities in children.

[Slide.]

When we look at the data for what we know about cognitive outcomes, most of the studies that have been published have been based on the POG-CCG-COG continuum of research.

We have very few data published on neurotoxicity or cognitive neurotoxicity using the Capizzi methods, BFM with high-dose methotrexate in other group trials around the world. So, this is an area that needs more work.

[Slide.]

POG 8602 was probably the first of the studies that eliminated CRT and used triple intrathecal chemotherapy for CNS prophylaxis. Early on, there were noted transient white matter changes. Rupert Nitschke and his group in Oklahoma found those, but they largely resolved when they did a year follow-up after the initial treatment with the TIT.

No cognitive changes were noted in a study

that looked at 1-year follow-up, but when they looked at 3-year follow-up after diagnosis, similar patterns seen for cranial irradiation were noticed, slowed, delayed recall, general non-verbal ability impairments, problems with attention, motor speed, visual motor integration, and we began to see what has now been shown in five or six unrelated studies that girls were at greater risk for these cognitive difficulties than were boys.

I like to pinpoint things. We submitted a grant proposal to the NCI to compare the CNS prophylaxis and the introduction of the intermediate dose methotrexate for POG 9005 in 1989 as the study was being developed, and you keep your pink sheets, and the one that I loved about that one was we got a good review, but the comment was this isn't relevant, we are not radiating anymore pertinent to Dr. Smith's comment.

[Slide.]

The original study involved comparison of triple intrathecal chemotherapy versus methotrexate only for CNS prophylaxis. There was an

unacceptable relapse rate on the methotrexate only, so that part of the study shifted completely to triples, but as the study progressed or early in the study, we found acute neurotoxicity, seizures, imaging abnormalities for about 7.8 percent of the 1,304 patients who were enrolled on the trial.

[Slide.]

This led to a change and a slowing down of the development of the A-linked studies, and the initiation of a study that originally looked at a sample of four institutions who had a total of 163 eligible patients. Forty-eight of those had acute neurotoxicity and were not occluded, 45 patients refused for a variety of reasons, leaving us with 54 patients who had no acute neurotoxicity, who received a non-contrast CT scan and a neuropsychological evaluation.

[Slide.]

Forty percent of the group had CT abnormalities, 50 percent of those involved calcifications, 30 percent white matter changes, and 20 percent involved both calcification and

white matter changes.

[Slide.]

Of real concern to us was the finding looking at cognitive function in this cohort of children, and this slide demonstrates that approximately 40 percent of the children had verbal or performance IQs on standardized IQ testing that fell below 85.

The typical percentage of the normal population is 16 percent, and of great concern was the 15 percent with verbal IQs less than 70 and performance IQs less than 70, 20 percent there. The number in the general population there is 3 percent. So, these were large numbers for any sampling model, admittedly given a small sample, but enough to give us some real concern.

[Slide.]

As we began to look at those specific functional areas in this particular group of children, what we saw was once again here, the group of children who wound up having verbal and performance IQ significantly greater than the

normal population, a high level of folks with 30 percent with difficulties in visual-motor integration, particular problems related to memory, both visual and verbal memory in this particular population.

[Slide.]

I didn't show this slide, but what we found is white matter changes were associated with both visual and verbal memory, calcifications primarily with visual memory.

We also saw a very significant and unique pattern of attentional problems, not hyperactivity, but a pattern of slow processing speed and lack of responsiveness rather than impulsivity in this population.

[Slide.]

As we move forward in our development of our ALL trials, we expanded to 9605, which involved high-dose methotrexate and triple intrathecal.

There has been one small single institution study with 24 children that found verbal and performance memory and visual memory

difficulties that are consistent with the findings that we had for 9005, and they also reported that 78 percent of their 24 children had MR abnormalities at some point in the study.

We are now looking in COG at ALTEO131, a late effect study that looks at MR-FLAIR and neuropsychological functioning in the follow-up of children on this study and one other trial.

[Slide.]

So, the questions that we have are what is the mechanism. There clearly is a potential vascular effect leading to the calcifications and the anti-folate effects of methotrexate in the folate/adenosine pathways are one of the real concerns. Elevated homocysteine has also been implicated as are many of the other biochemical mechanisms that Dr. Smith presented in his slide.

There are some questions about white matter changes and what is happening with the demyelination component, whether that is a difficulty with growth of myelin, whether it is axonal restriction.

There is also a question that came from our 9005 data, why only 40 percent, is there a pharmacogenetic risk that we can identify for prediction.

[Slide.]

This slide just simply maps out the model that we are working on that links the potential of the different types of treatment of children with cancer, of all types of cancer, what kinds of global impact that may have on brain development, how that is related to specific functional areas and what that translates into in terms of children's performance in school.

[Slide.]

The questions for the study that we are proposing is: Can outcomes be predicted using an interactive model of defined risk, genetic, pharmacologic, structural, and acute events, and neurodevelopmental trajectory?

[Slide.]

This point I think is one that is very important, I talk about this with families. But

when we think about toxicity, typically, in childhood oncology perspectives, we are thinking about acute cross-sectional sampling, but when we are looking at children, we are looking at children's brains that may be impacted in any given time, and that impact may affect what they can do at the time of the damage, but it may also, in very interesting ways, affect the growth and development of that brain for many years to come.

We do know that there are specific functional abilities that are tied to brain development at specific age periods. So, language and gross motor skills develop very rapidly and are the major consolidation point during the first two to three years of life.

During the period of 3 to 6, 3 to 7 years of age, we see development of the frontal cortex, and the processing speed, the visual-motor integration, the ability to tie your shoes instead of using velcro, the ability to draw within the lines, all of those kinds of tasks that come along, and this developmental course extends until the

early 30s when myelination and the development of connecting structures in the frontal cortex finally end, so most of us over 30 really don't have anything to look at.

[Slide.]

What we have found in some of our studies with children who have had high-dose irradiation for brain tumors that we would apply and think about in this area is that we may see development of the brain prior to treatment, that development remaining relatively intact and those functional abilities remaining intact over time, but we may see a slowed or even impaired development in those abilities that would occur after treatment.

[Slide.]

So, we have a fairly complex model developmentally, as well as treatment that we are concerned about, so that led us to the study that we have with the BCPA project.

The overall project goals are to determine the incidence and severity of methotrexate neurotoxicity associated with the Capizzi,

escalating those methotrexate and high-dose methotrexate treatments, and then to identify risk factors and possible mechanisms for neurotoxicity associated with methotrexate that lead to cognitive impairment.

[Slide.]

We have five projects that are associated with this. The cognitive outcome is the primary or the cornerstone of this to really be able to look at what happens to the cognitive functioning of these children over time, but we have other projects that will look at developing and identifying host polymorphisms that may predict who among the treated population are at increased risk to determine whether acute transient episodes of neurologic toxicity reflects similar biochemical vulnerability and are predictive of neurocognitive long-term effects, to be able to study the pathophysiology of neurologic dysfunction through an assessment of the impact of methotrexate on folate-dependent biochemical pathways.

I would pause right here to say that this

is a very important question because understanding that folate pathway may have real applicability to other non-cancer-based developmental disabilities where the folate pathway is implicated as in many of the neurodevelopmental disabilities that are genetically based, and finally, to identify areas of selected vulnerability within the central nervous system that may predict or correlate with neurocognitive outcome in using diffusion tensor imaging. That is a longer term initiative of the program.

[Slide.]

Dr. Smith has already described the study. We intend to enroll about 432 children who have high-risk ALL treated on ALL0232 or 0434 and a cohort of 72 sibling controls. Both of these studies involve comparison high-dose methotrexate with Capizzi. 0232 also compares dexamethasone with prednisone.

We do have some suggestions that while dex may have a therapeutic benefit, it may also be associated with a higher risk for neurotoxicity,

neuropsychological toxicity, and there is nelarabine randomization for 0434. None of the children in this study will receive cranial irradiation.

[Slide.]

This is a prospective repeated measures design that we are adding to the study. We will look at evaluations of children at the end of induction, 12 months after remission and 12 months off treatment, and looking at the various issues that I described a moment ago.

[Slide.]

We also plan to look at two age cohorts, one which is younger, 12 months to 155.9 months at the time of diagnosis, and an older cohort. Each of these age cohorts are being sub-grouped by age at diagnosis, with random distribution between the Capizzi and high-dose methotrexate arms, so we don't have an age confound, and then within each of those, we have three additional breakdowns.

[Slide.]

The areas of function that we are going to

assess, I won't bore you with the names of the psychological tests, but we will be looking at those things that we think are according to the model and previous data most important.

Global intellectual functioning, memory, both visual and verbal, attention, language base for fluency and vocabulary, the ability to plan and organize, specific achievement in the academic areas, and adaptive behavior and adjustment.

[Slide.]

All children in the younger cohort will be evaluated with the same primary test at Time 3, so that we have complete comparison there, and the same applies to the older cohort.

Neuropsychological tests, because of developmental issues in children change, and we need to be able to have a firm foundation within age cohorts, and the evaluation strategy for this primary neurocognitive outcome is applied to areas of specific function, so that we have cross-age samples compared at the same time point using the same tests in the areas of memory and attention and

visual-motor integration, and the like.

[Slide.]

I am not going to go through all of the hypotheses, those are in your handout, but they are driven by two primary concerns. One, we are hypothesizing that the children treated with high-dose methotrexate will have a greater risk for long-term neurocognitive toxicity, that there will be an age component where younger children are at greater risk, and that we will find and be able to build some models that will help to predict that.

[Slide.]

The concluding points. We know that neurocognitive toxicity is no longer seen as a rare event in treatment of children with ALL. It is now a significant late effect. However, we don't know to what degree this applies to treatment approaches outside that of the POG models of the 1990s.

The opportunity to both prospectively model, and I think the modeling component establishing the mechanisms that will enable us hopefully at some point to take a newly diagnosed

patient and say this is the child who is likely to have acute or long-term cognitive toxicity, and either adjust our therapy or come in with early intervention that may lessen that problem is unprecedented for us.

With that, I will stop, so we can move forward with questions. Thank you.

DR. REAMAN: Thank you.

Do we have any questions for either or both of the speakers? Dr. D'Agostino.

DR. D'AGOSTINO: The presentations were quite good obviously, and I think I followed most of them in terms of the details, but I have a few questions.

In terms of the studies that Dr. Smith was talking about, I am not clear on how the randomization in the 2 x 2 factorial is going to work. Are the subjects going to be assigned immediately upon entry, or do they have to go through a Phase I into Phase II, and then get assigned?

DR. SMITH: I believe for both of the

studies that the assignment is made after remission is attained--well, for the high-risk study, it has to be randomization upfront, the ALL0232, because that has an induction randomization, so patients are assigned at the time that they enter the protocol to one of the four arms.

For the other study, I believe it is the same approach, but they wait until after remission is attained, and then are randomized at that point to the four treatment arms.

DR. D'AGOSTINO: So, those that make it into remission get then randomized for a balance.

DR. SMITH: They are randomized to, yes.

DR. D'AGOSTINO: How long is the actual follow-up going to be. You talked about accrual, but I didn't catch the follow-up on it.

DR. SMITH: I don't recall details. Usually, it is about two to three years after the last patient.

DR. D'AGOSTINO: Similar to the Armstrong, you are going to have repeated visits through the sequencing.

DR. SMITH: For the efficacy studies, you know, for T-cell and for high-risk B-precursor ALL, typically, the events will occur in the first three to four years.

DR. D'AGOSTINO: How are you handling in some of the analysis with the dropout, and are there other rescue type of medications or other procedures? Maybe that is not the right vocabulary, but what will you be doing as people move into different treatments?

DR. SMITH: Patients who have a relapse are off study, and then they are able to potentially enter another COG relapse study, or to get--

DR. D'AGOSTINO: So, when they go into relapse, basically--

DR. SMITH: The primary endpoints are event-free survival, and that is the way it has been with ALL studies historically.

DR. D'AGOSTINO: Will there be dropouts in terms of follow-up, and that will be a problem?

DR. SMITH: There is some small rate, but

for childhood ALL, that rate is small.

DR. D'AGOSTINO: I have one question for Dr. Armstrong. I didn't understand the sample size. The studies that Dr. Smith was suggesting are going to be quite large, and you had, if I heard you correctly, just 432 or something. How do you select those and the controls?

DR. ARMSTRONG: That will be done on a continuous enrollment in terms of accrual across the institutional trial until we hit the power for this particular study.

This is driven by--this is a phenomenal support from the BCPA project, but it is a very expensive project.

DR. D'AGOSTINO: You will be doing stratification, and so forth?

DR. ARMSTRONG: We will be doing stratification as we move forward, so that we have each of the arms of the study represented, so that we are not confounding by the dex pred, nelarabine, and the age at diagnosis.

DR. D'AGOSTINO: Thank you.

DR. REAMAN: Dr. Adamson.

DR. ADAMSON: First, a comment following Malcolm's very nice historical review. I think the one lesson we pediatric oncologists haven't learned in 50 years is that we need to convene the caveat committee before the study, and not after the study, because I can guarantee you with the current set, the committees are already gearing up, because one group is not getting 6MP and one is getting asparaginase, so we haven't learned that lesson unfortunately, and the caveat committee will convene probably in about five years for these studies.

Now, my question for Dr. Armstrong, because I think this is a phenomenal opportunity to learn something after a study is opened. One is, is the idea that this is going to be happening at all COG sites, and are there neuropsychologists who are able to do this in a standardized way at all sites? I will give you all three questions because they are pretty straightforward.

Will there be central review of the

imaging for this, and lastly, are you going to be looking at folate status rather than looking at the drug, looking at its downstream effects to see are there fundamental differences in folate status in these children that underlie the ultimate differences?

DR. ARMSTRONG: The answers are--and I am not the biochemist, so I am going to be a little careful on that--but I know that the intention that we have is that yes to the third question, that we are not interested--we are interested in really looking at what happens to the folate pathway over time, and to not ask the question of what is the folate status is problematic.

Now, the question that comes in, that we don't know the answer to, and that will be moderately affected is that at the end of induction, when we are enrolling these children and collecting the pharmacologic samples, they will have already been exposed to induction therapy, and there is going to be methotrexate involved in the intrathecal component of that.

So, I am not sure the degree to which we will be capturing that initial pre-induction sample given the stratification, the enrollment that we have for this population. I don't know the answer to that question. We may have it.

The answer to the cognitive component, the neuropsychological question that you asked first, is we have really done a lot of work with this to ensure that we are going to be able to do the study including very significant travel dollars for families to be able to travel to a site where there is a psychologist or a psychologist to be able to travel to a site where the families are.

There are some licensing and credentialing and liability issues that have to be worked out, but we do have that in place. We have 163 psychologists in the COG right now who are on place, and we have also, for the first time, funded this study to cover, not only the testing, but all of the other components that are clinically appropriate, the development of a comprehensive report, a feedback session, and recommendations so

the families can follow up on the educational components for the children.

So, I think we have addressed some of the historic challenges to the neuropsychological testing components in this proposal.

DR. ADAMSON: And imaging central review?

DR. ARMSTRONG: And the imaging, yes, will be centrally reviewed.

DR. REAMAN: Ms. Eichner.

MS. EICHNER: Hi, Dr. Armstrong. Just to put this more in a layman's term for a parent to understand, your study is basically confirming what we already know, is that kind of a way to put it?

DR. ARMSTRONG: No, not actually. It will confirm what we found in some small studies, in a much larger sample, in a very systematic way.

I think that the thing that is most exciting about this study is that while we know that we have a risk for neurocognitive outcomes with this treatment, we have also seen, as Dr. Smith presented, this advancement in our treatment of ALL has had significant reductions of CNS

relapse and has had significant improvements in overall long-term survival, so there are some real benefits of this treatment.

What we know is that in the smaller studies that we have done, we have got a fairly significant neurocognitive outcome.

What this study will allow us to do, and what I am most excited about, is develop the interdisciplinary data that will help us to potentially map out why, and that is a crucial issue for us because at this point, with every newly diagnosed child treated on a high dose or an intermediate dose methotrexate protocol, we cannot at the time of their diagnosis predict who is going to have the problem five years later.

This mechanism will help us to potentially build the model. It is not a guarantee, but our hope is that it will help us to build the model that helps us understand what is the mechanism by which methotrexate causes these cognitive problems and will lead us five years from now to the ability to say at the time of diagnosis, you are at risk,

and then to get to the point of saying can we change our therapy, so that we lessen this late effect or are there other things we need to do for those children who are at highest risk, so that this is not a lifetime complication.

That for me is the step up beyond just saying what we already know.

MS. EICHNER: Another question is since there is some data out there, just posted on from one of the families, will this be incorporated as a standard late effect follow-up, since there is really no standard late effect follow-up for these children now?

You know, you would get off the treatment, you said yourself it's five and six years down the line that children start experiencing, I mean not always, but these effects, and these families are far away from treatment, far away from institutions, how are you going to follow these children?

DR. ARMSTRONG: I think the answer to that is that the Children's Oncology Group has now

developed a late effects program, and part of that late effects program is on our web site, is an updated evidence-based set of guidelines for every known late effect of childhood cancer.

There is a multidisciplinary group that meets by conference call once a month to review all new literature, and this list is updated once a month. That is a mechanism by which the broader community is being exposed to what needs to be done, not only for cognitive late effects, but for heart late effects, risk of secondary malignancies, and the like.

The interest in the late effect here is really high. I had the opportunity to do a teleconference for one of the national groups last year, was absolutely amazed that there were 1,800 phone lines with more than 2,400 parents who called in for that teleconference from 39 states and 17 countries.

So, I think the issue is that it is part of an educational process, and as education goes about, and we find out these kinds of important

data that we hope to learn from this study, then, we will have a more informed pediatric oncology treatment group that will be able to integrate the late effects into standard of care.

MS. EICHNER: Thank you.

DR. REAMAN: Dr. Finklestein.

DR. FINKLESTEIN: In your emerging cognitive deficit developmental pattern, you will have a vertical line, you know, right through the age of 3, which has been classically, from a clinical point of view, the age we have always been worried about in terms of, say, using radiation.

In your pilot data out of POG, did you find a significant difference in the younger children versus the older children in terms of some of the deficits as you would predict from your curves? That is part one of a two-part question.

DR. ARMSTRONG: We have a weak trend, but with only 54 patients, the power was really not adequate for that, and we didn't have as many younger children in the cohort as we did older children.

So, the answer is no, we didn't, but I am not sure what that means.

DR. FINKLESTEIN: Well, I would expect that you will.

DR. ARMSTRONG: I think we will.

DR. FINKLESTEIN: And then my question is from a statistical point of view, how do you build that into your study in terms of comparing the treated patients versus normal controls?

DR. ARMSTRONG: Well, in terms of the treated component, what we are doing is stratifying by those age groups within the arms of the treatment study, so this is a relatively carefully designed study, so that we have adequate numbers of patients at each age group treated with high dose versus Capizzi on both the 0232 and the 0434 studies.

It is going to take us a little bit of work to make sure that our sibling group also represents that same age distribution, so that we have some comparison, so we are recruiting numbers of children who fit into the younger category and

numbers in the older category that will match our sample.

So, we have a specific plan to make sure that that age distribution in the sibling group is also maintained.

DR. REAMAN: Dr. D'Agostino, did you have a question?

DR. D'AGOSTINO: I did have one, but it is probably not appropriate. I was wondering about the informed consent that is going to go on here with helping the children, but at the same time, hurting their cognitive function, and so forth, and I don't want to detract from the questions that are being asked.

DR. ARMSTRONG: I can answer the question real carefully. I mean that is part of our consent process now. We now know there is a risk for late effects. That is part of the consenting process, and most IRBs are now aware of the kinds of concerns we have and require that as part of the consent process.

DR. SMITH: To address the question are we

confirming what we already know, the one thing I would emphasize is that the POG data are using a treatment that is very different from either of the two arms here.

On the POG study, the methotrexate was given for 12 times, it was given every two weeks, so it was a certain type of leucovorin rescue and other intrathecal therapy. That approach surprisingly caused the level, you know, serious neuropsychological toxicity that Dr. Armstrong described.

The available evidence that we have for either of these two treatment regimens suggests that they are much less neurotoxic than this approach that POG 9005 and a couple of subsequent studies were, but we haven't looked close enough to be sure about that, so I think this is the kind of due diligence. We have got, you know, two treatment approaches that both have reasons to think they may be more effective, one than the other.

The kind of body of evidence would suggest

that they are not going to be as neurotoxic as the POG studies were, but we haven't looked closely enough to be able to know that that is the case, so I think this is trying to determine whether we, in fact, are safer with these treatment approaches than we were with either cranial irradiation at 1,800 or 24 gray, or with the kind of very intensive, frequent, you know, 12 doses of high-dose methotrexate that were used in the POG study.

I will say on the POG study, you know, we had signals there that led us to move away from that approach. There was a high rate of seizures and the observation of calcifications on CT scans, you know, it was thought that that was something that you only observed with cranial irradiation, and yet here it was being observed on patients who had never seen cranial irradiation, so I think this approach that we are taking here is very different from the POG approach that was tried in an attempt to avoid cranial irradiation and the side effects that were associated with that, but it actually

turned out to cause serious neurological toxicity.

