DR. MATHIS: There are actually now some labels that do thatB-

DR. ADAMSON: In oncology?

DR. MATHIS: I think that we are starting to evolve in oncology, and I will let Ramzi take the oncology-specific question.

DR. DAGHER: First, as Lisa was mentioning and even in some of these cases and others, when, as you have seen, there was a decision made that basically there is not enough data there, or it is inconclusive, or there is just not enough activity, you have seen the variability in the wording. When you see that wording of "has not been established" etc., in most of those cases we weren't adding that statement to the label. That was a statement that was already there from the previous labeling and we simply decided not to change that because we thought there was not enough new information or it was inconclusive. In some of the cases, as Victor mentioned, we thought that we should at least describe the studies and say there were only, you know, very few responses or I think in one it said

no significant clinical activity because there were, you know, a few partial responses so we didn't want to say there was zero activity.

So, these were the kinds of struggles that we dealt with in terms of one extreme, the carbo, where we didn't add anything to the label because we really thought you didn't have interpretable information to others where you saw a range. So, clearly, if you have ideas on how to describe the studies more clearly when you don't have a clear zero activity or, you know, 100 percent response rate, that would be helpful.

The only other thing I want to mention, Peter, because you mentioned the carboplatin example is that Victor described very clearly a couple of the considerations, the issue around the PK and many patients not reaching the target and some of the other issues. A third issue that we took into consideration that I just want to mention is that we also thought about whether there were new safety signals or some incidence of adverse events that somehow were not already known from the

label and from public knowledge about carboplatinB-myelosuppression, renal ototoxicityB-we felt that in that case there wasn't really anything new that we had.

Now, going back to the design, was that design the best design to get interpretable results? You know, I have to acknowledge that it probably wasn't the best design and, as you said, there is a learning process.

DR. SANTAN: Can I follow-up on that too. Can I, Mike? I am sorry.

DR. LINK: Yes, I just want to add one thing to answer a specific point. You could help the label by saying no studies have been done in children. It is very different from the efficacy has not been determined. I think that is what Peter is asking. You know, tell us what you did and not just sort of some statement where the interpretation could be anything. It could be you did them and didn't find anything; you didn't do the studies ever; or you did it and the drug just doesn't work. I mean, those are three different

things.

DR. WEISS: Can I just comment? We are trying to do more of that now, saying, you know, safety and effectiveness has not been studied or it has been studied and a description. You have to remember too that the label is not a very big piece of paper so trying to give useful information but not cluttering it up. Obviously, you don't go to the label to get the specific details. You know, you go to the literature. So, it is a balance but I think your comments are very well taken and we have been cognizant of that over the years, particularly for pediatrics but not only pediatrics but that is an important area where, you know, if labeling is going to be useful it needs to be more informative.

DR. SANTANA: It is exactly as you said, Mike. One is saying there is no data. The other one is saying the studies have not been done or the studies have been done and these are the results. Those are different messages and I think--

DR. LINK: Or the studies have been done

but they were badly designed.

DR. SANTANA: And that was my follow-up comment to Peter Adamson's comment. You know, we are here to take a step back and look at what we have done so we can figure out what we are going to do next, and I think the historical perspective, to use that phrase again, is very important. I think a lot of the studies, you are absolutely correct, that were submitted to be part of the Written Request and to satisfy it were data that were already out there. It was a way to launch many things, in retrospect, and therefore there were few new studies that were part of that.

I think as we look at that experience, I think we need to take a step back and say, okay, how will we do it in the next series of studies? What are the real important questions that this mechanism can help us answer so that we can get the sponsors and the cooperative groups and the investigators and the FDA at the same table? I hope that that will be the evolution. That we are not just submitting data and doing X studies; we

are really trying to answer a question that is going to help not only the patients but eventually satisfy something with the label because there is--as you heard, I am not a regulator although sometimes I think I amB-you know, they have a responsibility for the label in terms of the public information that is out there and the label has to reflect what you give them.

DR. LINK: Pat?

DR. REYNOLDS: I want to agree, first of all, with Jerry. This is a beautiful review I think. You know, it is great work and I think that one of the things that strikes me about this is that the consistent thing that is happening here is that what is getting into the label is what is going on with these drugs as single agents. Virtually none of these are used as single agents in practice.