I hope it is clear that this is a different approach and that we really don't know the answer to the question here of how severe or whether there are neurological toxicities, what they are, and what they might be associated with.

I did have one question for Dr. Armstrong. The group that you were looking at from your institutions for your study, there are 160 patients and you had data on 50 patients.

DR. ARMSTRONG: Right.

DR. SMITH: So, are there data that the 50 patients were totally comparable with the other patients, and might--you know, clearly, there is serious neurological toxicity, but could there be an overestimate of what it is because of the minority of patients being studied?

DR. ARMSTRONG: That is a good question. The way we got from 160 to 50, I think 48 of the 160 had acute neurotoxic events, so that was enough to be able, I mean they were eliminated from the study right off the bat, so we were down to about

115 total.

We had about 42 or 43, I think, who refused participation, and that is the group you are asking about, and we don't know. I don't know the answer to that. We had another 16 children who never completed a CT scan, so that is another group.

Their cognitive functioning didn't differ significantly from the group that we studied, but we don't know what their CNS status was by CT. So, it's an excellent question we don't know the answer, but it may affect the sizes of the effect that we found.

DR. REAMAN: Dr. Santana.

DR. SANTANA: Can you clarify for me, I couldn't determine from reading the materials or from the presentation, is neuroimaging a part of this study at the indicated time points in which there are neuropsychological assessments, and if so, what is the hypothesis behind that based on historical data, potential no relationship or relationships between imaging, and then functional

outcome?

DR. ARMSTRONG: The neuroimaging component of this hasn't been completely worked out. It won't be completed at baseline. The plan is--and, Dr. Reaman, correct me if I am wrong on this, because I know we have had a number of discussions in the last few weeks--but the plan is to look at the diffusion tensor imaging at the endpoint study, but not along the way, am I correct on that? Is that our latest thinking?

DR. REAMAN: Dr. Finklestein.

DR. FINKLESTEIN: My question is to Dr. Armstrong, but also to address perhaps Ms. Eichner's comment, and that is, we are aware as clinicians that patients will develop neurocognitive challenges, therefore, right at the beginning, we are starting to make our parents aware of this, our psychologists are aware of this, and we are starting active, shall we say, treatment interference to maximize our children's ability to function at optimal fashion.

Now, that is going to happen. How does

that affect your study in terms of long term, because some of these patients from day one will have an active program to maximize their potential, some will not?

DR. ARMSTRONG: We don't have a way to be able to control that particular intervention, but we will be collecting data on it, and one of the components that we have built in by adequately funding the complete evaluation and all of the clinical follow-up, which we have not ever done in any of our other studies, is also intended to be able to collect at the very beginning, what are the recommendations for that type of intervention that come out of the evaluation for each child and study, and we will then be able to collect those data, categorize them by types of intervention, and look at them as a potential factor affecting the outcome.

We don't have a way to do a randomized intervention trial of the educational intervention of a study of this magnitude. As you mentioned, there are other trials more carefully controlled,

that are looking at what are the specific interventions that will work both at the level of what happens when we have identified cognitive late effects and some of us who are now starting to think about can we use this model and develop interventions at the time of diagnosis it will prevent, but the best we will be able to do with this study is collect what was done to see what degree of an effect it has on the outcome.

DR. REAMAN: Dr. Blaney, did you have a question?

DR. BLANEY: It was answered.

DR. REAMAN: Any other questions? Dr. Weiss.

DR. WEISS: Are there still these gender-based differences that you described earlier on in some of the earlier POG data in terms of some of the neurocognitive effects of the treatments?

DR. ARMSTRONG: Well, we are going to look at gender as one of the variables, and as Dr. Smith said a few minutes ago, we don't know whether that is going to hold up with the treatments that are

being compared here.

It has been a fairly consistent finding over all the studies in the '90s, and there is at least one small study with about 30 patients out of a European sample, I think, a Scandinavian study, that also reported a greater incidence of risk for girls and boys.

So, the gender issue is something we will have to tease out, but we don't have the capacity to control for that factor in the study.

DR. REAMAN: Dr. Smith.

DR. SMITH: Could you comment on potential neurotoxic effects of steroids and dexamethasone and how that might affect, you know, looking at the methotrexate question here?

DR. ARMSTRONG: Well, I think that is a real issue, because we once again have had some studies that have suggested, and it is a small, I think there are two or three studies that have shown or have suggested that children treated with dexamethasone may have a higher risk than children with prednisone.

What we will be able to do in this study is that we are also enrolling children, so that we have balanced arms for the dex versus pred for the high-dose methotrexate versus Capizzi, so that we should be able to answer that question at the end.

Questions to the Subcommittee

DR. REAMAN: Maybe we will address the specific questions that we were given by the Agency with respect to methotrexate.

An objective of the two trials in patients with leukemia, that we have heard about, is to assess efficacy and safety of high-dose methotrexate versus Capizzi methotrexate, which incorporates increasing or escalating doses. Both studies seek to evaluate and answer questions about several potentially important drugs or regimens in pediatric leukemia.

Do the study designs, will they enable the isolation and comparison of the effects of high-dose methotrexate versus Capizzi methotrexate, and identify specific aspects of the designs most critical in delineating the effects of high-dose

methotrexate.

Please discuss which of the study outcomes are most relevant to assessing high-dose methotrexate efficacy and toxicity, and the adequacy and frequency of safety measurements to assess toxicity, particularly the neurotoxicity.

I think we have probably already addressed the adequacy and frequency of assessments. Any further discussion on study outcomes which are most relevant? Dr. Smith.

DR. SMITH: Could you comment in terms of the time points? Would you anticipate that this is something that is the first year, you know, should be detectable in the first year, two years, three years, four, you know, a chemotherapy-induced neurotoxicity?

DR. ARMSTRONG: What we would expect to see, based on prior patterns, will be if neurotoxic events are most likely to occur during the first 12 months, actually, closer to the induction than the end of the 12 months. There may be some signs of some difficulty that would show up, but most of the

studies have not found it at a year.

Our off-treatment, three-year evaluation is going to be the crucial endpoint, but the way that we have built the timing will enable us to really look at the pharmacologic pathways that I think are going to be crucial and help us to be able to look at the relationship of the pharmacodynamics to that long out point.

DR. REAMAN: Dr. Reynolds.

DR. REYNOLDS: You mentioned that you would be having a balance between the dex versus pred arm and the two methotrexate regimens. Is this study powered to actually detect an interaction between those two?

DR. ARMSTRONG: Yes, it is.

DR. REAMAN: I want to go back to Dr. Finklestein's question earlier about the fact that some patients may actually be receiving some interventions, remedial interventions, and just to clarify that although patients may be functioning more normally as a result of those interventions, being able to detect difficulties with the testing

panel proposed with a battery will still be evident.

DR. ARMSTRONG: Yes, absolutely.

DR. REAMAN: Dr. Adamson.

DR. ADAMSON: I wanted to make a comment on Question 2(a) about the comparison of the high dose versus Capizzi methotrexate. I think the great strength of the study being proposed is that we will learn almost independent of whether the primary studies sort that out, and the caveat committees may, in fact, hold the day, and we may not know the difference.

I think the general sense is that we are going to see heightened neurocognitive effects in the high dose versus Capizzi, but as Malcolm pointed out, perhaps not to the magnitude that we have seen in some of the earlier POG studies.

What we are going to take away from this, I am hoping, goes well beyond recipe A versus recipe B, and that is identifying the children who are at risk for methotrexate neurotoxic effects whether they be low, intermediate, or high dose,

identify those children who are at risk and then minimize that risk and make a much more informed decision as far as what the risk-benefits of our therapy are going to be.

The other fallout I think from this is I suspect as we do imaging in this large cohort, we are going to find a remarkable degree of patients who have imaging abnormalities, and right now--and I am not an expert here--but my estimate is we really have no way to interpret the large majority of those abnormalities, so linking this imaging to the neurocognitive outcome is going to be an extremely valuable resource, not only for methotrexate, but across a spectrum of drug-induced neurotoxicity.

So, I would urge that the Agency not focus exclusively or even primarily on the high dose versus the Capizzi, which is the primary aim of the underlying study, but rather a much greater understanding of drug-induced neurotoxicity in developing children that I think is going to emerge from this.

DR. REAMAN: Malcolm.

DR. SMITH: I would second Dr. Adamson's comment that I think there could well be children who are susceptible to the neurotoxic effects of methotrexate, and will it be able to identify those.

I would caution, though, in thinking that that high-dose methotrexate is going to be more neurotoxic than the Capizzi. I mean we thought that radiation versus high-dose methotrexate, you know, would be safe if we got rid of the radiation, and the oral methotrexate, the study that I mentioned from UT Southwestern, you know, you can induce neurotoxicity with oral low-dose methotrexate if you deplete folate, you know, the way they did in that study.

I think it really is unknown in terms of what the relative neurotoxicities will be between these two regimens, but I agree that a strength of this study could be in identifying, regardless of regimen, what children are most susceptible for pharmacogenetic or other reasons to this particular

toxicity completely.

DR. REAMAN: If there are no other comments, do those responses address the concerns of the Agency, or are there other issues?

DR. WEISS: I think that probably covers it. We knew these were very complicated protocols, answering a number of important questions, but I think the discussions were very useful, and the main issue is whether or not there was any additional input particularly as the second protocol hasn't been initiated yet, and there would potentially be time to make alterations if need be to try to improve again the quality of the data that would come out of that, but it is sort of hard to improve on something that has been so I think thoroughly vetted and worked out over the years.

DR. REAMAN: We will take a 15-minute break and reconvene at 10:35.

[Break.]

SESSION II

Phase 4 Requirements for Deferasirox (Exjade)

Novartis Pharmaceuticals

DR. REAMAN: We are changing topics here. We have a new panel of individuals, so maybe we will reintroduce ourselves for the sake of those new people.

Dr. Pazdur.

Call to Order and Introduction of the Committee

DR. PAZDUR: Richard Pazdur, Office Director.

DR. WEISS: Karen Weiss, Deputy Office Director.

DR. ROBIE-SUH: Kathy Robie-Suh, Medical Team Leader, Hematology, Division of Medical Imaging in Hematology.

DR. RIEVES: Good morning. My name is Dwaine Rieves, Deputy Division Director, Medical Imaging and Hematology Products.

DR. SHASHATY: I am George Shashaty. I am the medical reviewer for Exjade.

DR. D'AGOSTINO: Ralph D'Agostino, statistician, from Boston University.

DR. FINKLESTEIN: Jerry Finklestein,

hematologist/oncologist from Southern California, which is now warmer than Washington, D.C.

MS. O'CONNELL: Cathy O'Connell, Patient Representative.

MS. EICHNER: Marilyn Eichner, Patient Representative.

MS. CLIFFORD: Johanna Clifford, Executive Secretary to the ODAC and the Pediatric Oncology Subcommittee, FDA.

DR. REAMAN: Gregory Reaman, pediatric oncologist from Washington, D.C.

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

DR. ANDERSON: Barry Anderson, Pediatric Oncologist from NCI CTEP.

DR. BLANEY: Susan Blaney, Pediatric Oncology, Baylor College of Medicine.

DR. BERG: Stacy Berg, Pediatric Oncologist, from Baylor College of Medicine.

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

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

DR. SCHREIBER: George Schreiber, Epidemiologist, from WESTAT, Rockville, Maryland.

MS. WINNER: Susan Winner, Patient Representative.

DR. REAMAN: If I could ask Dr. Brittenham to introduce himself if he is on the line.

DR. BRITTENHAM: I am. It's Gary Brittenham, Hematologist at Columbia University in New York.

DR. REAMAN: Thank you.

We have another Conflict of Interest Statement, which Ms. Clifford will read for us.

Conflict of Interest Statement

MS. CLIFFORD: The following announcement addresses the issue of conflict of interest and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all

interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

In accordance with 21 U.S.C. 355(n)(4), a waiver has been granted to the following participant: Dr. Peter Adamson for ownership in a sponsor's stock valued at less than $5,001. This de minimis financial interest falls under 5 CFR Part 2640, which is covered by a regulatory waiver under 18 U.S.C. 208(b)(2).

A copy of this waiver statement may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

In addition, Dr. Patrick Reynolds has been recused from participating in this portion of the meeting.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to

exclude themselves from such involvement and their exclusion will be noted for the record.

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

Thank you.

DR. REAMAN: Dr. Shashaty.

DR. WEISS: If I may, while George is coming up to the podium, just to comment on this particular topic, just to let the audience and the committee know, we are here to discuss Exjade, which is an oral iron chelator.

It was approved by FDA early in November, I believe, of just this past year, so it has only been recently approved, but we thought, because of the importance of this drug in the pediatric hematology/oncology community, number one, it would be very good to review the basis for approval for this group of experts as this drug was taken before BPAC, which is the Blood Products Advisory

Committee, the end of September to discuss the data available in the marketing application, and was recommended for approval by the committee at that time.

But we thought it would be very important to discuss the basis for approval with this body of experts, as well, because of the use of this drug among the types of individuals that are represented around the table, and then also because the drug was relatively recently approved and there are there are a number of outstanding Phase IV commitments that have been agreed to between the FDA and Novartis, to ask the committee's input on how best to optimize the types of information that could go into Novartis' thinking as they develop the studies to meet the Phase IV commitments.

Thank you.

FDA Presentation

DR. SHASHATY: Good morning. I am George Shashaty. I am the medical reviewer for Exjade. Exjade is also referred to as deferasirox, and during the IND it was referred to as ICL670, if you

have any knowledge of those names.

[Slide.]

A few words about iron metabolism in general. There is a balance between iron intake and iron excretion. Iron is very highly conserved in the body. Generally speaking, particularly in adults, about 1 to 2 milligrams of iron are absorbed and 1 to 2 milligrams of iron are excreted. The normal total body iron is about 3 to 5 grams depending on age, sex, et cetera.

The normal liver iron concentration is usually less than 1.5 milligrams of iron per gram of dry weight, and there is a relationship between liver iron concentration and total body iron and milligrams per kilogram. If one multiplies the LIC by about 10.6, that gives you the total body iron.

It is believed by some that the safe liver iron concentration is somewhat below 7 mg of iron per gram of dry weight. One unit of blood transfusion contains approximately 200 to 250 mg of iron. When that blood is infused into a person, basically, none of that iron comes out.

After a person has received approximately 100 milliliters of blood per kilogram, translated to about 15 or 20 units of blood in a 50-kilogram person, it is likely that the LIC will have increased to somewhat above 7 milligrams of iron per gram of dry weight, and this iron affects primarily the heart, the liver, and the endocrine organs, and the main cause of death in such persons is related to heart disease.

[Slide.]

Exjade is a new oral iron chelating agent. It has orphan drug designation because of the numbers of patients who might be treated. Because of early promise, it was granted fast track designation at a priority review, and it received accelerated approval on November the 2nd of '05.

Its indication is for the use in the treatment of chronic iron overload from blood transfusions in both adult and pediatric patients who are at least 2 years of age.

[Slide.]

I am sure most of you are aware of this,

the traditional therapy for hemosiderosis has been deferoxamine. This drug has been available since the mid-1960s. The problem with the drug is that it must be parenterally administered.

Because of its short half-life, it has to be administered over half of the day, and it has to be given almost every day of the week, and this leads to problems with compliance. However, I think there is some reasonable knowledge that suggests that deferoxamine is useful in preventing death, particularly from heart involvement with iron overload.

In the trials that were conducted with Exjade, the comparator was always deferoxamine because it was believed that placebo trials could not be carried out.

[Slide.]

The studies that were reviewed in the evaluation of Exjade are listed on this slide. There were five studies. I would just say that the primary study that was looked at was 0107, which was a randomized, open-label, controlled trial that

enrolled 586 patients. All of these patients had beta-thalassemia and they were age 2 or greater.

In all of the studies, basically, the endpoints were liver iron concentration at baseline compared to liver iron concentrations at 48 weeks. Some of the studies, for instance, the 0105, was basically a dose-finding study.

In 0106, which was non-comparative, these enrolled only pediatric patients. There were 40 of them all together. Then, there was a non-comparative trial, which is supportive in patients who had either beta-thalassemia or patients who had other chronic anemias.

About half of the patients in this group had myelodysplastic syndrome, and then about 30 or so of the patients had Blackfan Diamond syndrome and about 20 patients had other miscellaneous kinds of transfusion-dependent anemia.

Finally, there was a Study 09, in which 95 patients with sickle cell syndromes were treated with Exjade, and this was reviewed primarily or only for safety although now the complete trial has

been submitted to the FDA for review.

[Slide.]

So, we are focusing primarily on Study 0107. As we mentioned, it's a randomized, deferoxamine-controlled, open-label, parallel group, multi-institution.

In this trial of the 586 patients, it should be noted that there were 299 patients who were less than age 16, and of those 299 patients, 154 received Exjade and 145 received deferoxamine.

The dose of the drugs to be used was to be based on the liver iron concentration at baseline. In other words, if a person had a relatively low increased value of LIC, a low dose of either Exjade or deferoxamine was to be used, a higher dose would call for a higher dose of either Exjade or deferoxamine.

The study was to be declared non-inferior based on the difference in what was referred to as the success rate in patients who received Exjade versus those that received deferoxamine, and there were significant problems with this, which I

basically won't get very much into.

[Slide.]

The demographics in Study 0107, Exjade on the left, deferoxamine on the right, basically, the demographics were very similar between the two arms of the trial.

[Slide.]

One of the problems, as I mentioned before, the Exjade dose was prespecified according to the baseline liver iron concentration. One of the problems with the study was that the deferoxamine dose was prespecified according to baseline LIC, however, in patients who had been receiving deferoxamine successfully prior to entry into the trial, those patients could continue on the dose that they were previously receiving.

What has to be brought forward here is that about 97 percent of all 586 patients entered into the trial had previously been on deferoxamine prior to entry into the trial. What happened was that a number of patients who, by LIC, should have had a lower dose of deferoxamine actually received

a higher dose of deferoxamine in comparison to the Exjade-treated patients who, in essence, all received the protocol-specified dose.

[Slide.]

The primary efficacy analysis revealed that the success rate, as defined by--and I am not going to go into exactly what it meant, but it depended on the liver iron concentration at end of study compared to the liver iron concentration at baseline--the success rate for patients treated with Exjade was 52.9 and deferoxamine 66.4 with a difference of 13.5 percent.

Now, the margin that had been selected by the protocol was that the difference, the 95 percent confidence interval for the difference between the Exjade-treated patients, deferoxamine-treated patients, could not exceed minus 15 percent.

One can see here that the 95 percent confidence interval revealed that it was at least -21, and therefore, the trial could not be considered successful in demonstrating

non-inferiority.

[Slide.]

However, analysis of secondary endpoints showed that in the Exjade-treated patients and the deferoxamine-treated patients, the change in liver iron concentration from baseline to end of study was -2.4 mg Fe/g dw versus minus 2.9 for the deferoxamine-treated patients.

I think that we have to remember that these persons were continuing on relatively vigorous transfusion regimens, and one would have expected, and I think the natural history would have suggested very strongly, and there was even some indication in patients treated with low doses of some of the drugs, that in the face of continuing transfusions, low doses of these agents could not lower the liver iron concentration.

[Slide.]

In addition, the patients who received Exjade in the higher doses, which were the 20 to 30 mg/kg/day, the lower dose patients, who had lower liver iron concentration at onset, received either

5 or 10 mg of Exjade/kg/day.

If one segregates out the patients who received 20 or 30 mg/kg/day, the reduction in liver iron concentration is even greater.

[Slide.]

This is the mean change in liver iron concentration from baseline by age group. They were divided into patients between 2 and 6, 6 and 12, 12 and 16, and greater than 16, and one can see that in all of the subgroups, there was a diminution in liver iron concentration over the 48 weeks of the trial.

Now, these are for all doses, not just 20 or 30 mg/kg/day. This is in comparison to the changes that were seen in patients who were treated with deferoxamine, and there is a reasonable equivalence over the age groups except that there is just this one group of from 2 to 6, whose reduction in liver iron concentration seemed to be somewhat less than patients treated with deferoxamine, and it just called our attention to that particular subgroup.

[Slide.]

At the time that the liver iron concentration was changing, there were also studies made on serum ferritins, and this slide shows the changes in serum ferritins depending on whether the patient was given Exjade in a dose of 5, 10, 20, or 30 mg/kg/day, or was given deferoxamine 25, 25 to 35, 35 to 50, and greater than 50.

One can see these are the Exjade-treated patients at low doses, Exjade-treated patients had an increase in serum ferritins over the course of the year at doses of 5 and 10 mg/kg/day, but at 20 mg/kg/day, they were reasonably stabilized despite receiving transfusions, and then in patients who received 30 mg/kg/day, there was a reduction of about 1,000 ng/ml of ferritin in those patients.

[Slide.]

So, the efficacy summary is as follows. Although the pre-specified primary endpoint was not met, treatment with either Exjade or deferoxamine reduced the liver iron concentration from baseline, and this occurred in the face of a continuing

transfusion requirement.

Secondary endpoints, including the changes in liver iron concentration and changes in serum ferritin levels are consistent with a treatment effect of Exjade.

[Slide.]

Now, in addition to Study 0107, there was a supportive study. This was a non-controlled trial, a single-arm trial of patients who had either beta-thalassemia, there were 85 subjects here. Most of these patients were described as not had good success with deferoxamine treatment or were non-compliant with deferoxamine treatment, and then there were 99 subjects who had other kinds of anemia.

As we mentioned before, about 45 of these patients had myelodysplastic syndrome, about 30 of these had Blackfan Diamond syndrome, and the remainder had miscellaneous kinds of transfusion-dependent anemia.

In this Trial 0108, 15 patients with beta-thalassemia and 20 patients with rare anemias were

age less than 16, so that was the pediatric exposure population.

The dosing scheme was the same as in 0107. Of course, there was no deferoxamine arm in this trial. The change that was evaluated was that in liver iron concentration.

[Slide.]

In this population, for all patients treated with Exjade there was a change in liver iron concentration of minus 4.2, again in the face of continuing transfusions. If one looks at the patients who received 20 or 30 mg/kg/day of Exjade, the difference in LIC at 48 weeks compared to baseline was -5.5 mg Fe/g dw.

[Slide.]

So, we believe that efficacy had been shown in this group of patients based on Study 0107 and Study 0108 as a supportive even though the protocol-specified endpoints did not reveal non-inferiority to deferoxamine.

[Slide.]

To move to the safety aspects of Exjade,

these are the populations of patients who received the Exjade therapy. There were 421 patients who had beta-thalassemia. There were 99 patients with rare anemias.

As I mentioned, we evaluated the sickle study only for safety because that is all the data had matured for, a 12-month study, 132 patients receiving Exjade. There was at the time of submission of the NDA, 51 patients who had been on Study 0105, which was a dose-finding study, who were continuing on an extension of Exjade therapy, and these had extended up to 35 months. They were all in patients with beta-thalassemia.

Then, there were an additional 237 patients, some of whom had beta-thalassemia, others, volunteers, who were in various studies, pharmacokinetics, there was a QT study, there were studies in maximum tolerated doses, et cetera, but there were 237 of those patients, but the bulk of the patients for clinical studies are here.

[Slide.]

The pediatric safety population, all

Exjade-treated patients, first of all, there were 52 patients that were between 2 and less than 6. There were no patients below the age of 2. Then, there were 121 between the ages of 6 and 12, and 119 between the ages of 12 and 16.

As can be seen, most of the patients had beta-thalassemia. There is a significant group of patients, particularly the somewhat older children, in the sickle cell population, as well.

[Slide.]

Now, I just wanted to show you some of the notable difference in adverse events that occurred. Now, we are referring only here to the pivotal Trial 0107, and one can see the Exjade-treated patients and the deferoxamine-treated patients, any adverse event, no difference, however, there was a greater frequency of gastrointestinal symptoms, 42 percent compared to 31 percent, and these chiefly had to do with abdominal pain, diarrhea, nausea, vomiting, et cetera.

Skin rash. Skin rash is seen in a greater proportion of patients receiving Exjade than those

receiving deferoxamine.

There was an increase in creatinine of greater than 33 percent on two consecutive measurements in patients treated with Exjade, 38 percent versus 14 percent in patients treated with deferoxamine.

There was an increase in transaminase in 5.7 percent of Exjade-treated patients compared to 1.7 percent of deferoxamine-treated patients.

There was a greater frequency of heavy proteinuria, 18.6 percent of Exjade-treated patient compared to 7 percent of deferoxamine-treated patients.

Then, there were hepatobiliary problems, particularly gallstones, cholecystitis, and the like seen in patients treated with Exjade 4.7 versus 1.7 in the deferoxamine-treated arm.

[Slide.]

So, the adverse events, we grouped into organs. First of all, in 0107, again only this study, the increase in serum creatinine triggered a dose reduction or interruption in about 11 percent

of the patients who were treated. That was based on the protocol which required the doses to be reduced when serum creatinine rose greater than 33 percent above the baseline.

The increase in creatinine appeared to be dose-dependent, 2.6 percent at 10 mg, 8.3 percent at 20, and 20 percent at 30. Now, there were no reports of renal failure even through these patients who had received the drug for up to 35 months, but there were only 51 of those patients, but there were no reports of renal failure.

In none of the deferoxamine-treated patients was the dose reduced as a result of an increase in creatinine. There wasn't a provision for that in the protocol.

[Slide.]

The second organ of concern is the liver, and in Study 07, increased transaminases of greater than 5 times the upper limit of normal occurred in 5.7 percent of Exjade-treated patients and in 1.7 percent of deferoxamine-treated patients.

There were two reasonably clear-cut cases

of drug-induced hepatitis including one who had a rechallenge, both of whom had liver biopsies. In addition, increased transaminases led to the discontinuation of Exjade in two additional patients, and increased transaminases led to dose adjustment or interruption in three Exjade-treated patients.

Bilirubin levels were not too helpful, because during the course of the trial, at one point or another, about a third of all the patients had an elevated bilirubin level, and that did not seem to be correlated with any of what were considered to be hepatic effects of the drug.

[Slide.]

There were adverse events that were noted in some of the special senses. In 1 Exjade-treated patient, age 18, the drug was discontinued because of cataract formation. In 2 deferoxamine-treated patients, age 18 and 36, cataract formation occurred, but the drug was not stopped.

There was diminished hearing in 9 patients receiving Exjade from ages 5 to 33, and in 7

patients receiving deferoxamine from ages 7 to 38, and the drug was interrupted in 2 patients because of that.

Diminished hearing and cataract formation have been well described in deferoxamine-treated patients. There was 1 patient who developed vertigo, 1 patient receiving Exjade who developed vertigo, but there was no intervention in that patient.

[Slide.]

So, our safety summary shows that the main organs of concern are the kidney and the liver particularly over the long term, that gastrointestinal and dermatologic adverse events appear to be manageable. In a lot of these persons, reduction in dose, temporary reduction of dose or interruption of dose, and then reinstitution of the drug overcomes the adverse events that are seen.

Our concern is that the frequency of uncommon and perhaps important adverse events is not known because the safety population is limited.

There were only about 700 patients all together treated with Exjade in all of the trials.

The frequency and types of adverse events associated with the really long-term use of this drug is not known, and, of course, the likelihood is that in patients who require Exjade, Exjade will be used for the remainder of their lives.

[Slide.]

There were some pediatric issues that caused us some concern, and these are the differences, and so on. The efficacy and safety of Exjade in children and adults appeared to be similar except possibly in children less than age 6.

In Study 07, there were 30 children under the age of 6, and compared to all the patients treated with Exjade, first of all, the clearance of Exjade was greater by about 50 percent, the mean iron intake from transfusion was generally greater in younger children age 2 to 6 than they were in the other population, 0.48 mg/kg/day versus 0.037, so they have a greater iron intake.

In this particular cluster of 30 patients in 07, there were increases in serum creatinine on two consecutive occasions in half of that population versus 36.8 percent in patients who were above the age of 6 who received Exjade.

In the age 2 to 6, rash and vomiting were less common, diarrhea was somewhat more common.

As best could be determined from the trials, and growth and development was an important part of the observations, as best could be determined over 48 weeks of the trials, growth and development appeared to be normal.

[Slide.]

The dosing of Exjade that appeared in the package insert, then, is that the recommended dose is 20 mg/kg/day, because we know that doses between 5 and 10 mg are ineffective in decreasing liver iron concentration, and that therapy should be commenced after the transfusion of approximately 100 ml/kg packed red cells with a persistent serum ferritin of 1000 mcg/L.

This business about persistence rules out

the other situations in which serum ferritin may be raised. It's an acute phase reactant, but when it is persistently raised, that really is compatible only with a diagnosis of hemosiderosis.

Changes in Exjade doses are based on frequent determination of serum ferritin, but it should be remembered that in the clinical trials, the dosing was based on liver iron concentration, but we have no reason to believe that in clinical practice, patients will have to have a liver biopsy at periodic intervals to determine the need and the dose for Exjade, and there is a correlation between serum ferritin and liver iron concentration, not perfect, but I think clinically acceptable.

[Slide.]

So, the benefit/risk assessment for Exjade, patients treated at the higher doses of 20 to 30 mg/kg/day, there was either a leveling or a decrease in liver iron concentrations even though the patients continued to receive transfusions, this, I think is an event in itself.

We are wary, however, because Exjade is

associated with some clinically important adverse events and laboratory abnormalities. Most of these appeared to be non-serious, but I think because the safety database is limited, we want to have a longer experience with the agent.

Although we have reasonably good retrospective data that indicates that the use of deferoxamine is associated with a reduction in morbidity and mortality, particularly from cardiac disease, we do not yet have data which indicate that there is going to be a reduction of morbidity and mortality due to transfusion-related hemosiderosis in Exjade-treated patients although I think anybody would think that the likelihood of that occurring is high.

[Slide.]

These are some of the post-marketing commitments, you will hear more about them shortly. We wanted to make sure we knew what was happening to children between the ages of 2 and 6.

We want to know more about the efficacy and safety of the dose of Exjade at 20 mg/kg/day in

persons with an LIC less than 7 mg Fe/g dw, because in the studies that were conducted in support of the NDA, these patients who entered the trial with an LIC below 7 were treated with either 5 or 10. They were not treated with 20 or 30, and we don't know, particularly I think about the safety in that cluster of patients.

In an attempt to get a handle on what is going to be the morbidity and possibly mortality of the improvements associated with Exjade, I think we need to know something about the iron concentration in the heart and cardiac function in patients who are treated with Exjade. We don't have that information at hand.

Finally, completion of the studies in patients with sickle syndromes, which was done, and completion of the ongoing extension studies, which are in the process of being done.

[Slide.]

There are the brief discussion and question, considerations for the panel: long-term use in pediatric patients particularly between the

age of 2 and 6, the use of Exjade among patients with lower liver iron concentrations at baseline, and finally, the cardiac effects of the use of Exjade.

Thank you.

DR. REAMAN: Thank you.

Sponsor Presentation

Novartis Pharmaceuticals

Post Marketing Commitments with Exjade (NDA 21-882)

DR. CAPDEVILLE: Good morning, members of the committee, Mr. Chairman, ladies and gentlemen.

I am Renaud Capdeville from Clinical Drugs Oncology at Novartis Pharmaceuticals. After the presentation of Dr. Shashaty which describes for you the basis for the approval of Exjade, the purpose of my presentation is to take you through the post-approval commitments agreed upon with Exjade in the treatment of transfusional hemosiderosis focusing on the pediatric aspect of this commitment.

(Slide.)

To address any questions you may have on

the management of these patients and on the interpretation of the data with Exjade, we have with us today two consultants. Both were involved in the clinical development of Exjade and both attended the last advisory committee meeting in September last year.

First, we have Dr. Alan Cohen, Physician-in-Chief and Medical Director of the Thalassemia Program at Children's Hospital in Philadelphia. Then we have Dr. Raimund Hirschberg, Professor of Medicine at the Division of Nephrology at UCLA Medical Center.

(Slide.)

So, in the context of what is a rare orphan indication, the risk/benefit assessment of Exjade has been based on the evaluation of a large and comprehensive set of clinical studies which enrolled a total of 1,005 patients followed for at least one year.

After the initial NDA filing, another six months of follow up became available in the context of 120-day safety update. But, importantly, 45

percent of these patients were children within the age of less than 16 years and 292 of these children were actually initially treated with Exjade.

Later on, as you will see in the extension, the majority of these children actually were treated with Exjade.

Now, despite the fact that a large majority of patients enrolled had received prior deferoxamine therapy, this pediatric population, in particular, had a very high level of iron burden at the baseline as measured by liver-iron content of serum ferritin and therefore was considered as having a very high unmet medical need.

But, obviously, the further evaluation of the long-term therapy of Exjade with Exjade in pediatric patients is a major objective of the postmarketing program. (Slide.)

Before Exjade became available, the only therapy that was available in the United States was deferoxamine. Because of its pharmacokinetic profile, the drug has to be given, as you have heard, as a continuous subcutaneous infusion at

least 8 to 12 hours every night, five to seven nights a week. This, obviously, leads to problems of compliance, to an altered quality of life and, ultimately, to many patients being treated suboptimally.

So, in this context, Exjade addresses a high unmet medical need and, in fact, provides the first orally available iron-chelation therapy in the country.

(Slide.)

This is the indication that was granted last November and it is for the treatment of transfusion iron overload for patients with an age of two years and above.

(Slide.)

Importantly, this indication was granted under the accelerated-approval mechanism or Subpart H. Accordingly, this approval had several possible commitments which are all listed on this slide.

The first was the pediatric registry is of obvious relevance to pediatric usage and I will discuss it in greater details. However, all the

others have also some relevance to the use of the drug in the pediatric population and we will also briefly discuss them in the rest of my presentation.

(Slide.)

Starting with the pediatric registry. This is a registry for the subgroup of patients with an age of less than six years. The major objective here is to obtain long-term safety data in this group of patients but in the context of routine medical practice. So, what we are planning to do, in addition to collecting general safety data, is to pay particular attention to the collection of data on serum creatinine, liver transaminase, on auditory and ophthalmologic assessments, growth, sexual development. In addition, serum ferritin will be collected monthly.

(Slide.)

To be eligible for this registry, the patient will have to have an age between two and five years, transfusion-dependent anemia and a chronic iron overload as defined in the prescribing

information and as shown on the slide. The patient may or may not have received prior deferoxamine therapy and we are also considering the enrollment of patients previously treated with Exjade either in the context of a prior short-term clinical study with the drug or as a prescription drug. The treatment will be administered according to the local prescribing information.

(Slide.)

The design which is proposed is of five years observational study. The goal is to enroll approximately 200 patients. This number was estimated taking into account first the small size of this particular subgroup of patients and also the rate of enrollment for these patients in the precedent clinical studies.

This is a sample size that will allow the detection of adverse effects with a frequency of at least 0.6 percent based on, and that is well in line with, the observed frequency of the adverse effects that have been reported in the other clinical studies. All the statistical analysis

will be descriptive.

(Slide.)

From a very practical point of view and, again, having in mind the very small size of the subset of patients, the registry will be implemented in several countries.

In addition to the United States, other countries will be selected if the drug has been approved and is commercially available in this country and if there is a high prevalence of children less than six years of age with thalassemia or other anemias.

Careful attention will be given to the selection of centers with a high level of experience in the management of these patients but, also, centers having the ability to perform all the safety tests that are required.

Our target is to start enrollment into this registry at the end of this year and we are planning for roughly 15 months enrollment period. This means that the final analysis will be available in 2013.

(Slide.)

This was for the registry. Now, the second post-approval commitment is to generate, again, long-term efficacy and safety data for up to five years with the patient enrolled into the extension studies.

These extension studies are essentially a continuation of the preceding core studies which were designed for one year duration. Importantly, the patients randomized to desferal either in the Study 107 in thalassemia or 109 in sickle-cell disease are all treated with Exjade into the extension studies.

So, in this slide, you have the total numbers of pediatric patients enrolled in these extension studies that are ongoing at the moment. So we have a total of 414 patients with an age less than 16 years. Out of them, 72 are actually in the group of less than six years.

(Slide.)

Here is the third post-approval commitment. This is to generate additional data in

a cohort of patients treated at a dose of 20 to 30 milligrams per kilograms per day but with a low iron burden as determined by a liver-iron content less than 7 milligrams of iron per gram dry weight. This was a particular emphasis on the safety.

To respond to this commitment, we are proposing to use the subset of patients with a LIC of less than 7 enrolled in the planned study 2204 which is summarized on this slide. The objective of that study is to evaluate the efficacy and the safety of Exjade when dose is based on the monitoring of ferritin and creatinine. Patients are eligible for the study if they have an age of two years or more and they have a cumulative amount of prior transfusion greater than 100 milliliter per kilogram and have a ferritin level above 1,000 micrograms per liter.

Treatment with Exjade will be started at the dose of 20 to 30 milligrams per kilograms per day and thereafter adjusted depending on the patterns in ferritin and creatinine. The overall sample size for the study is 300 patients to meet

the requirement of the efficacy endpoint which is a decrease in both the liver-iron content and serum ferritin.

Now, based on the characteristic of the patients enrolled in the precedent clinical studies, we estimate that approximately 50 patients with a LIC less than 7 will be enrolled in that study. However, it has to be understood that additional data will also be available from approximately 170 patients who entered into the extension studies with a LIC less than 7 at the time they started into the extension studies.

(Slide.)

Now, moving to the next post-approval commitment, here considering that sickle-cell disease is usually diagnosed in early childhood, this commitment is more directly relevant to pediatric usage. So the commitment was to complete the 1-year analysis of that study which was a randomized study comparing Exjade versus deferoxamine in patients with sickle-cell disease. The primary objective of the study was safety.

In short, the results showed that a safety profile and the efficacy results were similar in that study in comparison with the data in other studies in thalassemia or different anemias. But of note, out of 195 patients enrolled, a total of 98 were children less than 16 years of age and 67 of them were treated with Exjade.

The report, as Dr. Shashaty said, was submitted to the agency in January.

(Slide.)

Now, the last post-approval commitment is to evaluate cardiac iron content in patients treated with Exjade. So, to fulfill this commitment, the protocol of an ongoing multinational study has been amended to introduce a cardiac substudy. This substudy will be open to patients with an age of ten years or more and with a cardiac iron overload determined by MRI with the so-called T2* technique.

These patients will have normal cardiac function and elevated liver-iron content. The patients will be treated with a dose of Exjade at a

dose of 30 milligrams per kilogram per day. The primary endpoint here will be an improvement of the T2* after one year of treatment and 85 patients are required for that. The protocol for this amendment was submitted in January.

(Slide.)

So, in conclusion, the description of the pediatric post-approval commitment for Exjade is to take into account the large numbers of pediatric patients enrolled in this program. Since all registration studies were designed with a one-year duration, Novartis fully recognizes the need to further evaluate long-term therapy with Exjade and this is particularly relevant to pediatric patients who typically require life-long treatment.

This is, therefore, a major objective of the clinical program we have undertaken that includes a range of ongoing and planned clinical studies as well as a pediatric registry in children less than six years old.

So, with this, I would like now to finish my presentation and we are very much looking

forward to receive comments and recommendations from the committee.

DR. REAMAN: Thank you.

Open Public Hearing

DR. REAMAN: I think we have an Open Public Hearing. We have some people who have expressed an interest in addressing the committee. Before so, I will read this statement.

"Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the Open Public Hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

"For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors.

"For example, this financial information

may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement. to advise the committee, if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking."

MS. CLIFFORD: Thank you. Our first registered speaker is Gina Cioffi with the Cooley's Anemia Foundation.

MS. CIOFFI: Thank you. I have no financial problems. (Laughter.) I have no financial conflicts. Thank you.

So very often, since the FDA issued its approval for the marketing of Exjade, many of us at the Cooley's Anemia Foundation have thought about the next generation of families and our hopes about how their lives will be dramatically improved.

We have a video that we show chronicling the lives of the families and patients. I still

look away at the image of a parent sticking their child with a needle and just imagining the emotional and the physical pain of this nightly chelation ritual motivates us to focus on our relentless mission for improved treatment and the cure for thalassemia.

Exjade's approval has given families a chelation option that will lead to increased compliance and healthier outcomes, we believe, and we are very grateful to the company for its tenacity in establishing a solid research path to gain approval from the FDA for this improvement in care.

We are also very grateful to the FDA for its responsiveness to the concerns of the iron-overloaded patient population and the need to provide an option for care under its accelerated-approval regulations. We are confident that Novartis will expeditiously carry out the postmarketing commitments that are specified in its submission and appreciate the FDA's continued interest in guidance to ensure that the protocols

remain on schedule. Vital results from this research can, then, answer positively that this drug is safe and effective over the long term.

We realize that today you are focused on the pediatric registry. In your evaluation and consideration of this registry, we ask that the company continue to consult with the clinicians and, perhaps, consider involving an academic center to run the U.S. patient registry.

Granted that U.S. births are low compared to worldwide births, there is a precedent for this collaboration. The Hemophilia and Thrombosis Research Society runs the registry for Novo Seven under a phase 4 protocol. There are advantages to having an academic center run statistics on the data that will benefit ultimately patient care.

We know that the company is helping the society complete the registry and we understand that the company pays for data collection at the sites. We think that the NIH-sponsored Thalassemia Clinical Research Network is well established and would provide a suitable partner for carrying out

the registry. It could also incorporate several international sites which are already involved in chelation studies.

Key questions that we believe need to be addressed by the registry which can't readily share the treatment centers under the ongoing studies include our patients using combinations of Exjade with other chelators or patients using doses in excess of 30 milligrams.

If so, how are these doses being administered; by increasing the one-daily dose or by initiating twice-daily doses. Is liver status being measured through ferritin or through other means? If the latter, what method is being used and what results are being obtained, and what fraction of patients that have rising liver iron or ferritin levels will on treatment?

These questions are fairly straightforward but, with additional resources, the registry could be broadened to encompass all patients and could also capture the transfusion burden of patients and other detailed and comprehensive information

including continuing to look at elevated creatinine among all patients on Exjade as well as heart function.

As the FDA knows, cardiac disease is the leading cause of transfusion-related death among our patients. So, in addition to the studies the company has planned and those which the FDA recommends, we particularly look forward to the cardiac study results and hope that they demonstrate that Exjade is effective in removing cardiac iron.