So, I would like to pick on topotecan as an example. I think that very few recurrent neuroblastoma patients make it very far without being treated with cyclophosphamide and topotecan

in combination these days. So, to say that topotecan has noB-it is true to say that there is no demonstrated efficacy of this drug as a single agent but, yet, as a combination we know it works.

This committee, I think it was three or four years ago, I know it was on St. Patrick's Day, recommended to the agency that nonclinical data would be used to inform the labeling process. You make that point of how can we inform the PWR process with nonclinical data. Well, I think it is very critical that we consider that we cannot go back and reinvent the wheel and ask what is the contribution of topotecan and cyclophosphamide in children. We can do it and, in fact, multiple people have done in the laboratory and there is a lot of robust nonclinical data that combined with the response rate that exists out there for the combination could perhaps address this and be incorporated in the label. Is that possible?

DR. SANTANA: I will let the agency answer that but let me give you another perspective on one of the issues you are touching on, I think, on a

different level. I think we have to be very careful that industry, the FDA, investigators, cooperative groups, and the patient community are all partners in this. But everybody has a different agenda. By agenda, I mean a mission to accomplish, not a negative agenda or a positive agenda but a mission to accomplish, and I think we have to be very careful to see where those agendas overlap so we can take the best out of that. But, clearly, COG has an agenda that is very different from a sponsor's agenda or it may be very similar and they may overlap. So, where those opportunities overlap is where we need to dig in to make sure that this process works.

What I am trying to say is let's be careful. First of all, the FDA can't make the agenda for the cooperative groups or for the NIH or NCI. You know, this is a sponsor voluntary process so the sponsors have to have a mission of what they want to get out of this besides the exclusivity and the issues associated with the finances. And, we need to begin to understand how those agendas

overlap so we can take advantage of where they overlap because, clearly, everybody has a different agenda and I think it wouldn't serve us well if everybody had the same agenda because it is different. Right? The cooperative group has a mission to accomplish which may be very different than the sponsor's mission for a particular drug. So, I think we need to be very careful about that because this is ultimately a voluntary process as it relates to BPCA and it is those areas of overlap that are really going to make the process work. It is not the areas where they diverge because it is voluntary and they will say we don't want to do it. That is just an observation; just a general comment.

DR. BLANEY: As we all know, we have very limited resources as far as patients in pediatric oncology and the information that we gain from these studies, particularly pharmacokinetics, is invaluable and many times we are not going to be likely to repeat the studies in the future. So, I think we need to think of ways as we go forward of

how we can maximize the information that we are getting from patients willing to participate in these studies.

We have seen that in all of these studies there are some patients that respond so what is different about the responders versus the non-responders? There is a lot that we don't know about the drugs that we prescribe but we are learning more and more about the pharmacogenetics of the tumor as well as the host, and if we can find ways, which I know won't be easy, to take samples and bank samplesB-in leukemia it is easy to get the tumor [sic] from the host as well as from the tumor. I think we need to look at that prospectively because we are not going to have in many instances, particularly for active drugs, an opportunity to repeat the experience.

DR. LINK: Ramzi?

DR. DAGHER: On a much simpler scale, a lot of things we have learned along the way, for example, to maximize somewhat, not nearly as much as what we are hoping and what you just described

is that, for example, even in a limited rubric when you have just Phase 1 and Phase 2 data there wasn't always PK sampling incorporated into the Phase 2 studies where, in fact, you could see there would be a lot of reasons why for a most focused population, etc., etc., there would be reasons to include that. More recently we have done that more routinely to incorporate that when possible. Whether it is Phase 1 or Phase 2 or randomized trials in the pediatric populations, they are small populations so you can't just rely on the dose escalation studies to get all the PK information that is going to help drive future studies. That seems minor in the big picture but that is one element that we have tried to incorporate into that.

Another is that Lisa mentioned that the template had, you know, a suggestion of certain sample size in terms of numbers, and we have really tried to be much more flexible but also much more careful in terms of not really basing it on some reflexive number of patients because it is not so

much the number of patients, it is also, you know, what populations you are looking at; in what situations are there requirements for the different age groups going to be more relevant than others. Clearly, if the ultimate use of the drug is going to be in a sarcoma like osteosarcoma or Ewing's the concerns about having PK data in two-year olds is not so relevant as if you are talking about neuroblastoma or leukemia. So, in those kinds of situations it is not just important how many patients you have and how many PK samples. It is what age groups and also when is that important and, you know, are you likely to get as much information as you want from the sampling.