Finally, we recognize that the FDA has recently been criticized for not compelling drug makers to complete needed studies and that legislation has been introduced to authorize the agency to require drug makers to follow through on their promised commitments.

We believe the patient-advocacy community also has a duty to monitor the progress of these studies and remind both parties of their obligations to patients. However, we fully anticipate and believe that the company will

continue its remarkable efforts to thoroughly study the long-term efforts of Exjade and we look forward to reviewing its results.

Thanks.

MS. CLIFFORD: Thank you. Our next speaker is Ms. Harriet Lewis.

MS. LEWIS: Thank you. Good morning. My name is Harriet S. Lewis and I am the Executive Assistant to the President of Sickle Cell Disease Association of America, better known as SCDAA. I am standing in today for our President, Dr. Willarda V. Edwards, who, because of a schedule conflict, is unable to be here. Thank you for including SCDAA on your agenda for public comment.

In the interest of full public disclosure, SCDAA receives financial support from Novartis Pharmaceuticals as part of our education, outreach and awareness-building effort dedicated to those with sickle-cell disease and related conditions and the general public.

This past year, we also received financial support from Icagen/McNeil Pharmaceuticals, Perdue

Pharma, Pharmaceutical Research and Manufacturers of America and Pfizer. The names of all contributors and corporate sponsors supporting our information-outreach efforts are listed each year in SCDAA's annual convention souvenir journal which is distributed to all convention attendees and available to the general public. No financial assistance was received related to today's brief statement.

SCDAA is the only national organization with an extensive track record of working full time at the community level to solve the problems caused by sickle-cell disease. Dr. Edwards' brief statement is as follows:

"Because of its convenience and the ease of use, SCDAA believes that the availability of Exjade presents a significant advancement in the treatment of chronic iron overload. Exjade could help many patients who are unable to comply with infusion therapy and, therefore, are not being treated for their iron overload.

Our membership was pleased to hear and

appreciated the news that SCDAA had supported this new medication. They have and will continue to look to SCDAA to keep them informed about all new developments that may be of benefit to them in their struggles with sickle-cell disease and its related conditions and in the ongoing search for a universal cure."

Again, thank you for giving our association this opportunity to address you today.

DR. REAMAN: Thank you.

Questions to the Subcommittee and Subcommittee Discussion

DR. REAMAN: We will open questions for both the agency and the sponsor for Dr. Shashaty and Dr. Capdeville. Dr. Adamson?

DR. ADAMSON: I had just two small sets of questions. The first is if we could get a little more information on the basis of the nephrotoxicity either from preclinical or clinical models, what type of renal injury is it and is it in any way correlated to peak exposures versus steady-state exposures.

DR. CAPDEVILLE: In the clinical studies, the elevation of creatinine that was considered of interest was defined as a 33 percent increase over baseline. This was done in consultation with the Renal Safety Board that was appointed specifically for this program.

However, for the pediatric patients, recognizing that the level of creatinine to start with are lower, particularly in the young patients, and then a small fluctuation may be difficult to interpret. The protocol recommended dose adjustment in pediatric patients only if the increase was not only above 33 percent but also above the upper limit of normal.

So this is the first point.

(Slide.)

When we pooled all the studies together that is basically our safety database, that is the number that we have. So, 652 patients treated with Exjade across the different studies versus 353 treated with desferal. So you can see in this dataset the different frequencies of the increase

in creatinine above 33 percent and, in the next column, 33 percent and above the upper limit of normal.

So, yes, there is some variation between the different age groups but, considering that the numbers of patients, particularly in the young population is relatively small, it is difficult to be very conclusive here.

Now, what is the mechanism of this phenomenon? I think here I would like to invite Dr. Raimund Hirschberg to come spend a lot of time on this particular question.

DR. HIRSCHBERG: Not that much time. In your questions, you included that there is renal injury. We don't see any evidence for structural renal injury. We kind of view this within our independent advisory committee that consisted of five outside nephrologists as function of a probably hemodynamically determined change in glomerular-filtration rate. This is much different than nephrotoxicity leading to tubular necrosis.

It is also probably very worthwhile to

point out that, in particularly the young patients, less than 6 years of age, wherein Dr. Shashaty's presentation, it was pointed out, that half, 50 percent, had a rise by our safety definition of 33 percent in serum creatinine.

None of these patients reached or exceeded the upper limit of normal as defined by their age group and, therefore, no dose adjustment had to be done as by our safety definitions and none was done and no progressive abnormality, progressive renal failure or progressive measure of damage happened.

We have used this as a transient increase in creatinine that turns--at a given point in time, that is gone the next time the creatinine is measured. Again, no progressive renal injury by any parameter could be determined.

We believe that there is a hemodynamic abnormality or the drug affects, somehow, glomerular hemodynamics and glomerular regulation of ultra-filtration independent of any structural injury. That is our view.

DR. ADAMSON: Can you expand that? On the

preclinical side, there was no evidence, structural evidence. But, clinically, there were no renal biopsies done in these patients; is that correct?

DR. HIRSCHBERG: No. Apparently no renal biopsies were done and, particularly, not in pediatric patients because, again, there is no evidence for renal injury. How would you justify a very invasive diagnostic procedure in a child who has no evidence for real renal injury. So it wasn't done.

DR. ADAMSON: No, I am not advocating that. But what about in the preclinical setting, was there any evidence in preclinical models of nephrotoxicity?

DR. HIRSCHBERG: Probably I give this to Dr. Capdeville.

DR. CAPDEVILLE: In the preclinical screens, there was some evidence more on tubular toxicity, that it was sort of different. But that was also intimately related to the degree of iron overload in these animals because if you do the toxicology experiment in normal animals, then we

observe this phenomenon.

But then we repeated these tox studies but in animal models with an iron overload and then we have much less of a problem.

DR. BRITTENHAM: Could I comment? This is Gary Brittenham.

DR. REAMAN: Go ahead. You can ask your question.

DR. BRITTENHAM: I would just like to point out that renal toxicity is seen with several other chelators. So it is likely to be also related to the iron chelating effect, itself. So it seems with the desferrithiocins, for example, and with many of the chelators that have been examined in preclinical studies.

And a second point that should be made is that, during the year-long trial, it should be recognized that a substantial proportion of the patients were undertreated partly because of difficulties in assessing their body iron. So it may well be that the available data underestimate the risk of renal toxicity. Those are just

cautions for the future.

DR. REAMAN: Dr. Blaney.

DR. BLANEY: I have several questions related to the pharmacokinetics and pharmacodynamics. One, could you just comment on the pharmacokinetic profile for Exjade. Two, were there any correlates between that profile and either toxicity or efficacy as measured by that total-body iron content.

Three, are there any changes in pharmacokinetics over time into patient pharmacokinetics particularly over a long period of time and especially in those patients that have evidence of either renal or hepatotoxicity.

DR. CAPDEVILLE: I would like to ask my colleague, Dr. Skerjanec, who is the pharmacokineticist on the project to give you this response.

DR. SKERJANEC: Andrej Skerjanec, Novartis.

(Slide.)

Answering your question in terms of

potential time-dependent effect of the pharmacokinetics and the disposition of ICL670 in children, this slide depicts three profiles. On Day 1, Week 2 and Week 4 in children between two and 11 years of age and between 12 and 17 years of age and we do not see any time-dependent effect over a period of four weeks.

We have also monitored plasma levels, trough levels, beyond four weeks and they remain consistent over a period beyond a month.

DR. BLANEY: How about over the longer term in the steady-state concentration?

DR. SKERJANEC: Like I said, over a long term, beyond four weeks, the trough concentration, steady-state concentration, remains stable.

DR. BLANEY: All right.

DR. FINKLESTEIN: Greg, those slides are at 10 milligrams per kilogram, if I am reading it correctly. The prescribed dose is 20 milligrams per kilogram. Do you have any data at the prescribed dose?

DR. SKERJANEC: We do not have full

profiles. This was done in a study where extensive pharmacokinetic sampling was done. In a pivotal registration trial 107, we did monitor trough concentrations at the end of the dosing interval and they remained stable.

Generally, the pharmacokinetics of Exjade in a population including adults is very consistent and dose-proportional. There is no evidence of any deviation from dose proportionality.

DR. BLANEY: Were there changes in, or any correlations, between the PK profile and pharmacodynamics?

DR. SKERJANEC: We have not done directly the correlation analysis between PK and efficacy because there is a close correlation between exposure, systemic exposure, if you will, and the dose. We correlated the effects with the dose and those have been described before.

DR. BLANEY: But what about toxicity?

DR. SKERJANEC: No. We have not seen any correlation between plasma systemic exposure and toxicity.

DR. BLANEY: Just the interpatient variation, that was for the population. How about for those patients that had evidence of toxicity? Was there any difference in those patients?

DR. SKERJANEC: I can offer you some numbers in terms of variability. Exjade behaves very well in the patient population. In terms of overall variability, we observed 20 to 30 percent variation across patient population which we believe is very reasonable.

DR. REAMAN: Dr. D'Agostino?

DR. D'AGOSTINO: With regard to the registry, is there any discussion--I may have missed it--about having some comparators? It was described as generally descriptive statistics. Do there exist presently, for example, registries on existing treatments? Is there anything on chelators in general? Is there any kind of context that your data will be put into?

DR. CAPDEVILLE: I think there are historical registries or databases collected by different groups in the world so that is a

description that we may have.

DR. SANTANA: I want to follow up on that. With chronic oral administration of drugs, there is always this issue of how do you monitor compliance. I am just worried that, outside of the context of a very rigid clinical research study in which we attempt to try to monitor compliance, in a registry, it is a little bit more loose how those patients are monitored.

So how are you going to account for this issue of compliance with oral medication over a long period of time and then what are your estimates, based on other registries of dropouts, that could potentially influence the 200 target?

DR. CAPDEVILLE: Any discussion of any kind of comparator group, there is another confounding factor that the administration of desferal on the young patient population may not be the same as with Exjade. I mean, desferal is typically started at evaluable age in these children waiting the anticipated benefit of a sister [ph] risk. I think Dr. Cohen could explain

to us how this is done in practice.

Now, Exjade is, of course, more convenient to use so it may also change the practices slightly. So I don't know if you want to make a comment, Dr. Cohen?

DR. D'AGOSTINO: But there are the issues of compliance--I don't mean to interrupt--but the issue of compliance and the issue of comparators. You are going to have numbers, now, that won't be able to say anything about it except, "Here are the numbers."

DR. D'AGOSTINO: Dr. Finklestein?

DR. FINKLESTEIN: I have a number of questions, but the first one is with regard to the registry. Novartis is controlling the distribution of this drug in the nation. There are only three pharmacies, I know, in our area that we can use to obtain the drug. There is a lot of paperwork involved in obtaining the drug. I don't know if the FDA knows this or not, but you have to go through various hoops to get the drug.

We submit the request. The pharmacist

that is approved obtains the insurance okay and the California CCS okay and the Medical okay, gets it approved. Then the drug is actually sent to the family. That is what is happening in the State of California.

Now, there is an advantage to this. Then, obviously, we have to see the patients on a systematic manner because there are requirements of monthly biochemical and so forth evaluations.

Now, I think all this has a built-in registry in it because you, at least in the State of California, have indicated, at least in Southern California, there are only three pharmacies that we can go to. So you have a built-in registry that, in actual fact, can be expanded upon.

Alan, I don't know if you want to comment on that and I don't know if that is going on elsewhere in the nation.

DR. CAPDEVILLE: Dr. Cohen?

DR. COHEN: Thank you. Thank you, Jerry. Alan Cohen, Children's Hospital, Philadelphia. The program you described, and it may be discussed in

more detail, is a national program. So what you described for Southern California, unlike a lot of things that happen in Southern California, in this case, has national applicability.

I think you make a very good point about the registry, how, in fact, to coordinate what is essentially an investigative effort, a postmarketing investigative effort, with a drug-distribution scheme could conceivably be tricky to work out but it does provide a basis from which to have a better accounting of the number of patients who were there and, perhaps, to be a fundamental basis for a registry.

DR. FINKLESTEIN: I understood that the registry was to be multinational. How will you deal with that particularly if you use this distribution program in this country?

DR. CAPDEVILLE: I think, at this point, these are considerations because we are concerned about the ability to recruit 200 children in this age group in a reasonable time frame. So this is why we are thinking that it might be appropriate to

involve other countries as they were involved in the registration program. But, again, it is very much in the planning phase so that is a discussion that is ongoing.

DR. D'AGOSTINO: Dr. Adamson.

DR. ADAMSON: Could you clarify in the two- to six-year-old population how dosing was handled as far as rounding was concerned. It looks like 125 milligrams was the smallest tablet. What struck me was that the clearance was so different. But, clearly, the rounding of the doses had the greatest impact in that age range and, along those lines, if you could talk about the formulation, if patients had to swallow the capsules whole or if they could dissolve them and so forth.

DR. CAPDEVILLE: I think, Carole, if you may want to come and comment on the administration of the drug.

DR. PALEY: Good morning. Carole Paley, Novartis Oncology. So, as I understood it, I think there were two parts to the question. One was concerning rounding of the dose and the other I

thought concerned palatability and ease of administration to young children.

As far as rounding of the dose, in the actual registration trials, the dose was calculated pretty much exactly so that mixtures of different strengths were used. Subsequent to that, now, in the distribution of the drug, we have done calculations where we are rounding to the nearest single strength to order to make it easier for patients.

Using that dose-rounding in all but the very lowest weight children, it results in a maximum variability of 10 to 15 percent which was well within the PK variability anyway. In a 10-kilo child, which would be a one-year-old and unlikely to be chelating, the variability would be as high as 20 percent.

As far as how well children are able to take it, the great majority of the feedback was very good. There are definitely children who didn't like the gritty texture of it. At this point, now, the drug can be administered in water,

orange juice or apple juice and we are looking at more flavorings and other juices so, hopefully, it will be easier for children.

It is actually a tablet that dissolves, not a capsule.

DR. REAMAN: Although there may not be a large number of children under two who require chelation, is there a reason why the drug was only approved for children above the age of two?

DR. PALEY: Based on the literature with desferal, certainly those instances where toxicity was seen in terms of growth retardation or metasticeal bony changes, this was seen predominantly in the youngest children who had the higher doses relative to their iron loading. So, when you do a risk/benefit analysis, looking at the degree of iron loading, it has been felt to be safest to start at two years of age.

With desferal, typically, chelation isn't normally started until three or four years of age mainly due to those safety concerns as well as the inherent difficulty of putting a needle into the

abdomen of a two-year-old. So weighing risk/benefit, it is felt that two years is a reasonable age to start chelation.

DR. REAMAN: Dr. Blaney?

DR. BLANEY: Is the recommended dose for the two- to six-year-old age group the same even though the clearance is 50 percent higher?

DR. CAPDEVILLE: Yes, the recommendation is the same. The principle is, in fact, of individual titration of the dose based on the monitoring of ferritin and creatinine, and the recommendation is to do it monthly.

DR. REAMAN: Dr. Finklestein?

DR. FINKLESTEIN: I have two series of questions. One, perhaps, to Dr. Shashaty. In the slide, your Slide 12, you indicated the two- to six-year-old group, there were 27 patients did not compare in terms of efficacy with Exjade.

But my question regarding that slide and your adverse liver slide, in terms of effects and the creatinine slide, did you tease out the 20 milligram per kilogram dose because that is the

dose we are going to focus on as clinicians, in terms of adverse effects and in terms of efficacy.

Then I have a second question perhaps for Dr. Cohen or to anyone else. With the newer techniques of evaluating iron overload such as the magnetic resonance, the T2* technique, is liver biopsy still acceptable?

DR. SHASHATY: If I may make a response just to your first question, in regard to the dose dependency, I think that if you look at Slide No.--I believe it is 20; I can't read too well--there is a relationship between dose and increase in serum creatinine. The numbers were 2.6 percent at 10 milligrams per kilogram per day, 8.3 at 20 and 20.2 at 30 milligrams.

I think that this is one of the problems because I think that, no one is going to be treated really at the lower doses. If a person needs to get Exjade, the effective dose is going to be 20. There was some proposal that maybe one could prophylactically treat persons with 5 or 20 milligrams but there was no data to support that.

So we felt that if a person needed to get treated, then they should start at 20 because that is where, over a one-year period, the liver-iron concentration was at least stabilized while receiving transfusion.

In regard to the liver issue, there weren't enough cases of apparent hepatotoxicity that one could make a determination of a dose adverse-events relationship. It just wasn't possible.

In one of the patients who was rechallenged, the dose was started at a lower dose and then she appeared to be reasonable stable for several months. The dose was then increased and, at the time of the increase, her liver functions again became abnormal and she was discontinued from the trial.

But I can't say that there is a correlation between dosing and liver abnormality.

DR. WEISS: Could I also add to that? The numbers get exceedingly small when you talk about the patients between the ages of two and six, just

pulling them together. That is not even separating out among that population who got 10, who got 20, milligrams, the different doses based on liver-iron concentration.

One thing that I learned from this whole application was also my misimpression that perhaps the younger children would be the ones that had the lower LICs. But, in fact, the data actually did not support that. In fact, it is really the other way around, that they tended to have somewhat higher LICs.

But that was, also, one of the big reasons for asking for this additional registry focused on that age population is that there is the issue with the clearance being somewhat different. Perhaps the efficacy is not as good but it is really hard to say with those small numbers.

We just felt that we wanted to have a larger experience in a fashion we felt appropriate for a registry-type of collection to gain more data in that population.

DR. COHEN: Just to answer Part 2 of the

question, as you have suggested, there is certainly a huge impact of the new availability of non-invasive measures of tissue iron on the overall management of patients with transfusional-iron overload.

This is something that Dr. Brittenham and others have been working on for many years and is now coming to fruition. To quite specifically answer your question, I think the indications for liver biopsy have been drastically reduced both by the availability of noninvasive measures and by the absence of other diseases such as hepatitis C that might make histology an important issue.

As far as the T2* goes, it clearly opens up a wonderful window to begin to evaluate cardiac-iron overload.

DR. REAMAN: Dr. Santana.

DR. SANTANA: I want to get back to the issue of toxicity because I didn't have access to the whole application. This renal toxicity, what is the timing of the toxicity in relation to therapy? I don't think that has come out yet. I

think that will be important in the context of the registry, when and how often do you monitor these patients. Then I have another question about the registry once we finish that one.

DR. HIRSCHBERG: Maybe I can have this slide projected.

(Slide.)

This is a fascinating thing which is one of the major reasons, and I repeat this, that I do not think that this is any structural toxicity nephrotoxicity rather than a hemodynamic, glomerular dynamic, effect.

The hypothesis of chelation has also been discussed in our committee and was brought up by the committee member on the telephone. Those two hypotheses may well be mutual because there are enzymes regulating glomerular ultrafiltration that actually use metals as co-factors.

You see here that a rise in creatinine, and these are mean values for different age groups, whichever you want to look at, occurs within the first measurement which was taken after four weeks.

So this rise in serum creatinine occurs within hours up to four weeks and we don't know when it actually happens.

This is classically seen if a drug has a hemodynamic effect as compared to a toxic effect. In a toxic effect, gentamicin, you expect a rise in creatinine that gets worse and worse and worse and then some subjects will develop renal failure. That is not the case.

So this gives you the answer on what the timing is and it gives you the answer of what the progress is. I believe this data strongly supports a functional rather than toxic effect.

DR. ADAMSON: I just wanted to follow up, not to demonstrate my lack of nephrology knowledge, can you give me an example of another drug that has this classic pattern?

DR. HIRSCHBERG: The most classic example is, of course, Ace inhibitors and angiotensin-2-receptor blockers. Here we understand the mechanism extremely well because the Ace, or the renin-angiotensin mechanism and its

regulation of glomerular ultra-filtration is known in all details. This is exactly what happens when you take either of these drugs. So that is a very good example.

There are a number of less well examined examples such as nonsteroidals. It is not as clear cut with nonsteroidals.

DR. REAMAN: Dr. Blaney.

DR. BLANEY: I thought you said this but I just want to clarify. So, in those patients with the rise in creatinine who then have the drug stopped, did their creatinine then return to normal, or to baseline; I'm sorry, because they weren't above normal to start with.

DR. HIRSCHBERG: If I talk about the young children that I mentioned before, the ones less than six years of age, there is a 50 percent rise in creatinine, didn't reach the upper limit of normal.

In those patients, it was just a transient increase that, on subsequent measurement, returned. So nothing happened in those children from a

medical point of view. There was a transient increase in creatinine. It went back in other subjects outside this age range.

In many patients, values decreased towards the previous baseline. In some patients, levels remained elevated. In none of the patients problems progressed toward anything we would call renal failure.

Maybe Dr. Ford can comment on this in addition.

(Slide.)

DR. FORD: This is actually a slide which summarizes these creatinine increases. We had, in the total ICL population of 652 patients, there were 36 percent who had at least two consecutive increases in creatinine. The majority of those patients, however, it went back to normal or it was very intimate in the increases and they were not dose reduced.

There were about 13 percent or so who were actually dose reduced because of sustained increases in creatinine. Of those 13 percent,

about a quarter of them returned consistently to the baseline levels. About 15 percent of them fluctuated between baseline and maximum increases and the remaining 60 percent of creatinine increases remained stable at around 30 to 40 percent above baseline.

DR. REAMAN: Dr. Santana, last question.

DR. SANTANA: So tell me who is going to populate this registry given the issue of other competing studies, small population of very targeted patients. Where are you going to get these patients from? Is it feasible to do a registry given the current environment?

DR. CAPDEVILLE: Well, we hope so. That is an important question. I think the children enrolled in the clinical--I mean, there are children enrolled in the clinical studies but there are also children who may not have access to clinical studies and who could be considered in the context of a registry. This program was run with 32 centers worldwide, so I think there are ways to address these needs.

So I think the situation at the moment with regard to this patient population, I mean is based on--here I have a slide.

(Slide.)

That is focusing on the patients less than six years of age. So the top part of the slide that is all the children in this category that are currently being treated into the ongoing extension study, 72. So, then you have this registry that we are discussing now. We are considering to offer to patients who are currently in short-term studies--short-term being one year study, typically--to eventually transfer to the registry at the end of that study.

At the moment, 41 such children have been enrolled in different ongoing studies so that may be a way to go. We discussed earlier the use of this e-pass system as a way to capture a patient who may not be in a clinical study and may be on prescription drug at the moment and who could be willing to enroll into the registry. So these are different options on the table.

DR. REAMAN: Dr. Schreiber, did you have a question? I'm sorry.

DR. SCHREIBER: My question was about the 11 percent that were either discontinued or dose reduced. But I think it was answered. One of the things, though, I would just like to point out is that, when BPAC reviewed this, we had the same concerns that you all have raised.

One of the recommendations that we made was that it was acceptable for age six and above but it was not approved, or we felt that the safety and dosing information was not acceptable for those less than 6 years of age.

That was, I think, a vote of 4 to 10, four for and ten against, so that we had some reservations, particularly with this age group. I think that the idea of the registry can add and can resolve a lot of the outstanding questions. It probably is very doable as described. We are doing a lot more registry studies now with rare diseases like Marfan's, even.

So I think that this should be very doable

and should help allay people's fears. The other thing that I think we were concerned about is, really, the issue of cardiac iron and that there was no evidence at all for the children, or very little for the other population, whether Exjade really was significant in reducing the cardiac iron and maybe the new MRI tests will be able to be used to test that.

DR. REAMAN: Maybe given those concerns and the fact that the registry has been a commitment, we have some specific questions from the agency about those phase 4 commitments with a request to identify other outcomes which may be important to recommend.

So the establishment of a registry for children aged two to six, or less than six years, to enroll approximately 200 patients and follow them for five years to collect monthly renal function and blood pressure and growth and development yearly.

Are there additional outcomes to consider for the registry that may be able to provide

meaningful evidence of long-term effects, efficacy, activity and safety, serum ferritin, correlations with transfusion, history of growth of development, endocrine status, hepatic and renal function?

So can we have some brief discussion centering around that question?

DR. ADAMSON: One thing I would recommend considering in that these children are relatively frequently monitored is to get a better handle of clearance, or apparent clearance, that is really significantly different than this population, is to do a population approach that is timed with the safety monitoring samples to look at steady-state levels, to again better address are we starting at the right recommended dose.

I know that is a step away from a registry as far as if you start obtaining steady-state PK but, especially in the two to six-year range, it may shed some light. If you time it with safety labs, it wouldn't be additional venipunctures for the children. So something to consider.

DR. BLANEY: I was just going to say I

agree with Peter, Analogous to our discussions this morning, we don't want to be down the road 20 years and not have the information that we could have prospectively acquired.

DR. BRITTENHAM: It is Dr. Brittenham. Could I ask another question in the area?

DR. REAMAN: A question related to the questions that have been posed to the committee or is this a--

DR. BRITTENHAM: No, no; it is just an extension of your current discussion. It is a clarification, because the five studies that have been described were commitments that were conditions for accelerated approval of the drug, of the Exjade. I understood that there were additional studies that Novartis had also committed to. So the question is about the status of those.

The reason for asking at this time is that that includes some other studies that are relevant here. For example, ophthalmologic studies, examinations in patients with an elevated baseline creatinine, those patients were excluded in the

previous trials. So it is just there seems to be a commitment for other studies and I just wanted to ask about their status.

DR. REAMAN: Maybe Dr. Capdeville could answer that question.

DR. CAPDEVILLE: It is true that we discussed essentially the possible commitment in the context of the accelerated approval but there are others. I think they are summarized on these slides.

(Slide.)

That is on the white column. One is to generate additional data in patients who has myelodysplastic syndrome and to generate long-term follow up in these patients, then to do pharmacokinetic studies in patients with liver-function impairment. That is a drug-drug interaction with medazalan. Then a study to generate additional ophthalmologic evaluations.

DR. WEISS: In answer to Dr. Brittenham's question, though, those are--I think he is asking also the status of those but I believe those are

probably earlier on in their planning stages; is that correct?

DR. REAMAN: Jerry?

DR. FINKLESTEIN: I don't think the late effects is a mystery because we had presentations from the Cooley's Anemia Foundation. We have had presentations from the sickle-cell experts. There are standards of care for following patients with hemoglobinopathies who have long-term transfusions who are on desferal which would automatically just be utilized for patients receiving Exjade and, if the child, as it should be, is taken care of at any hematology-oncology center, this is daily practice of our discipline.

So I don't think this is a big mystery. Some of the pharmacokinetic studies require extra effort but the late effects is something we do every day. This is standard of care.

Now, it is up to the Novartis people to get the data from us because it is sitting there and that can be done with the appropriate communication.

DR. REAMAN: So is there agreement as to the recommendation that there should, in fact, be additional outcomes, measures, parameters, that are included or at least recommended to the agency as part of this registry requirement in addition to just a serum creatinine and a blood pressure.

DR. ADAMSON: I would just ask that, given the data we have seen, is monthly determination necessary over five years? Is that standard of care, monthly creatinine in patients on this and is that really necessary given what we know? I think we need to know it, but I don't know if the frequency is--

DR. CAPDEVILLE: At this point, this is how it has been done in the clinical studies and that is our recommendation, the basis to assess whether dose adjustments are necessary. I think that is the best we can say today.

DR. REAMAN: But maybe our recommendation could be to add additional parameters but to reconsider the frequency at which they are measured and going forward in carrying out and implementing

the registry.

DR. REAMAN: Dr. Smith, did you have a question?

DR. SMITH: It is possible you could lengthen the frequency although it is still fairly early in the number of children studied. So be cautious about that approach. It should be evidence-based when you do make that recommendation to lengthen the frequency.

DR. REAMAN: One of the other post-approval commitments was to develop a study to evaluate Exjade in patients with transfusion-dependent congenital or acquired anemias who have liver-iron concentrations less than 7 milligrams per kilogram dry weight.

Are there clinical protocol-design considerations with respect to including pediatric patients which need discussion here and also we have talked a bit about need for liver biopsy, are there alternative measures and, again, the duration of observation necessary to detect safety concerns.

DR. WEISS: To preface this, one of the

concerns that was brought up at the Blood Products Advisory meeting to a limited extent was this "issue" we have of over-chelation and the concern about specific toxicities--maybe Dr. Brittenham could even address that a little bit--with excessive dosing of a chelator.

So there was the concern if we don't have a lot of experience with this dose in the pediatric population, even though you could be following them with serum ferritins, could we, in fact, be--are there potential concerns, toxicity concerns, with this phenomenon of over-chelation?

DR. BRITTENHAM: I think this concern came from the preclinical studies where, as you heard briefly earlier, that, in the animal studies, renal toxicity was seen in normal animals or those with a low iron load whereas animals with higher body loads seemed to have less of a risk of that. So I think that was the concern that was raised at that point.

Since we are talking about this, there is one other potential difficulty that I would like to

raise. The dose range is very narrow, the recommended dose range in the labeling is very narrow, from 20 to 30 milligrams. So I think there is the question that one should follow to see what proportion of patients would not be well managed, well chelated, with the upper dose of 30 milligrams and is there any thought of extending that upper limit.

DR. REAMAN: Dr. Capdeville?

DR. CAPDEVILLE: No, I think that is an important question. In the dose-finding studies, we had a study with four weeks of treatment and that study went up to 40 milligrams per kilogram so we have some very limited experience here.

Now, the protocols from the ongoing extension studies have been amended and now allow to escalate the dose to up to 40 in case the response, in terms of ferritin, is judged insufficient by the investigator. The data are not available yet. I think I am aware that perhaps a little more than 30 or 35 patients have been dose escalated, but this data will be available shortly

and probably will give a first answer into that question.

DR. BRITTENHAM: That is reassuring.

DR. ROBIE-SUH: Just a couple of things. I was just wondering. I think you said you estimate that about 50 of the 300 patients that you plan to see will probably have less, have iron burdens of less than 7 milligrams per gram of dry weight in liver?

I also wanted to ask you this sort of general kind of thing, and maybe this is for the practitioners. Do you think that, as we now have an orally available iron chelator, there will be a trend to start patients at lower iron burdens, thinking again about this group that we have the least amount of experience with.

I know we have that idea of seven being a sort of cutoff for danger, or something.

DR. CAPDEVILLE: I think starting with the second part of the comment, I mean, yes; it is perfectly possible that patterns will change. However, today we know what we have observed in our

clinical studies and this estimation is based on actually these numbers that will appear that summarize the values.

(Slide.)

This is characteristics at baseline considering the 1005 patients in the program by age group. Here we add, to produce these numbers, as you may have read, not going into the details, but some patients, the majority, actually, had their liver-iron content measured by biopsy and a small subset had liver-iron content measured by SQUID, a noninvasive technique.

However, the SQUID produced a value that is probably half of the one that you get with biopsy. So, for these numbers, we corrected that with a factor of 2. So, that being said, you have between 13 and 20 percent of the patients enrolled in this program who had a LIC less than 7.

So that is our basis for this estimation and that is what we have at the moment.

Dr. Cohen?

DR. COHEN: If I could just add, perhaps,

a word to the second part of your question. I think it is absolutely right on target. I think that, with deferoxamine as a parenteral agent, there were a couple of reasons reflected in the high liver-iron concentrations why chelation therapy was not started early.

One is it was a very difficult therapy to introduce, especially in families that were already facing other large therapies such as chronic transfusion therapy. The second is that there were toxicities associated with the drug that were particularly visible either in early childhood or perhaps related to dose of drug versus iron level.

So, as a result, the drug was generally started later and, again, I think that is reflected in the high liver-iron concentrations that you were pointing out. There is no doubt in my mind that one would prefer to avoid that and to introduce chelation therapy earlier. I think an orally active agent provides the opportunity to do that.

DR. REAMAN: Just to follow up on that, how early is early since we have no information in

patients less than two years of age and the drug is not approved for patients less than two years of age?

DR. COHEN: So, in a sense, I guess, at the practitioner level, whatever we choose is going to be arbitrary. But, to the extent that it can be based on data, we at least do have the studies going down to the age of two. Since we know, as best we can, that there is no long-term toxicity that is initiated in that first two years of life, I think that is probably a very reasonable age to start at remembering that transfusion therapy in the majority of children with thalassemia, in any event, rarely begins before around eight to 12 months of age so it is not quite the gap and, in patients with sickle-cell disease, it is almost uniformly after the age of two.

DR. REAMAN: Did you have a question?

DR. BERG: Just related to that, at the practitioner level, it strikes me that many people actually use ferritin and not liver-iron content, and as data to correlate in the registry might be

actually ferritin as opposed to liver-iron.

DR. REAMAN: Good suggestion.

DR. FINKLESTEIN: I question that suggestion because there is a lot of data which was referred to that ferritin may not be as accurate as looking at liver-iron. Now, the question about liver-iron is whether the new techniques are better than the ferritin. I notice you took your SQUID value, times it by 2, so now we have got to find out the data where you started doing that. But that is okay.

So, once again, I would like to go back to maybe Dr. Cohen to comment on ferritin which--we published on ferritin which is a little tricky compared to some of the newer techniques for liver-iron.

DR. COHEN: I think, at the practitioner level, this has always been a little bit of science and a little bit of artistry in terms of how to use those two parameters for an individual patient.

I am not sure that any of us would agree on exactly what the artistry piece of it is except

to say that we need to look at individual children and decide what the best method is to judge when to start chelation therapy or how to monitor it.

I would just point out that, in a child who is not chelated, we know exactly how much iron is going in. All you need to do is count the red cells going in. So my own belief is that it is probably not an issue of liver-iron concentration or ferritin level, although those may be helpful. But we know how much iron has accumulated and that, to me, would be the critical issue.

DR. REAMAN: I think the suggest was just to add it to the registry, not necessarily make decisions. But I think, as Dr. Santana points out, it would be easier to get a monthly ferritin than it would a monthly MRI of the liver in this day and age.

So, have we satisfactorily addressed the over-chelation issue, Dr. Weiss?

DR. WEISS: Yes; I think so. Thank you.

DR. REAMAN: So we will now turn to the next question, again pertinent for pediatric

oncologists, and that is to discuss additional cardiac function assessments which may be important recommendations to the sponsor as far as other assessments that may be useful in monitoring these patients.

DR. BRITTENHAM: It is Dr. Brittenham, if I might make a comment. The T2* has been very helpful but it should be remembered that it changes very, very slowly. Even in patients who are treated with 24-hour-a-day deferoxamine, it changes very little over the course of a year.

So it is an indicator. But I think the studies importantly should include still assessments of function of left-ventricular ejection fraction has been shown to be helpful. So you really need to include not only measures of iron but also measures of cardiac function, itself.

DR. REAMAN: Dr. Brittenham, could you just elaborate on maybe not starting those assessments until patients have been treated for a year and, if so, how long would you recommend those types of assessments?

DR. BRITTENHAM: Are you talking about measuring liver iron or cardiac iron or both?

DR. REAMAN: Measuring cardiac function, or assessing cardiac function and/or cardiac iron if there is an easy way to assess that with biopsy.

DR. BRITTENHAM: Are we talking about children of this age, of two to six?

DR. REAMAN: I think yes.

DR. WEISS: The study that Novartis presented, in terms of their thoughts of looking at a substudy, talks about children with beta-thalassemia that are greater than or equal to age 10. I certainly think that everything is fair. Actually, one of the questions was why they were choosing that age cutoff. It might just be some of the feasibility issues.

I think, certainly, we have questions about relationship between chelation, iron stores and cardiac iron at all ages, though, clearly, the effects of iron overload are not seen until--well, you know, it takes decades probably to develop those effects.

So I think there are some open questions about what are the appropriate ages to try to evaluate and look at these correlations and functional assessments.

DR. BRITTENHAM: Yes; and as a practical matter, you see it is very difficult to do virtually any of the noninvasive techniques. The child has to be able to lie still for a certain period of time so it is very difficult in younger children.

Probably the reason it is a reasonable choice to choose arbitrarily ten or something around that age where it becomes possible to have the children lie still enough to have a measurement with MRI or other methods without having to use sedation.

DR. REAMAN: Any comments? Dr. Shashaty?

DR. SHASHATY: I believe that the Novartis proposal calls for the--in regard to cardiac iron and cardiac function, calls for patients to have normal ejection fractions in order to be admitted into the study. Is that correct? Or that is the

proposal.

DR. CAPDEVILLE: The proposal of the study that I showed is widely in patients with normal cardiac function. This is really to look at the effect of treatment on the cardiac iron store over time.

DR. SHASHATY: But, if they have normal ejection fractions and cardiac function, and they have a lot of iron, when they have a little iron, do we have super-normal ejection fractions? I think it would be useful to have patients entered into the trial whose ejection fractions are quite variable. You then know what the myocardial iron is. You know what the ejection fraction is.

You treat them. You find out what the myocardial iron is and what the ejection fraction is.

DR. CAPDEVILLE: In fact, that is the study we are proposing in the context of this post-approval commitment. But we are also planning another study here in a different context that is in patients with mild to moderate cardiac

insufficiency plus a cardiac iron overload and then to look at the effect of Exjade measuring the ventricular ejection fraction and, of course, the T2*.

So, in fact, we have two different studies.

DR. WEISS: And, in fact, even though you may not expect to see much alterations in cardiac function perhaps in the pediatric populations, this is also going to be used in adults with myelodysplastic syndrome. Just as we had concerns about creatinine abnormalities as you get into older populations that have transfusional hemosiderosis, you might also be able to pick up certain cardiac dysfunctional effects in those populations.

How much you can extrapolate that down to pediatric populations, I am not sure but there might be no other opportunities, like George said, to look at people with varying ejection-fraction abnormalities.

DR. REAMAN: Are you satisfied with the

discussion for the questions which you have asked us to address?

DR. WEISS: One of the examples that we had asked about in terms of looking at the--attempts to look at cardiac overload and function included a number of questions also to think about such as, I guess biopsy was in there but it is probably not considered to be really viable, but various types of exercise tests as well. Is that something that people think would be of potential utility in this population?

DR. BRITTENHAM: This is Gary Brittenham. I would just say that, unfortunately, most other efforts haven't contributed anything beyond what the left ventricular-ejection fraction, itself, shows. So trying to do stress tests or even early diastolic dysfunction isn't--hasn't proven to be very useful.

DR. REAMAN: Dr. Adamson?

DR. ADAMSON: All I was going to say is, in these situations, we usually talk to our pediatric cardiology colleagues and get their

advice. Echocardiography and ejection fraction is pretty standard in this age range but anything beyond that, we would turn to our pediatric cardiology colleagues for guidance.

DR. REAMAN: I would think that logistics would probably really govern their response and would, again, depend on the age group of patients. If it is patients over ten, I think consideration could be given to some of these. But it would be hard to imagine doing many of these tests without anesthesia. Then you couldn't do much of an exercise-related echo with anesthesia. The treadmill doesn't work very well.

So that concludes our morning session. We will break until 1:15. Thank you.

(Whereupon, at 12:35 p.m., the proceedings were recessed, to be resumed at 1:15 p.m.)

A F T E R N O O N P R O C E E D I N G S

[1:15 p.m.]

Session III

CDER's Process for Handling Drug Shortages

DR. REAMAN: Dr. Weiss, do you have any remarks to make for this session?

DR. WEISS: Just very briefly, just to mention that this afternoon session will be on the topic of drug shortages. This is the topic that you all at the last meeting you had in October mentioned as one of the things that you wanted to have a session devoted to, so you get what you asked for, but we do think that it is a very timely topic.

We have basically two presentations, one from an industry representative, who will give some of the perspective from the industry side on the what and hows and whys for drug shortages, and then a presentation from Mark Goldberger at the FDA, who heads up the Drug Shortage Group in the Center for Drugs, just about how the Agency responds and acts in the face of drug shortages and what are the

FDA's limitations.

After those presentations, then, we just hope to engage in some additional discussion with the committee.

DR. REAMAN: We need to go around again and reintroduce ourselves.

Call to Order and Introduction of the Committee

DR. PAZDUR: Richard Pazdur, Office Director.

DR. WEISS: Karen Weiss, Deputy Office Director.

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

DR. KEEGAN: Patricia Keegan, Director, Division of Biologic Oncology Products.

DR. GOLDBERGER: Mark Goldberger in my role as the CDER Drug Shortage Coordinator.

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

DR. D'AGOSTINO: Ralph D'Agostino, statistician, from Boston University.

DR. FINKLESTEIN: Jerry Finklestein, UCLA.

MS. O'CONNELL: Cathy O'Connell, Patient Representative.

MS. EICHNER: Marilyn Eichner, Patient Representative.

MS. CLIFFORD: Johanna Clifford, Executive Secretary to the ODAC and the Pediatric Oncology Subcommittee, FDA.

DR. REAMAN: Gregory Reaman, Children's Hospital, D.C., and George Washington University.

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

DR. ANDERSON: Barry Anderson, NCI, CTEP.

DR. BLANEY: Susan Blaney, Baylor College of Medicine.

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

MS. HAYLOCK: Pamela Haylock, oncology nurse and Consumer Representative.

DR. SMITH: Malcolm Smith, pediatric oncology, CTEP, NCI.

DR. REAMAN: We have a Conflict of

Interest Statement that Ms. Clifford will read.

Conflict of Interest Statement

MS. CLIFFORD: The Food and Drug Administration has prepared a general matters waiver for the following special government employee: Dr. Ralph D'Agostino.

The committee members are participating in today's Pediatric Subcommittee of the Oncologic Drug Advisory Committee meeting to discuss matters concerning CDER's process for handling drug shortages. This meeting is being held by the Center for Drug Evaluation and Research.

Unlike issues before a subcommittee in which a particular product is discussed, issues of broader applicability, such as the topic of today's meeting, involve many industrial sponsors and academic institutions.

The committee members have been screened for their financial interests as they may apply to the general topic at hand. Because general topics impact so many institutions, it is not practical to recite all potential conflicts of interest as they

apply to each member.

FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussions before the subcommittee, these potential conflicts are mitigated.

A copy of the waiver statement may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

In addition, we would like to note that Dr. William Rackoff is FDA's invited guest speaker. Dr. Rackoff is participating as a representative of Johnson & Johnson.