DR. WEISS: I just wanted to get back to one of the questions that Pat Reynolds raised about the preclinical or nonclinical data which, I totally agree, can actually certainly be used if there are reasons to look at, for instance, the contribution of one particular entity when it is not really feasible or ethical to go back and do that in a clinical setting. It is certainly very

appropriate to do those. Now, how, or if, or when it is part of a Written Request is a different issue and I think Lisa already mentioned that these are sometimes incorporated as part of the information, but those types of data wouldn't stand alone as sort of a basis for exclusivity.

I want to comment that there are timesB-I mean, we have new legislation now called the Animal Rule and it is a very unique situation for counter-terrorism which does allow companies to develop their efficacy trials solely in animals. But that is, you know, for areas where it is just not at all practical or ethical to conduct studies in patient populations. But, clearly, nonclinical data are important and relevant, and much of that helps in terms of defining contributions of the drug and also information that ultimately lends itself to the label, which is an important document that the FDAB-like Lisa, before I came to the FDA I didn't pay much attention to drug labels. When you come to the FDA you really understand and to some extent appreciate the complexities of what is in

the label and the information that is in there. As people are probably aware, there are also new labeling rules now that are going to change the look of the labels and, hopefully, make them much more user friendly compared to what they are currently.

DR. REYNOLDS: Karen, if I can just comment real quick, I want to clarify that I wasn't trying to suggest that we use nonclinical data for this alone but in the context of the combination of clinical data that is robust just to address the relative contribution of the individual agents.

DR. LINK: Make the comment brief because we are running over, although a lot of these comments are very pertinent to the post public hearing discussion so they are very relevant, but you might save them for that discussion because we are going to address all these issues. But go ahead, Cindy.

DR. SCHWARTZ: I guess I just wanted to say two things. One, just listening to this, first of all, that it is very helpful seeing all the things

that have come out of this process and with it potentially the October deadline and thinking about what happens next. It seems that we should remember as we worry about these things the benefit that we have had for children by these processes and being able to study and all the Phase 1 data that has come out of it. We shouldn't, as we talk about it, give the impression that we want to throw out the baby with the bath water here but that it is important.

There are two things as I am learning this system that I seem to think I need to know more about, and maybe is an area where something could be done is, number one, the Written Requests and how to make them more specific; what processes and people are involved. It sounds like PhRMA and FDA and those people are involved a lot. I don't think I know the depth to which COG and other groups may be involved in making these Written Requests relevant to the drugs and the tumors, etc. Also, whether they ca be redone later as new things evolve.

So, the one thing was just a little bit of a focus on Written Requests. The second was the labeling and not only what goes into it initially but are there processes for updating it or even saying, well, we don't see efficacy but such studies haven't been done, so ways of making sure we don't close the door and make insurers and other people make it so that kids can't get these drugs.

DR. LINK: So, this is what we should be discussing after our public hearing. Why don't we take a ten-minute break and we will be back here after that for the public hearing.

[Brief recess]

DR. LINK: A couple of announcements. The people on the phone and are trying to dial in are actually the European medical evaluation agency. It would be nice to have them on the phone. So, that is why you are talking into your microphones so that our colleagues can actually hear what we are up to.

We will now turn to the open public hearing. I believe we do have one request to talk.

Let me read the announcement about that. 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 any company or any group that is likely to be impacted by the topic of this meeting. For example, the financial information may include a company's or a group'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.

Open Public Hearing

DR. WEINER: I am Susan Weiner. I am president for the Children's Cause for Cancer advocacy and, as I often say, I wish I did have conflicts of interest but for the purposes of this meeting I have none.

First of all, I would like to thank the subcommittee for this timely review of FDA's actions regarding pediatric oncology, BCPA and PREA. The re-authorization of these two mechanisms is supported by the Alliance for Childhood Cancer, of which the Children's Cause for Cancer is an active member. BCPA and PREA have resulted in important new data for the safe treatment of many diseases that children experience, but for childhood cancer these tools have had limited value. Our children are a precious resource and our willingness to enroll them in studies constitutes a statement of trust that we will add to the value of the data.