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

With respect to all other participants, we ask in the interest of fairness that they address

any current or previous financial involvement with any firm whose product they wish to comment upon.

Thank you.

DR. REAMAN: Thank you. We will start this session on drug shortages with a perspective from industry and Dr. Wayne Rackoff from Johnson & Johnson.

An Industry Perspective: Drug Shortages in Pediatric Oncology

DR. RACKOFF: While we are setting up the slides, I will just thank Dr. Reaman and Dr. Weiss for inviting me again. It has been a couple times that I have been able to try and represent an industry perspective.

I don't represent Johnson & Johnson here today. I hope I represent a perspective of somebody who is working in industry, try and give some idea of what issues are involved in drug shortages, not being a manufacturing person, but having consulted with them, and finally, to answer questions, but also as somebody who has been involved in the COG Industry Advisory Committee

where we addressed this issue about three years ago.

So, some of what I will talk about today really derives from that discussion and what suggestions were made at that time.

[Slide.]

The topics I would like to touch upon today are really again derived from a meeting we had about three years ago at the Industry Advisory Committee at the Children's Oncology Group.

There, we were presented with a list of important drugs, and I will cover those today, because I think they illustrate, the drugs on that list illustrate some of the problems that may be somewhat unique to pediatric oncology.

I will also touch upon, and I think the FDA may, as well, recent shortages to I hope represent fairly that this is not just an issue for pediatrics or for pediatric oncology or for oncology, that there are shortages of all kinds of drugs all the time and for different reasons.

I will next cover some of those reasons as

were delineated in a piece that was put together in a pharmacy industry journal. I will talk briefly about the manufacturing process at which there are all kinds of places where things can go wrong, and then come back to some of the problems that are unique to pediatric oncology and some suggestions that we had three years ago that I think are still relevant today.

[Slide.]

Here is the list that the Pharmacy Committee of the Children's Oncology Group came up with three years ago as important drugs to watch for shortages, because they were key parts I think of widely used regimens in pediatric oncology.

When I dug out this list again a few months ago when I was invited to this meeting, I tried to do a little research on manufacturers, were they single source, were they generics, and really the first issue is highlighted by this list.

These are very hard to track through the FDA web site, not by reason of the FDA not maintaining the proper information, but just that

information on manufacturing per se, on who is making the drug and who isn't, on the number of generic makers that may be involved, it is very difficult to track for anybody.

What is clear about this list is that essentially all the drugs are generic except probably PEG-asparaginase. E. coli asparaginase and PEG-asparaginase are the only drugs that have, as a year of approval, in the 1990s. All of the others, as you can see, are 30 and 40 and 50 years ago.

The other thing is that E. coli asparaginase has that as the year of approval, but I think that must be a new formulation. Again, that is why it was difficult to track all of these, because what is maintained on drugs at FDA, as many of you know who have been there, are really sort of the labeling history for a particular formulation.

So, I think this represents the first issue, that there are a lot of old drugs that are crucial to pediatric oncology, and I think all of us who have practiced pediatric oncology recognize these drugs as such.

[Slide.]

The second point I think from my perspective is that when one goes through the recent shortages, you see that, for example, this is when I prepared the slides back in February, there were six drugs ongoing. There was only one drug from oncology, and that was BCNU.

There were no drugs that were absolutely crucial to pediatric oncology, either on the ongoing or among the 13 drugs that were in total listed on the resolved list, which I don't know the exact period of time during which drugs remain on the resolved list, but I presume those are fairly recently resolved.

[Slide.]

So, I think there are some things that are unique to pediatric oncology, some of our crucial drugs that were used, when I used them when I was in the clinic, they are still used in the clinic, are old, they are generic, but it doesn't suggest a solution to the issue. I mean they are still being manufactured.

This is a list of reasons for shortages that is greatly abbreviated from a very good paper which I cited on the slide, because I think it is of interest to those who are interested in this issue.

I am only going to touch really on the first two, because I think they are the ones that are the most crucial, the ones that can be addressed most reasonably by not only the FDA, but by group of people who are in this room.

Economics, I will stay away from, because I don't think that is an issue. I think we had a case with mercaptopurine a few years ago where GlaxoSmithKline was very dedicated to keeping that drug on the market, has worked very hard on it, and it had nothing to do with economics.

We have the same issue at Johnson & Johnson with Pancrease, a very difficult drug to make, essential to cystic fibrosis patients, and no generic house is going to take it on probably anytime soon that I know of.

Regulation and enforcement, I will leave

to the FDA.

[Slide.]

So, manufacturing is a much more complex process than I think any of us, even I, who have been in industry, can imagine it to be.

From the standpoint of the amount of regulation that is involved, it is second only in a drug manufacturing plant to--this has been said, you know, by them, whoever "they" are--that it is second only to the amount of regulation that you might see in an atomic energy plant. I think that that is probably true if you actually sat down and tried to quantitate it.

So, this is a highly, highly regulated environment in which, as I will show you in the next slide, there are many points at which things can go wrong, the first of which is this.

The raw materials that can be used in the manufacture of a particular drug, and you have got to start from certain raw materials, and not just, you know, calcium chloride. It has to be the calcium chloride that you have specified in your

NDA to the FDA, and deviations from that require regulatory input.

So, if there is a raw material shortage in general, let's say, of calcium chloride, or if there is a raw material shortage just from your particular supplier, from the particular item that you have specified as your starting point in manufacture, then, you could be in a shortage situation.

There are regulatory issues, I think the most acute of which have been seen recently, not in crucial drugs, but I think, you know, we all know of the cases where plants are shut down because they are not following good regulatory practice.

Now, that is something that is a direct issue between the FDA and the manufacturer, but they certainly arise, and although I think most of them can be attributed to things that should have been fixed, occasionally, they are not.

The third thing I think is probably one of the most crucial factors in manufacture. First of all, when I came to industry, I figured that there

was a Tylenol assembly line, an adriamycin assembly line somewhere, where every day, at the end of the day, they boxed up the adriamycin and sent it to pharmacies.

That is the furthest thing from the truth that is possibly imaginable. Virtually, every one of these drugs that is on the list of important drugs is made in batches. Those batches are sometimes schedules for one of the drugs for which I direct a clinical team, oh, maybe 10, 12 times a year.

They happen to be made in a factory that if it burns down, would affect all of oncology worldwide, you know, big time, because almost--well, I can't say "almost" all, because it's proprietary information in some cases, I don't know how many--but I would say that a very good proportion of oncology drugs, because of the specifications required by OSHA, in the case of the U.S., are made in a limited number of facilities.

Often these are a limited number of contract facilities, over which the manufacturer of

the drug doesn't always have perfect control in terms of timing of manufacture.

These are made in batches. When you have a batch failure, you don't have drug coming off the line the next day, so if you have a drug, let's say--and I don't know that this is necessarily the case, but I imagine it is--if you have a drug like preservative-free hydrocortisone, for which they mainly run a batch once or twice a year because of the level of use, if you lose that batch, you have got a huge gap if you have not enough drug in the warehouse for short expiry dates.

So, batch failures are a big problem, and they often are the source I think, and I would like to hear the FDA's view on this, but I think they often lie behind short-term shortages in particular.

I have already talked about the limited worldwide manufacturing capacity for cytotoxics related to the safety issues for the people who make them. The plants have to be up to specs, both here and abroad, that are much different than a

plant that might be making acetaminophen.

[Slide.]

Now, going back to this batch and release timeline and why the gap is created, if you lose a batch anywhere along this process, and you can see that it starts when you prepare the batch records at day zero, and at 16 weeks, you will have the drug out to pharmacies or ready to ship to pharmacies, and this is a typical batch of an oral pharmaceutical.

It is not necessarily a cytotoxic, but the person in manufacturing who supplied this to me assured me that it is probably not much different for a cytotoxic, that you are not talking about one day in a plant, you are really talking about 16 weeks in both the regulatory and manufacturing life of a drug.

So, it starts with preparing batch records, which are subject to regulatory review, manufacturing the bulk supply, so that you have barrels of, let's say, Tylenol, acetaminophen, sitting around. Those go through quality control

release testing, and then you can have quality control release testing for that and then for the compressed drug itself, which is often a different process in a different plant.

You have packaging, labeling, then, quality assurance release, and shipment of supplies. Things can go wrong at any one of these stages where you can lose a batch. We once lost a batch of an experimental drug because little bits of cardboard had gotten into the vials.

It was an ad-hoc thing where we were trying to package a pediatric formulation for one of our drugs. We hadn't done it before in a long time. The vials themselves, because of the machinery, got a little bit of cardboard from the box that they had been sitting in prior to weighing and loading the drug.

Now, we never released that and we went to another process, but if you think about that kind of as a model for some of these drugs that aren't made very often, although that is an experimental drug, the situation is very similar.

We had to go to a different process. It turned out to be much simpler. Sometimes the third or fourth effort, you finally get, why don't we do it that way, you know, why are we so dumb trying to do it a complicated way, and everything worked fine, but it took six, eight weeks to get that up and running, and we had lost six or eight months of time developing the first process.

So, there are lots of pitfalls in this process, it is, in general, a batch process, and losing a batch loses a large chunk of time, not just a day or a week or a month.

[Slide.]

The second issue, which I think is very important, and which we did identify in the Children's Oncology Group, is that there just aren't the lines of communication in terms of supply and demand between pediatric oncology and the manufacturers, whether they be generics or drug houses like ours, that there is in adult oncology.

There are large databases in the U.S. for sales and use that can drive your demand figures

through your manufacturing process. We just don't have that for a drug that is being made once or twice a year in small batches and being used in a very limited basis.

I think that one of the problems is that although it is a very limited basis worldwide for the pediatric oncology community, it may be that, you know, 50 percent of the patients get vincristine, but that is not true of oncology worldwide, and the volume is very small.

So, the ability of a company to detect the need in pediatric oncology is very limited, either for marketing data that we routinely collect, or from the contact with manufacturers, which you may see at the level of a Medical Affairs person visiting, a university visiting an office, or even a salesperson, who might be able to come back to the company and say, "You know, I think they are starting to use this more, we had better make sure we are not in a shortage situation."

The last one, which is I think very unique to pediatric oncology, is that COG protocols, CYOP

protocols can create a unique spike that you don't see in adult oncology, because in adult oncology, there are only ever a few percentage of patients ever going on a study.

If for some reason, people decide that we are all of a sudden going to give every pediatric oncology patient a formulation of asparaginase, let's say PEG, that hasn't been used widely before that, and that information is not somehow communicated to the manufacturer, you very easily end up in a shortage situation.

So, I think there are things that we can do on both sides to communicate when there might be a spike especially in an old drug.

The final point on this slide is that a single source may leave the market without warning, and that is why I think it is important to maintain on an ongoing basis for that key drug list, communication, and it may be worth employing somebody at the COG to maintain this communication on an ongoing basis to be sure that a single-source manufacturer doesn't decide I only made and was

able to manufacture and sell a minute amount of this if I am a generic house, I am going to use my plant for something else next year.

I don't think any reasonable drug manufacturer would go out of that business with the knowledge that kids with cancer were not going to get the drug, but I think part of the issue is getting that knowledge to the proper place.

[Slide.]

So, in summary, you know, pediatric oncology is a small population, makes it difficult for manufacturers to track use statistics. We, in general, are using older drugs because of there not being label indications for many of our drugs in children, which is I think slowly being corrected under the BCPA, there is little contact between pediatric oncologists and manufacturers, like there is in adult oncology. It's the one good thing about marketing, is that there is contact between people.

Finally, the spikes in use, and I don't think this is a major problem, but it is something

that I think we need to be aware of, that pediatric oncology, because it treats 80, 90 percent of the kids on a protocol, can really drive demand for a couple years' time that nobody may have seen in the previous two or three years if a new drug is being added that is not a brand-new drug.

[Slide.]

So, in response to these issues, at the fall 2002 COG meeting, we really actually ended up with these action items, which I think were supposed to be carried out by the Pharmacy Committee.

I don't know, to be honest, to what extent they have been carried out and maybe Greg can comment on that, but there was a suggestion that there be established points of contact at each company that manufactures a drug on the critical pediatric oncology list, that there were established lines of communication between the FDA-ODSM and COG to obtain and disseminate information on shortages as it became available, and to establish a COG input into that management

plan, and finally, to establish a communication plan with PhRMA.

Now, this is a personal representation by me, this is what happened at the meeting. I think that establishing direct lines of communication to the individual manufacturers is probably going to be much more effective than spending time establishing communication with PhRMA, but on the general level, it is probably not a bad idea.

So, those are a few issues really just to put on the table for discussion, and I am glad to stand for questions although I hope you realize that my bent is as a pediatric oncologist in industry, and not as a pediatric oncologist representing all of industry.

DR. REAMAN: Thanks, Wayne. Maybe we will have Dr. Goldberger give his comments, and then we can ask questions of both of our speakers.

CDER Drug Shortages Program

DR. GOLDBERGER: Besides being the coordinator of Drug Shortages within the Center, which is kind of an unofficial position I have had

now for about 15 years, I am also the director of one of the review offices, the one that actually handles antimicrobial products, ophthalmology, and some transplant products.

[Slide.]

I am going to try to give a little bit of an overview of our program, which has evolved greatly since 1990, talk a little bit about the management process, some ongoing issues related to shortages, and then just provide a little bit of information about who to contact, which may, in fact, be useful for some of the points brought up in the previous presentation since we probably can provide some assistance in dealing with manufacturers, at least if the number is not that large since we do that on a regular basis for a number of products anyway.

[Slide.]

Some of the people who do the work in drug shortages are here, sitting over there in the first row I guess of the FDA seating are Val Jensen and Jouhayna Saliba, Drug Shortage Project Managers,

and sitting in the middle of them is Harvey Greenberg, who is the representative from the Office of Generic Drugs, and in the audience is Chris Moser, who handles a lot of our database management.

This is an informal program. There are actually three positions that have been dedicated to drug shortages, one is currently vacant, these project managers, half of one other position. Everybody else from all these other offices, the Office of Compliance, Generic Drugs, the Review Division, Drug Information, Chemistry, all do drug shortage activities, as well as whatever their ongoing jobs are.

Over the years, the drug shortage activity has become much busier, so it is good that we now have a few full-time people to kind of manage things and keep too many things from slipping through the cracks.

[Slide.]

Well, we do a lot of work with other groups. I mean we work a lot with the CDC. A lot

of issues have come up with certain antimicrobials, certain other issues related to counterterrorism. We do, as you can imagine, an enormous amount of interacting, for instance, with regulated industry to see what is going on, to assist in dealing with problems. I will talk about that in a few minutes.

We also do a lot of work with various professional associations many times because they are complaining to us about the non-availability, for instance, of specific products, some international organizations, and have a great deal of interaction with the public, which is one of the sources by which we find out about whether or not a shortage might exist.

[Slide.]

The previous speaker talked a lot about the reasons for shortages. If you look at this slide, first of all, you have got some of the manufacturing issues, the top one, the bulk drug or the API--that stands for the Active Pharmaceutical Ingredient shortage--manufacturing difficulties, compliance issues. I think those to some degree

have already been covered.

Then, there are a lot of other issues, and a couple of things worth mentioning that are all sort of linked together, for instance, are changes in clinical practice. That was sort of alluded to in the previous presentation.

A drug may be an innovator drug, may become a generic drug. New drugs come out, it becomes less interesting, less profitable. It then becomes solely a generic drug, then, after a while the number of generic manufacturers who make it gradually dwindle to the point where there may only be, for instance, one manufacturer who is making the product.

If they decide to leave the market or something happens to their manufacturing, there is a problem. That is where sometimes we see the market concentration or limited capacity.

Other times what happens is the following, and one of the worst shortages that we had to deal with in the last five years, was a shortage of some products for anesthesia, of which the most visible

was naloxone, which as you know would be an extremely bad product to run out of.

There were several companies making this product, but one of the major companies with, I don't know, about 40 percent of the market, ceased manufacture for a while to retool, I think, their facilities.

They did this in a voluntary manner, nonetheless, as a consequence of this, the remaining companies could not take up the slack. They were also making a couple of related compounds and almost immediately we went into back order on naloxone, and would have, in fact, clearly have run out nationally except for the fact that we were able to bring some product in from Canada, from a manufacturer about whom we knew a fair amount although it was technically an unapproved product, and they were able to make enough drug to supply the U.S. marketplace.

To get an idea of the visibility of this shortage, I had to go down and speak in front of the legislative group of the American Society of

Anesthesiologists, and the speaker right before me was Richard Gephardt. That was when he was still in Congress, I might say.

So, that was a fairly visible shortage, so market concentration can be a problem even if there are several people making the product.

Related to some of these issues of changes in clinical practice, et cetera, are corporate decisions, that companies will decide that, for one reason or another, it is no longer profitable for them to continue making the product.

They may be downsizing their manufacturing capacity, or I like to use an analogy. When I was growing up, you went to a department store. You could buy virtually anything you want in a department store.

Today, when you go to a department store, you notice what proportion of a department store actually is clothing, often private label clothing. One of the reasons is, is because per square foot of display space, you can make more money selling that than you can trying to compete in books,

electronics, et cetera.

There is probably some of that going on, as well. There is a finite capacity of manufacturing particularly for certain types of manufacturing.

Some of that was already alluded to, as well as to the broader issue, which I will try to mention in a few minutes, of manufacture of sterile injectables, which is where we have had the most serious shortages. That capacity is finite, so it is generally going to go to the folks, to the products where you can get the best return.

Occasionally, we see shortages that are more hospital pharmacy based. Some of these, in fact, relate to the fact that a given company leaves the marketplace for a product.

Sometimes their product is being handled by a specific distributor, a healthcare organization has an exclusive contract to get the product from that company, so other manufacturers are making that same product, but the healthcare entity doesn't have the contract with them, and

there can be a delay sometimes and a temporary shortage while that kind of problem is worked out. So, that is, for instance, something that happens from time to time.

[Slide.]

If you look at a breakdown we did of reasons for shortages over the last few years, about 40 percent are all kinds of manufacturing, and I think that was pretty well covered in the preceding talk.

It is important to notice that there is the issue of if a batch of product has a manufacturing problem, I mean there is the issue of trying to make another batch, and that can be very variable how long it takes.

In general, we know that for many products, you can find between what is in the manufacturer's warehouse, what is at the distributors, and what is at the end user pharmacy, probably two to three months of product on average.

So, one of the things we learned when we were doing some preparations for Y2K, so there is

some product out there, but beyond the time it takes to simply get a new lot manufactured, you have to keep in mind it has to be fit in. That is to say that many times the manufacturing lines are scheduled for other products, so you have to find a slot where you can actually do this, and that can produce some added delay.

About 40 percent manufacturing, 40 percent discontinuations, 10 percent active pharmaceutical ingredient issues, and then 10 percent assorted reasons.

More and more of the active pharmaceutical ingredients are coming from outside the United States. From an economic point of view, this is not surprising, since many of these products can be more efficiently made in large amounts.

So, instead of having a number of small manufacturers produce them, it may be more cost effective to lower prices or at least restrain price increases to have a given company make a lot of it, but if something happens to their supply, that can produce a fairly substantial problem.

We have had issues like that from time to time, where we have had to work with manufacturers to identify new sources of active pharmaceutical ingredient.

[Slide.]

Well, we learn about shortages from a variety of places, from pharmaceutical companies, professional organizations, healthcare providers, patients. We have public e-mail accounts, phone numbers, et cetera, other FDA offices.

One of the areas where we have probably made the most progress from the early 1990s is getting a more global awareness within the Agency of drug shortage issues. There was a time when I first started doing this, when some compliance and enforcement actions were taken without regard to the medical impact of the non-availability of the product, but I think we are much better now in making those assessments.

I will tell you there are times when an enforcement action must be taken against a product even when it is clearly medically necessary, I will

talk about that in a few minutes, simply because the defects in the product are so great, i.e., bacterial contamination within the vial, mold contamination within the vial, metal shavings within the vial, but other times there is a little more flexibility, and there are sometimes ways to use product while manufacturing improvements are underway.

[Slide.]

Well, one of the first things we do is try to make sure if we get a report that there is a real national shortage. Sometimes all that has happened is there is a shortage of a particular presentation, that is, strength, number of tablets, whatever, et cetera, other forms are readily available, or we call the manufacturer and it turns out that this is temporary, they sort of didn't quite plan correctly, another week or two, the product will be available. We don't try to deal with those types of problems.

We try to see whether there is a real shortage and it looks like it is like to be

persistent. We deal with the companies. We have pretty good contacts now again, particularly since September 11th, with the wholesale distributors where we can really find out sometimes what is actually happening out in the marketplace.

We have access to IMS status, so we can really look at how much product is being sold, et cetera, and then we also have contacts with various professional organizations, so we get some idea of what is going on, what their members are reporting, et cetera.

[Slide.]

One of the things we try to do is initially, when we find out about a shortage that appears to be a legitimate shortage, is we get what we call a determination of Medical Necessity from the appropriate Review Division.

The CDER New Drug Review Divisions with the clinical expertise in that area make the decision regarding medical necessity. On occasion, we have actually gotten input from outside organizations, as well. We have considered

off-label uses, as well as labeled uses, and investigational drugs, as well.

[Slide.]

Now, in determining this, we try to look at the seriousness of the disease, the availability of the alternatives. We get information from the firm about what is going on, and the reason we are doing this is, in other words, we concentrate our efforts on dealing with products whose absence from the marketplace is likely to have a significant public health impact.

There can be products that are gone that may be a nuisance or an inconvenience. There are other products that can be life-saving, and many others that are important for serious disease. This is where we focus our efforts, and this is where, when necessary, we will sometimes bend some of the rules to allow the product to continue being made available. The fancy term for bending the rules is called "enforcement discretion."

[Slide.]

This is the definition we have used of a

medically necessary product. It is used to treat a serious disease or medical condition, there is no other adequately available source of that product or alternative that is judged by the medical staff to be an acceptable substitute. "Inconvenience" alone is an insufficient basis to classify a product as a medical necessity. That might mean you have to take it twice a day instead of once a day. We might not consider that a medical necessity.

This decision is made by the folks in the Review Divisions who deal with the drug on a daily basis, presumably have interaction with the professional communities, et cetera, understand a little bit about what patients may think, and these are the products that we focus our major effort on.

[Slide.]

To give you an idea, in 2005, about two-thirds of the shortages were determined to be medically necessary, and this figure of being more than 50 percent has been--the last time we checked it several years ago, it was not much different

than this. So, the majority of products that reach this stage are generally considered to be medically necessary.

[Slide.]

Let me give you a couple of examples of things that have gone on that you have probably heard about. There was the methotrexate problems recently due to GMP problems. That means Good Manufacturing Practices at a manufacturing site. It was shut down to upgrade the facility.

Two of the firms that used that site had a lot of the market share. Other suppliers were eventually able to increase production, but, of course, this doesn't happen overnight, to cover the shortfall.

One firm that supplied the same product for ROW--that is the rest of world--and the Division expedited approval of the New Drug Application for that, and in that interim, we allowed product that was labeled for use in Canada to come in and be used in the United States.

This took a fair amount of time. The

company we were dealing with was an ex-U.S. company. It was fairly complicated. I think now we are back to a relatively stable situation with that.

[Slide.]

5-fluorouracil. Again, Good Manufacturing problems. This involved some glass particles in the vials. The affected lots were quarantined. We worked with the Oncology Division. We, in fact, do a fair amount of business overall with the Oncology Division certainly over the years, and they have always been quite responsive to the shortage requests.

So, we worked to resolve this. The product in this case was released with corrective action. This is what I mean by "enforcement discretion." Normally, if there was product with glass in it, that would be the end, but if it's a product that is life-saving, you find some type of filter needle and again use it like that, let patients know about this, and eventually, this problem was fixed.

This also illustrates again, you notice both of these are sterile injectable products. There tends to be less sources for those products, and they tend, in general, not just in Oncology, to be used for more serious illness.

[Slide.]

So, one of the things we do is we try to develop a plan for short term and long term plan for shortage management, and that means short term may be is there some way to keep the product in the marketplace, can we talk to other companies who may have some supplies, or to have them start to increase production.

Some of them actually can do that quite rapidly. Longer term may mean looking for new sources of raw material, working to find a new applicant to submit a new NDA, working with the company or having our Compliance people work with the company to improve their manufacturing, so there is the short term to try to keep product available, the longer term to try to remedy the problem.

The other thing we have gotten better at over the years is really trying to get information out. We have a drug shortage web site, which provides information on current shortages, information how to get the product.

We have a very good relationship with the American Society of Health System Pharmacists, and our web sites are linked. They provide a lot of additional information about shortages, and unlike our web site, where we are very limited in what we can say about alternatives, they can actually give medical recommendations about alternative therapy that might be able to be used.

[Slide.]

Some of the things that we can do to talk in a little more detail about shortages, sometimes we use approaches of limited distribution, either in some cases, there will be some sort of protocol that will limit the product to the patients with a condition who really need it, and some of the off-label or other indications, product won't be available.

You have to find someone who is willing to run that protocol. Sometimes that can be a little bit of an issue to do that. Sometimes the company will take that on.

One thing that you always learn early on with this is if you want to stretch the supply of the drug, you always manage it centrally, and the reason is--unless you need it instantly--the reason is, is because a lot of product gets soaked up between distributors, between hospital pharmacies, et cetera, so you have got a lot of product around on the shelves, all over, sometimes for relatively smaller number of patients who need it at any moment.

If it's a product that you don't need instantly, keeping it centrally and Fed-Exing it out allows you to manage the situation with a small amount of product overall. When there are issues like impurities that go above a certain allowable level on the product, we try to get our pharmacologists, toxicologists to look at this, see if they represent a problem.

Again, if there are manufacturing issues, the chemists--CMC stands for Chemistry Manufacturing Controls--will look at the issue. We work with the inspectors, et cetera, to find out what the problems are, how serious they are, et cetera, and look for folks who can actually, if necessary, submit a new New Drug Application or abbreviated New Drug Application.

Some of these, for instance, in the Office of Generic Drugs, can be expedited, which can speed up the overall process.

We help look for alternate sources of raw materials. Sometimes that is something that we actually do, not simply in the U.S., but actually worldwide.

An issue that came up in the previous presentation is the issues when companies plan to discontinue a product. We have had any number of discussions about products over the years that companies have wanted to discontinue, that we have been able to induce them, and remember we have no actual authority to require a company to continue

manufacturing, but nonetheless, that we have been able to induce them to continue manufacturing for some additional period of time.

We can let other manufacturers know, without necessarily going into all the details, that it is desirable for them to consider increasing the production of a product to cover the loss of product from the marketplace, you know, if someone who we know either has problems or is going out of business.

As I mentioned, utilize regulatory discretion, and finally, in certain rare occasions, we do bring in unapproved product, after getting information on manufacturing, into the country to deal with shortages. The anesthesia drugs is probably one of the best examples. We have done that maybe three or four times in the last number of years. That is kind of the last resort, but in certain circumstances, it actually has been necessary to do that.

[Slide.]

FDA cannot force a manufacturer to produce

a product or to continue to produce a product. It is always important to remember that.

The manufacturers are not required to report plans to discontinue producing a product unless it is a sole source product for a life-supporting/life-sustaining condition.

That is actually now in the Food, Drug, and Cosmetic Act, they are supposed to give advance notice, but notice it is a sole source. They could have 75 percent of the market, and somebody else could be producing it, and there is no requirement for reporting for a life-supporting/life-sustaining condition, and all they have to do is report that they plan to do it. That doesn't mean they can be required to continue producing, but they just simply have to tell us they are going to stop.

Overall, however, I think it is fair to say our communications with firms have gotten much better. They tell us generally in advance if they notice a problem as opposed to waiting until it gets to the point where actual spot shortages begin to occur.

I think we get better information when discontinuations are occurring, and that is certainly very helpful. It sometimes gets a little confusing. We are dealing with a shortage situation now in a non-oncology product where it has been a little more confusing because one generic firm was purchased by another, and establishing communications with the new owner, plus the firms themselves working it out has slowed down a little bit our getting the necessary information.

[Slide.]

This is the actual rule about the discontinuation, and interestingly enough, as far as I know, within the drug regulations, this is the only place where anything really relating to drug shortages is mentioned.

Although we have this program, and have been doing all these activities, there is no specific basis for it in the regulations. It is something we do from a public health perspective, and I think everybody agrees it is very important,

but it kind of formed gradually on its own, not with regards to any particular regulatory mandate.

[Slide.]

Some of the ongoing issues that we still deal with are trying to get as much advance notice of problems. We have gotten better at the early determination of impact of shortages, because we have better access to data now. We have a little bit of money, so we are able to get data from IMS and other things, so we understand a little more what is going on in the marketplace.

There are an increasing number of shortages and greater public interest. Periodically, there are articles dealing with drug shortages. I always keep a file of them on my computer, so then when I want to talk about some of the egregious things that happen, which I otherwise could talk about, I can just quote from the articles that are already in the newspaper.

But basically, there have been some serious shortages, some of them due to maybe unavoidable things. Others do because in some

circumstances, some firms have not been as diligent as others in maintaining their manufacturing base and their manufacturing facilities.

Some of the plants where sterile injectables are made, may be 30 or more years old, and frankly, are not up to today's standards, and have more problems associated with them.

We try to enhance public access to shortage information through the mechanisms that I outlined earlier. I think that has been very helpful, so at least people have some idea of what is going on.

[Slide.]

We also have, in terms of other things we are doing, we have a Critical Product database that monitors a variety of important products. Many of these are related, but not all, to issues of counterterrorism and related matters, but we have been steadily adding products here.

This is a place where we probably could add some additional oncology products to, as well. We find out periodically from the manufacturer what

is going on. We find out how much stuff they are producing.

We will sometimes go to the point of finding out what are the rate-limiting steps with regards to their ability to increase production, et cetera. So, this has been an ongoing activity that has increased very substantially over the last several years.

We have very good contacts with many of the manufacturers, the distributors, so we find out what is going on, better communications with the Generic Pharmaceutical Association, the Parenteral Drug Association, as I mentioned before, the American Society of Health System Pharmacists, various professional organizations.

That is sort of a lot of the things that are currently going on. The industry and trade organizations are more aware of these problems. I think that they are more inclined now to talk with us earlier, talk with us about contingency planning.

We have done a little bit of that with a

few products, as well, just thinking about potential impacts of shortages, some of the things that could be done to alleviate them, and those types of scenario planning are actually quite useful and do give you a little better handle on some of the rate-limiting steps involved in manufacturing.

[Slide.]

So, the contacts, that's our phone number, the e-mail, and then we have the web site, so we certainly would be happy to try to help with some of the products on the oncology list. Although we can't deal with dozens of products, certainly, the list that was shown before would not be any problem to assist in attempting to continue to track that.

You can always e-mail us at drugshortages@cder.fda.gov, and then we have our web site, which is fairly prominently listed on the FDA web site under Human Drugs.

Thank you.

DR. REAMAN: Thank you.

Are there questions for either of the

speakers?

Subcommittee Discussion

DR. FINKLESTEIN: I have just a generic question. Maybe, Wayne, you can answer it.

What percentage of drug do you think sits on the shelf in a pharmacy or the distributors, so let's say you make 100 or 1,000 units, what percentage do you think just sort of sit out there? I don't know if there is an answer for the question.

DR. RACKOFF: I am not on the manufacturing/distribution side. I don't know if you have got statistics on that, Mark, but a lot of it.

You know, some of it's warehoused, but I think as was alluded to in Dr. Goldberger's talk, much of it is out in the system, so that when you hit a shortage situation, one of the things that the FDA has been I think very diligent about is trying to centralize the process along with the manufacturer, so that there is not product sitting out there.

DR. GOLDBERGER: It is also our impression that there is less stuff sitting on shelves, particularly for some of the more expensive product, simply because it's too expensive to keep it on the shelves.

I think probably there is a little more reliance maybe on just-in-time shipping from some of the distributors. The down side a little bit of just-in-time shipping is every so often it is probably not quite just in time, but I think it's our sense that there may be a little more of that, as well, so I don't think there are huge quantities.

It really becomes a problem if you have got a product that is in relatively short supply, and you have got a relatively short expiration date on it. You know, some products have an expiration date of several years, so the expectation is it is likely that it will get used.

If you have got something with a shorter expiration date, that could be a problem, but in some areas where there have been shortages,

hospitals or healthcare organizations within a given city will also share. They will call each other up to see who has a product.

Now, ideally, you would like to avoid having to do that, but yet that is another option in terms of acute drug shortage management.

DR. REAMAN: Dr. Pazdur.

DR. PAZDUR: I have a question. I realize that there is variations to the complexity of the manufacturing process.

The two questions that I have, one, if a company realizes that there is a batch problem and they cannot distribute that drug, is it the tendency, then, to automatically do that batch process over again as soon as this is observed, or do they just say, well, we will wait until the next scheduled batch distribution or batch process that we had planned out?

Secondly, I don't have a concept of how long it takes, once a decision is made to start a new batch up, are we talking about if somebody is making a plan of running drug X, does it take them

a month, does it take them a week, does it take them two days to run these batches of drugs?

I realize there is variations here, but can you address some of the timing issues?

DR. RACKOFF: I can only address it with regard to the examples I work with most directly, so I have to be a little bit circumspect there.

In terms of what you can do when a batch fails, which happens all the time, especially in sterile product manufacturing--not all the time, you know, every batch--but I mean I am sure every week, somewhere around the world, a batch fails on somebody for various reasons.

The more difficult the drug is to make, obviously, the more it happens.

I think in terms of how and when you can reschedule a batch depends on what your cushion is, first of all. So, if it's a drug for which there is a fairly high demand, there is usually a cushion built into the manufacturing process. You expect to lose maybe a batch a quarter.

It is when you lose that batch. Let's say

you plan 12 batches a year, and you lose one, then, midway through the year you lose another one, and you lose another one and another one. The bad part is it is like, you know, turnovers in a basketball game. If they are spread out over the game, it's okay, but when you have 10 in a row, then, you are 20 points down pretty quickly. I think that is what is the problem.

Now, the second problem that both of us alluded to was that there are plants where there are multiple oncology products being made, for multiple manufacturers, by very good contract manufacturers, but when you lose a batch, your contract controls what is done about that.

It doesn't mean that you can reschedule a batch the next day, or sometimes you can, sometimes you can't. It becomes a negotiation with those folks.

I mean those are some of the issues that I have seen.

DR. GOLDBERGER: Let me make a couple comments also. One thing is when you look, if

there is a failure in manufacturing, if it's a situation where there are episodic failures, then, you may have some understanding of what the problem is, but even then, and certainly if it's an unexpected failure, before you can sometimes go and remanufacture a new batch, you have to figure out why the failure occurred.

That sometimes can be fairly complex, because you have to look at your machinery, you have to look at your raw material. Sometimes you have to look at even your excipients can make a difference, so that is one thing.

Then, the other thing is, you know, it depends again on how much capacity you have. We did some work with a manufacturer of a product that has been used in some counterterrorism situations and other areas, and they went through with us what it would take to manufacture new drug, and they could actually do it probably, once they had the raw material, in as little as six weeks, but that really depends, of course, on having manufacturing lines ready to go and having an adequate source of

the raw material, the starting material.

In some situations, you have to realize that in addition to the drug itself, there may be the vial that it's in, the stopper that is used for the vial. Any problem with the availability of any of those things can be very serious.

I think we had an explosion at some factory in the last couple of years that made many of the stoppers for drugs, and that was potentially a problem in terms of some of the sterile injectables.

So, all those things have to come together to be able to rapidly replace product when there has been a manufacturing deficiency.

DR. RACKOFF: Just to follow up on that and answer your second question, for example, something like stoppers, if you are distributing the drug just in the U.S., and you want to put a stopper in that has an animal-based lubricant as opposed to a vegetable-based lubricant, you know, if you have the proper clearances with the Agency, that's okay, but there are certain countries in the

world where you can't make that replacement.

So, if you are making batches that are going to be distributed in countries where, for religious reasons, and health authorities have dictated this, you can't put an animal lubricant on the slip, to slip the stopper in. You know, you get into those kinds of things. It can be quite esoteric.

Not, in terms of timing, I mean the drug itself, let's say, for sterile, one of the ones that I have been involved with over the years, from the time it goes into the line, from the time it comes out of the line is 10 days, just that. That is just doing the chemistry, doing all that stuff, but that doesn't account for these other week's worth of batch testing and release, pre-testing, you know, batch paperwork.

So, for that, our batches I think for that drug might run several months. The manufacture itself is 10 days, but that is the minority of the time it takes to get the chemicals in the door and the drug out the door.

I will make one comment in follow-up to Mark, because I think the best way, you know, one of the things obviously, manufacturers discontinue drugs, and those are obviously business decisions. I think one of the best ways to influence that for this group is constant and fertile contact with those companies at a high level on those drugs that are critical to pediatric oncology.

DR. GOLDBERGER: For instance, we have with certain products that have limited use in certain infectious diseases, including sexually transmitted diseases, sometimes if there is an issue, rather than our trying to convince the company by ourselves, we will get the CDC involved, or it's the CDC who came to us originally with a concern, so we will have a joint telecon with the CDC, beat on them a little bit, and that in the past, has been reasonably effective in maintaining supplies at least for longer than the companies originally planned.

DR. RACKOFF: Most reputable companies would have a hard time with the concept of I am

cutting off a drug to kids with cancer, and that is legitimate. I think if any company, if our company knows that a drug is absolutely essential, I think there are companies--I mean GSK makes a couple of these drugs or used to be the source primarily for them, and they kept making them because they knew they were the only ones making them.

So, I think if they know, and I think it's a little harder for generic manufacturers to know, because they haven't been involved in the research and development of the drug, it's pretty hard to stop cold without working with the Agency, finding other sources.

DR. REAMAN: It may be hard to stop cold, but I was a little concerned that you left economics off your list, because it is not always hard for them to make a decision to stop making the drug, sell the drug to another company, and then there is ramp-up time in manufacturing and distribution, which, in essence, creates a shortage if they are a sole source manufacturer and distributor, and we have had that situation.

I don't know who it is that you talk to high up in the command of a pharmaceutical company, because we are not necessarily privy, and why, after 42 years, does Merck decide that they are not going to make Elspar, and they are selling it to another company.

I just assumed that this was something that the FDA has as part of its mandate. I know now that that is not the case, and obviously, when shortages do exist, I can't say enough about the help and the assistance that the Drug Shortage Office provides, but it just seems that there really ought to be some mechanism by which potential shortages are averted.

In the situation in pediatric oncology where we have unfortunately not given ourselves an alternative, we have a single drug, there are no alternatives that can be used within a specific treatment regimen for a specific disease, that's it. When there is no drug, you can't treat it.

DR. GOLDBERGER: What we will try to do is if we get advance notice, sometimes the companies

will tell us that they are selling a product, we will see what we can do about trying to ensure that during the transition period, there will be product out there, that the company will make some extra material, the company that is phasing it out, so that that product will last until the new company can take over.

Now, keep in mind there is a couple issues there. One is you are transferring a manufacturing process, but that manufacturing process may be transferred to a new facility. There is no guarantee that in the time planned for, that new facility will be up and running, making the product. So, there is always the uncertainty about that.

So, that is one part. The other part, which unfortunately came out in the New York Times--I am sure many people saw it on Saturday--is that sometimes when a product is transferred, the price goes up fairly dramatically.

One thing I didn't say was that an area that we really can't do anything about is what the

product is being sold for. Where this problem comes up periodically is in the following. There is originally an innovator product. Then, the product becomes generic, as well, so the innovator may continue to make it, but in limited amounts. Most of the product comes from the generic industry at a lower price.

Then, something happens to one or more of the generic companies. The innovator may have product available and may be able to increase production, but it is not going to be at the price that people are used to paying, and that is a problem. We recognize it's a problem, but our goal is to ensure an adequate supply of the product.

We can't really do much necessarily about the mix to ensure that it's an adequate supply at a reasonable price, and that is problem for which we don't really have a good solution.

DR. RACKOFF: I think we talked about this several years ago. The situation you mentioned, I don't want to pick on any particular company obviously, but that was on the list actually. So,

if there had been, I don't know, an ongoing communication, which there usually isn't between pediatric oncology and the companies, for obvious reasons, so it has got to be initiated probably from the pediatric oncology side.

I think maybe and involving the Drug Shortages Office, as well, maybe to do their job only that they can do, you might have had a smoother transition there. I don't think you could have prevented this, nobody is going to prevent the sale, that is a business decision, but to try and work with them, with a lot of the methods that Dr. Goldberger has used to smooth the transition might have worked.

That is really I guess, in our economy, in the way that things run in this country, that is the most you have.

DR. PAZDUR: I just wonder if some of this could come under the jurisdiction also of the FTC, Federal Trade Commission, and let me tell you kind of the flip side of this.

We frequently get consulted--I shouldn't

say frequently--we have been consulted when companies are undergoing mergers and acquisitions if they have competing products, for example, two taxanes or two products with the same indication, and the FTC generally will ask our advice whether the company should divest one when they undergo mergers and acquisitions, so that there is a free trade that exists there.

That is another area. For example, if a company was undergoing a merger, they may just decide to not produce the competing drug, and that also is a fear that could potentially happen to the situation.

I have a question for Mark, perhaps he could answer it, not from his perspective of the drug shortage, but also from infectious disease, since this is an infectious disease issue.

That is, panic indications, when the public perceives that there is a need for a drug, and obviously, what I am talking about is Tamiflu, and what is the FDA's role in this, if you could give us kind of a thumbnail.

DR. GOLDBERGER: Actually, we have the classic example. Tamiflu has not been so bad. I mean the real example was in ciprofloxacin in the fall of 2001, and that was pretty bad. Basically, as soon as the anthrax cases, you know, people became aware of it, Cipro was one of the drugs being pushed very hard as a potential drug to be used for prevention or even treatment.

Tom Brokaw, I actually was watching the news that night, picks up his vial and says, "In Cipro we trust" on national TV. That really exacerbated things.

You have to realize that one day's normal production of ciprofloxacin would have supplied every person who possibly, conceivably, from an epidemiologic point of view, would have needed therapy for prevention even for 60 days, so there was plenty of drug conceptually available.