I would like to thank Dr. Santana for his thorough review of BCPA and the BCPA experience with oncology drugs. It is telling, from our perspective, that there was one new molecular entity in this list of 11. Parents, survivors and the pediatric oncology researchers share a vision that would define success that current treatments for childhood cancer will be able to make use of the insights resulting from current research technologies. We work to bring the day closer when therapeutic agents can exploit the aberrations of cancer cells to destroy them while leaving the rest of our children's bodies to grow and develop normally.

PREA is a device which has yet to advance us towards that goal. PREA has, however, attracted fresh attention in many companies to the pediatric implications of the oncology drugs in their pipeline, an essential benefit but an inadequate one for advancing modern therapies for our children.

We also face, of course, an even larger

and looming challenge that PREA is inadequate to meet, how and whether we can approve new for pediatric specific cancers given the low incidence and the rarity that these cancers have in the current regulatory framework. The process used for adult evaluations of cancers does not fit the realities of pediatric oncology research. It is the process, not the science.

As a community of dedicated advocates and researchers, I believe we need to address this challenge collaboratively. Occasions when agents, for example, are under FDA review either for PREA, for BCPA or through ODAC or in proprietory settings, these occasions need to serve as opportunities for the agency, for researchers and patient representatives together to devise strategies for solving the complexities of pediatric oncology drug development. Whether drugs are ultimately approved for pediatric indications or not, whether they are labeled or no, there are essential lessons in the history, design and conduct of clinical trials and data analyses which

we cannot disregard if there is to be progress. When it takes decades to evaluate potential treatments for life-threatening diseases, like osteosarcoma, brain tumors and neuroblastoma, the agency, NCI, the cooperative groups, academic researchers and patient advocates have an obligation to analyze each success and failure for ideas about how to improve the process.

The Pediatric Subcommittee of ODAC is one forum in which new strategies for solution can be examined, and today's meeting is a start in that direction. We would hope that the Critical Path discussions taking place internally would also include the Critical Path application to pediatric oncology. NCI, professional groups and patient advocacy settings are situations in which we can work together on strategies for improving the process.

Families and survivors are increasingly frustrated at the seeming lack of progress in the debates about pediatric oncology drug development over the past decade. We urge the agency, the

cooperative groups and industry together not to shift the responsibility from one party to another but, rather, to work together on how novel treatments for pediatric cancers can be efficiently brought about. Thank you.

DR. LINK: Thank you, Susan.

DR. FINKELSTEIN: I would also like to thank Susan who has been here since day one in trying to proceed with this process. There is someone in the audience-because one of the things we asked is moving this process forward, and one of the comments I made was the comment that PhRMA and the American Academy of Pediatrics have been working very closely together, and one of my questions was where is the process-there is a gentleman, named Mark DelMonte, from the American Academy who is in the audience and I really think, if this is permissible, if he could address us to let us know where the process is in terms of re-authorization we all may be a little smarter. So, I assume, Mr. Chairman, this is permissible.

DR. LINK: Yes, I know Mr. DelMonte. He

could give us a short update.

MR. DELMONTE: Good morning. I appreciate the opportunity to speak. My name is mark DelMonte. I am an assistant director for the Department of Federal Affairs for the American Academy of Pediatrics. I have no conflicts to report. I only work for the Academy.

I am happy to give you a little bit of an update on sort of where the process is for the re-authorization of these two critical pieces of legislation. The re-authorization is well under way and nearly complete. The re-authorization bills in the Senate passed last month at 93 to 1 as a part of a larger package of FDA regulatory changes, including drug safety legislation, the re-authorization of the Prescription Drug User Fees Act, Medical Device User Fees Act and others. There were nine bills, two of which were BPCA and PREA. The House just acted at the subcommittee and full committee level last week, and both BPCA and PREA passed out of those committees by voice vote.

So, I think the history of those programs

have enjoyed large bipartisan support, both in the first and second passage of BPCA and the first passage of PREA. There are a couple of remaining issues, although I think that the Academy and other partners, and industry partners and groups, including the Alliance for Childhood Cancer and others who have been really important stakeholders in moving these bills forward have achieved a couple of things in the bills as they stand now.

Now, knowing that those still have to pass the full House and we have a conference report, it is not over until it is over, as they say. But two particular innovations I think in the Bill that are responsive to some of the discussion that I heard this morning are that there is a new requirement in both versions, the House and the Senate versions, that, one, Written Requests be made public after the Written Request has been completed. So, there will be a greater opportunity to actually review that document by folks who are interested in that and can provide some clarity about what actually was asked of the company. That is a

non-controversial provision that I expect to see passed into law.