Nevertheless, we began to run out of product. There were spot shortages all over. When one tried to match up the number of prescriptions being written to the amount of ciprofloxacin going

out, they didn't really seem to match up, suggesting--it wasn't clear what they were suggesting.

I got home one night, and I got a message on my answering machine from my cousin up in New Jersey, whose husband is a pharmacist, asking what product he should bring home for the family, Cipro or doxycyline, et cetera.

There, our management was truthfully, at that point, we were probably already a little bit behind the 8-ball, so there, our goal was to work with the manufacturer in ways to frankly increase production, so that the shortages ended, not because you needed billions of doses, but simply by helping to end the shortages, I think it kind of calms people down, and we were able to do it.

Bayer had had some contingency planning in place, and they were able to handle the increased manufacture, but it was a lot of work, because product would be flown in, you know, raw material would be flown in from out of the country, it would get here, and then for reasons that would be

obscure, it would be held up at Customs, because they were unhappy with something in the shipment.

Then, we would have to get someone from our Compliance Office to call over to Customs to get it released. Then, it would have to be shipped to the Bayer facility, but they did a really good job.

So, there, our goal was to actually catch up. In the situation like Tamiflu, the demand really has not been that bad. There, what we like to do, when you can identify a problem ahead of time, is we prospectively tried to look at what is going on in the marketplace.

We have done that for--Tamiflu is a good example--we will talk to the manufacturer, ask them about, you know, how much product they have, what are their plans for allocation, are they holding some in reserve, and Roche, for instance, you know, had put out a public announcement about this, so they were fairly, in fact, proactive about it and were able to manage supplies adequately, truthfully, because this was probably not such a

bad influenza season that really pushed people so hard.

What we do with certain products that we think might be prone to this is we try to have surveillance ahead of time, and the other model we used is we had a major operation underway for Y2K. Because I was doing this drug shortage job, I was then given the responsibility with a small group of other people of assessing the readiness of the pharmaceutical industry for Y2K, which was basically a job that took about a year working part time while I was doing my other job.

That allowed us to get an understanding of a lot of the planning issues, which have been important to this day, but what we also did is set up some formal surveillance using a product, a commercial product from a company that supplies that type of data, and we set up informal contacts with all the distributors and with manufacturers of a particularly critical product that was very prone to hoarding, because it was a product that is a little more easily available than many of the

things that you get from your pharmacy.

So, that model of talking with the manufacturers on a regular basis is something that we do from time to time in dealing with these problems, as well. Whenever possible, we like to stay ahead of the curve as opposed to playing catch-up as we had to do with Cipro, but that was one of these unexpected things that happened, and then you have to work after the fact.

That is one of the reasons we maintain a Critical Products database, so that we have an idea of what the capabilities are, how much product is generally in stock, et cetera, how quickly it would take companies to increase their manufacture in the case of an emergency.

So, those are some of the things that we have done to deal with these problems. As I mentioned, we do have these good contacts with the major distributors. I think there are three distributors that do most of the work in the United States, and by talking with them, get a pretty good handle on what they are having in terms of any

potential shortage situations.

DR. REAMAN: Can I just ask, the Critical Products list, how do you get to something on that, who controls the Critical Products list?

DR. GOLDBERGER: That is where you get into real power, to have control over the Critical Products list.

DR. REAMAN: I don't want control over it, I would just like to be able to add something.

DR. GOLDBERGER: Basically, the Critical Products list, I am not sure how it emerged. It basically emerges, I mean we run that. Again, it's one of these things, it is nowhere in the regulations, and it is by no means meant to be every critical product.

Much of it represents products that are important in some way for counterterrorism-related indications. There are some products that are related to products that the Government maintains in certain stockpiles for emergencies, and then periodically, we have sort of added products, in other words, if you are worried about, for

instance, influenza, you might, for instance, want to monitor the supply of influenza, you know, drugs for treating influenza, but then you would expand to consider monitoring the supply of the antibacterial drugs that might be used for the bacterial complications of influenza.

So, it is things like that. We have added some products recently. That is an area where if there are some oncology drugs that people are very concerned about, we can add that. You can contact either Val Jensen or Jouhayna Saliba, who are sitting here, with the information, and we can make some contacts with the companies.

Remember, in a way, although there is a limit to how much we can do, it is more efficient for us to do some of it than to have you set up separate committees and all, because this is something that we are doing on a regular basis anyway.

We already have a format for tracking the data, et cetera, so it's just, you know, a little easier. We know what questions to ask, et cetera.

So, I mean that is something that we can provide.

It is kind of an ad-hoc thing, but it has become increasingly useful, because you can only begin to imagine, but hopefully, not totally, when various problems come up with influenza, with anthrax, the level of inquiries that come down from higher up in the Government. I hope, truthfully, you cannot understand what that could be like.

But to deal with that, we have set this up, because usually, you get the same inquiry from different people about 10 times, sometimes from the same person multiple times, so now we actually have some of that data.

So, that is what we use it for. So, we certainly can assist with doing that, you know, if you have some products.

DR. REAMAN: I think that would be very helpful, because we don't know, I mean who all of the manufacturers are maybe and when they change, particularly since these are old products that the innovator may still be making, but obviously, there are other manufacturers, as well. We will take you

up on that.

Dr. Finklestein.

DR. FINKLESTEIN: I want to be very concrete. This is pediatric oncology. Now, what I am hearing is Greg Reaman, Chairman of our group, is to contact you or Dr. Jensen when we think there is going to be a drug shortage, and I am being videoed right now.

I mean I want to know, because we have been suggesting this for years.

DR. GOLDBERGER: It's fine to contact--in other words, actually, it is more efficient to contact them, but you are welcome to contact me. They have to do the work.

DR. FINKLESTEIN: No, no, no. Then, who do we contact? We want one person.

DR. GOLDBERGER: Actually, my slide, what you do is you dial 301-796-1300, and you ask for one of the Drug Shortage project managers--

DR. FINKLESTEIN: I don't do well with answering machines. I would like a single person.

DR. REAMAN: Well, Jerry, I already call,

and we communicate. The issue is not who do you call when there is a drug shortage. The issue is what do we do to prevent drug shortages. When I become aware of a shortage, because I get 10,000s similar calls, like you get, trickling down from Government, but we have that mechanism and I know who to call.

What I would like to do is to just prospectively or proactively avert this, and if there is a way to communicate with manufacturers in advance, I think that would be very helpful.

DR. GOLDBERGER: The reason I am actually giving you the number also is because that way, on any given day, there will be someone or a couple of people from the Drug Shortage program there, but it won't be necessarily the same person on every day. So, if you call that number and ask, you will get connected to someone who can help you.

If you ask otherwise, you may, in fact, get somebody's voice mail, so we are trying to give you a more personalized answer.

DR. FINKLESTEIN: But that won't help you

completely. The other thing is years ago, when we set up this committee, PhRMA had put up their hand through Steve Spielberg and said contact me, we will take care of also that kind of problem. What has happened with PhRMA?

DR. REAMAN: Steve Spielberg isn't with PhRMA anymore, so I don't think he would be of much help to us.

DR. RACKOFF: Steve is the Dean of Dartmouth Medical School now, which is a good thing for Dartmouth, and he left our company to do that, so we miss him.

As I said, I do not speak for PhRMA, and I think that PhRMA ought to be involved in the decision. If it were me, knowing what I know from where I sit, I would rejuvenate the Critical Drug list that we had three years ago.

I would take it to Dr. Goldberger's group. I would try and get those drugs that are absolutely critical on that list, so that they could do the tracking for you, because what we set up before was we should track these, but I guess it didn't happen

within the group, and they are set up to do it, and they do it every day.

Once that happens, maybe then you have a quarterly meeting where you find out who you need to call, and that is when you call PhRMA and the individual companies, so that it is more directed, and I think it will be very effective.

DR. GOLDBERGER: But one of the reasons why calling--calling PhRMA, I think is extremely useful to discuss the broader policy issues, some of which have come up here, like companies discontinuing product, companies transferring product to someone else to make sure that they keep enough product, to encourage the member companies to stay interested in pediatric oncology, but remember, PhRMA is a link, you know, is a trade organization.

For actually dealing with an acute problem with a given product with a company, dealing with PhRMA, first of all, they don't deal with that, and second of all, some of the representatives to PhRMA from the companies might not be the people you want

to deal with anyway, so that is one of the reasons.

Furthermore, some of the generic companies, of course, are not in PhRMA, they are in their own organization. That is why in some respects, it is a little easier for people to make their inquiry either directly to the company, although that can be sometimes difficult, or to FDA, because we can at least get more information about what is going on. We can't always publish it, it depends what the problem is, but at least we can get a little better idea generally of what is happening.

DR. RACKOFF: The company will always call back when the FDA calls them. I don't know, I can't make the guarantee Steve made, but I can make that guarantee that that will happen.

DR. SMITH: I am with you in terms of how do we prevent this, not how do we respond to a shortage, so my questions would be in terms of our ability to prevent, do we know what drugs, for example, have a single manufacturer, do we know what their stockpiles are, are there ways of

knowing those things, are there ways of being proactive about preventing shortages, so that we don't come to the point where we finally reach the day that this drug is just not available and these dozens of children aren't going to get the drug, and we just haven't been proactive, and they are suffering because of it.

DR. GOLDBERGER: A few years ago, actually, it was in 1999, when we did our work on Y2K, we were tasked with not only finding out what was going with the pharmaceutical company, simply by having people call them up and talk to their IT people, but we were tasked with also developing an inspection program, which there was money for, to look at some companies and to find out whether they were really ready based on a 2- or 3-day inspection.

So, one of things we had to do was we had to identify a priority and who were the companies, and we ended up at that point developing a list of the top 200 prescribed drugs, sole source products, and orphan products.

So, at that point in time, you know, in 1999, we had such a list. We don't have a list like that anymore, because that was extremely difficult to develop, however, we have a little easier task here, because you can, as a starting point, start with the drugs that are no longer, for instance, under patent.

In other words, if a product is still under patent, you pretty much know there is a single manufacturer if it is an innovator product, so you don't need to do any more.

For the products not under patent, if you generate a list, and I saw a list up here that was of manageable size, since we are starting with the name of the drug, it is much easier to then determine (a) who is making it.

We can actually determine if there are multiple manufacturers, what the market share is, and often some idea of what the company's--how much they have or what their plans are in terms of could they increase production.

So, some of that we can do when we are

starting with a product. It is much easier that way. So, that is something that is manageable. It just depends how long the list is, because there is only, ultimately, when we fill our vacant position, be three project managers who do this.

So, we can do some of that, and we have been doing that on a regular basis, and we actually have Harvey Greenberg, who is sitting there from Generic Drugs, has helped us enormously in doing that with the generic companies, as well.

DR. SMITH: If we have a sole-source manufacturer, do we know anything about how much drug they have on hand, whether a shortage is pending? If it's a life-saving drug, what do we know about their ability to supply that drug?

DR. GOLDBERGER: We can get information from them about--we can find out how much of the product is being sold, what they manufacture, what their manufacturing capabilities ultimately are, but keep in mind there are still certain unknowns.

You know, we can find out a little bit about where their raw material is coming from.

That doesn't mean there couldn't be an interruption in that. That could be a totally separate company in a totally different part of the world.

The fact that we know something about the company doesn't mean they won't run into a manufacturing problem subsequently. You know, if we are really worried, what we will do is we will ask our Office of Compliance. We will find out specifically where a product in question is being manufactured. We can try to find out if we have got any kind of inspectional profile on that facility, which gives us an idea whether it looks okay or not.

I do know, in addition, we supply data from this Critical Products database. Our Office of Compliance, because there is only so much in the way of resources to go out and do inspections, many of which are not only all over the United States, but all over the world, is currently now developing sort of a risk-based approach to inspections.

So, products that have more potential medical impact, hopefully, those facilities, those

companies will be higher up in the list. So, there are things we can do.

I mean starting with a list of products actually in some respects simplifies it, because again, for you to do this, it is not so much an enormous undertaking, for all intents and purposes, it wouldn't be possible, because you wouldn't be able to get much of this information from the company, et cetera.

We can actually get more. Whether we can get everything, keep in mind that maybe one thing I didn't emphasize, is we get a lot of cooperation from companies, because, in part, we keep the information they want confidential, kept confidential.

All the information we get from companies is voluntarily submitted. We have no means to--in other words, if we want to know how much you can make, what are your critical areas that limit that, many of the companies will cooperate, but they are cooperating on a solely voluntary basis.

So, that is one of the things always to

keep in mind. We may not be able to share that information widely although if we see that there is a problem, at least, you know, we can look at it and see if there is something we could do about it.

DR. SMITH: I guess the process you are describing, though, it is not clear whose responsibility it is, that there is a drug that is critical, you know, maybe there is a sole manufacturer, and whose responsibility is it to see that a shortage is avoided.

The process that you are describing is one that could, in principle, be in place, but it is not clear that it is, or when it is and whose responsibility it would be to say that it should be in place with these drugs.

DR. GOLDBERGER: I think the answer to your question, which will not be very satisfying to you, goes back to a comment I made during my presentation, that beyond this issue of six months notification, there is nothing anywhere in our regulations or statute for drugs that really talks about this type of drug shortage management.

So, we do it, but it's not based on formal legal authority. There is, however, for the moment, I am not sure who else could do it. The companies, you know, take some responsibility, but they have no legal obligation to continue manufacturing.

We have assumed this to some degree by default, but you have to keep in mind, because we have assumed it by default, it doesn't mean that companies that don't want to participate, they don't have to. That is part of the problem. This is nowhere legally mandated that there needs to be tracking of these certain products, you know, and that's the law. That doesn't exist.

DR. SMITH: So, if it were legally mandated, then, you would be in a position to track these things.

DR. GOLDBERGER: Well, in other words, we do it anyway, but we would have more authority to do it, but, right, presuming if we were tasked with doing that, then, we would, of course, continue to do a lot of what we are already doing anyway, but

we might have, in the case of a recalcitrant company, more authority.

In truth, I don't know if either of you want to comment about what the level of cooperation is generally, because that will give you an idea really what actually goes on. I can talk sort of theoretically, but they are the ones who actually have to talk to the companies.

MS. JENSEN: I would say overall their cooperation has greatly improved over the last, I would say over two or three years, since we started our Critical Products program.

It started out with about 20 drugs. Now, we are up to 350. So, the companies, you know, they know that we contact them on a regular basis, they are willing to provide this information, and I would say that the main thing that has really come out of this program is that they let us know when there is a problem.

So, having that communication with them, telling them these are important products, that we want them to make sure to let us know if there is

any issues, they do that, and that is something we have seen more and more of.

DR. SANTANA: I am going to turn the conversation around a little bit and put it upon ourselves, as a group, to potentially be more proactive with the communication.

Maybe the Children's Oncology Group, Greg, we should empower, like the Pharmacy Committee, to do a resource drug utilization for every protocol, and when the protocol is approved, we do that internally at my institution. Whenever a new protocol comes along, we have this resource utilization, how many CBCs, and does that mean we have to hire another technician in the lab to do them.

But maybe we should turn that around, as the Cooperative Group, and have the Pharmacy Committee look at protocols once they are approved, looking at the drugs, the potential resource impact of utilization of those drugs, and then identify both at the Agency and in PhRMA where that information goes, so that we are proactive in

communicating our needs early on.

Now, this is a very complex problem, and that is not the solution, but I think we need to think about how we can be proactive early on in the trial approval process, so that these guys know that yeah, there is going to be, you know, a thousand patients on this study that are going to require asparaginase, and although that is a small fraction of potentially the whole population, I think it gives some indication of resource drug utilization, so maybe that is something we should take upon ourselves, too.

DR. REAMAN: I think we can certainly do that, but I am not sure that it's necessarily a research issue or a protocol-specific issue. I mean these are drugs, for the most part, that have been around for 30, 40, 50 years, and whether children get them as part of their participating in a protocol, or as standard of care, they are the only drugs that can be used.

So, I think our list would be relatively short. I can't imagine that it would add more than

six drugs on your already existing Critical Product list. I wasn't aware that that existed. I think now that we know about that, I think that certainly is a mechanism that we can use to have the Agency help us and to have individual companies possibly help us, as well.

Pat.

DR. REYNOLDS: Greg, I would like to second Vic's suggestion that this may be something that the Pharmacy Committee for the COG might want to take a little bit more role in, in monitoring this. I am concerned that this list is not as inclusive as it should be.

For example, there was a rumor floating around approximately a year ago that there would be a shortage of injectable melphalan. This turned out to be potentially true. It was dealt with, with some calls to the Agency, and they helped clarify that that wasn't going to be the case, but you are right.

There are other ways you could treat a patient with high-risk neuroblastoma than use

melphalan and transplant, but when you are four years into a randomized study, and that is your primary consolidation therapy, you really don't want to have to switch in midstream, so I think that the COG needs to take an active role in monitoring that these drugs are going to be there year after year.

MS. EICHNER: Most of my questions were answered, but just as a parent, to clarify what I am hearing in this room, is that basically, pediatric oncologists have no idea from the drug companies when a shortage is coming down the line. Can I get clarification on that?

So, my question to the committee is show is protecting our children? I don't think that the list would be that long. I don't understand why there is no communication between the drug companies and oncologists. Children are treated in institutions. It is a relatively small group, thank heavens, but it is not like adult oncology. I don't understand why that communication is not there, so who is protecting the children, and how

can we come up with ideas to solve this.

I mean we can talk about if a clinical trial is coming down the line and a drug company hears that we need more methotrexate, but then there is a drug shortage, well, the kids that might suffer will be the kids that are blocked out of that trial, because it might be closed, so in a small institution, those children might not receive the drugs.

I don't understand why the pediatric oncologists are not receiving this information beforehand.

DR. REAMAN: We don't understand it either, which is partly why we have this as an agenda item to discuss it today, and I think there have been some suggestions that we can put in place and utilize prospectively to try and at least increase our level of information and avert the disasters.

I mean as they relate to trials, I mean that is important obviously, but not having drug available for treatment of children when it is the

only drug that is available, or that works, or that is effective, is really the issue here that I think we need to address. We have heard some suggestions, and I think we can put them in place.

Let me just add one more thing, sorry, and I think what we have also heard is that in order to really give the Agency more teeth, although they do have the Drug Shortage program, there is no legislation which enforces that. So, there is the opportunity to introduce some legislation that maybe would, in fact, codify that responsibility, and that is something that we could consider doing, as well.

DR. GOLDBERGER: The area that people have identified, although we are not supposed to, working within the executive portion of the Government, talk about what would be useful legislatively, is that the requirement for advance notification is pretty limited in terms of the number of products that it covers.

It would be nice if there was a little more information. Now, in truth, we are getting

more information. Again, it is mostly voluntary, but still things have, over time, improved, but that is a potential vulnerability sometimes.

DR. ADAMSON: I think we can make this from very simple to extremely complex. I am hearing on the table a very concrete quantum step forward in what to do. The number of acronyms we have for treatment regimens far exceeds the number of drugs we actually use, so I wouldn't be shy.

We have got nine for the immunologic malignancies about, toss in another six, we have got all of pediatric oncology covered with rare exception. We are talking 15 drugs plus or minus two. Let's not bang our heads against the wall. Let's send you the list, you do what you can, and then we can convene all the committees we want to try to get more proactive, but this is the first concrete step we have had.

Let's just get it to you. I think there is going to be rare exception that we can say this is not a drug for this cancer that we know how to easily substitute. There are some of those, but

for most of the drugs we are using, as Wayne showed, I mean these were approved between 1953 and 1978.

So, if we get the 53 to 78 drugs covered, I think we are in excellent shape, and there are not that many of them even though we juggle them in different ways.

DR. RACKOFF: Again, the one that is on there that is very interesting to me also, and I wouldn't forget these, are things like preservative-free hydrocortisone, which you don't think of as an oncology drug, but without it, we can't do CNS prophylaxis.

DR. REAMAN: Even with that, I think we would be hard pressed to get to 15.

DR. RACKOFF: There were I think nine on the list, and this list came from the Pharmacy Committee three years ago.

DR. REAMAN: I think it is not necessary for us to go over the specific questions. I think this has been a very useful discussion, and I think we have all learned something here, and I know that

we will definitely follow up with you after this meeting to put this in place, so this was very helpful.

Does the FDA have anything else?

DR. WEISS: No, I think this discussion achieved its purposes I think of making everybody aware of the processes and the limitations, and I am very, very pleased that there has been some concrete steps.

I think that we will all help Mark and the team in terms of what we can do for pediatric oncology uses.

DR. PAZDUR: Like testicular cancer, if you ran out of cisplatin, you know, here again you might think, well, these drugs are being used in such great quantities, but remember one of the examples was 5FU, which most oncologists would consider ubiquitous in treatments and all regimens, the lymphoma regimens. They have some drugs that weren't on there.

DR. ADAMSON: We will let you add to a few to our list.

DR. WEISS: I just wanted to thank everybody especially those of you who stayed to the bitter end of this discussion, and like I said, I am very, very pleased with the discussions and your involvement in the entire day, so thank you again for you all of your input.

DR. REAMAN: Thank you. The next meeting will be sometime in the fall, I am informed.

[Whereupon, at 3:05 p.m., the proceedings were adjourned.]

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