The other one, which I am very happy to report has passed both sides, is the elimination of that language, "safety and efficacy have not been established in children." That will not be on labels anymore. If a family works with a researcher and makes the very tough decision to put their child in a clinical trial, the fact that that clinical trial occurred, the results of that clinical trial, good, bad or inconclusive, should be on the label. That is the Academy's position. That is the position that we have fought for and I think that we have largely made good progress in achieving that. I expect that to be a part of the re-authorization.

There are a number of other innovations in those bills which I won't go into because I was told to be short; I could go on and on. There are a number of innovations to increase the transparency, consistency and uniformity of the operation of both BPCA and PREA together. As you

know, they were passed separately originally so they have kind of been functioning side by side, not really working together very well. So, there are a number of initiatives, I am happy to talk to you about in the hallway, to make sure that those go well.

With respect to this committee, in both sides of the bills that have passed the House in subcommittee and full committee and in the Senate completely, the Pediatric Oncology Advisory Committee is re-authorized for another five years. Also, we have asked, and largely achieved with support from stakeholder groups, that this committee also be given an opportunity to provide recommendations to the Food and Drug Administration on implementation of the re-authorization bills after they are passed. So, all of the amendments that happen to PREA and to BPCA that make it out of the Congress and onto the President's desk will be laid before this committee in order for you to be able to make recommendations to FDA about particular needs in pediatric oncology that need to

be addressed as FDA is continuing to implement the amendments of these programs.

So, I hope that those are two important and useful things that we have been able to achieve in this. I want to thank Susan and Children's Cause for their tremendous help in helping push these bills forward, and our partners in industry and also our partners at FDA. It has been a very good and healthy dialogue and I think that we should be wrapped up with this process. The bills are coming to the House floor July 9th, sometime in the week of July 9th. We expect that to be wrapped up. Then, conference reports should be wrapped up, hopefully, by the end of July and then we should have a bill signed by the end of July or early August if "the creek don't rise." I am happy to take questions but I thought those would be some of the high points.

DR. LINK: Well, I think we are going to avoid the questions and proceed. I think you have made Dr. Adamson happy at least.

DR. SMITH: Could I ask a question?

DR. LINK: You would like to ask him a question? Okay, I guess.

DR. SMITH: Earlier there were comments about the preclinical studies. Could you comment on what that language-Byou know, if there are any issues related to the inclusion of that language?

MR. DELMONTE: Sure. I wasn't here for that part of the conversation but I think I know what you mean.

DR. SMITH: The Written Request.

MR. DELMONTE: Yes, in the Written Request, as it stands now, the language can include preclinical studies for the first time. That language was broadened on purpose because there was reporting from a number of fronts that when you start to study, particularly older drugs or things, you really have to go back pretty far. You know, it is not sufficient just to do PK or PD. You really have to start. NICHD experienced this tremendously when they had to go back to animal models on some of these medications to sort of really demonstrate basic stuff. It is a "may" and

not a "shall." So, if necessary and needed, preclinical is available to FDA to ask for as far as the Written Request.

DR. LINK: I am going to take a little prerogative here, and that is, some of the questions that came up in the hallways were a little bit more about labeling. So, if we could hear from the FDA staff for maybe five minutes about what goes into the label; who sort of interacts to make it; and whether it is actually ever responsive to subsequent data that becomes available after the initial submission. I think that is maybe some of our not understanding it and it also may clarify the discussions that we need to have subsequently.

DR. WEISS: I am going to go ahead and get started but then I am going to invite my other FDA colleagues, including Dr. Santana whom I still consider and FDA colleague for the next two more days, to comment on perspectives on labeling.

Labeling is a very interesting issue. I mean, it is defined in regulations. The

regulations state that basically information-well, first of all, that the product should not be false and misleading, but information that goes into the product labeling is generally a whole cadre of information, of course. Anybody who looks at the label, you know, there is some preclinical information, particularly as it relates to things like reproductive, repro. toxicity types of things. That is pretty much, you know, standard and in regulation. There is information on drug mechanisms and formulations, and that kind of thing.

But in terms of the safety and efficacy, in general those are based on what is described as adequate and well-controlled trials to establish the drug's effectiveness. Information for pediatric specific areas-Lisa I think mentioned that back, I guess, somewhere in the '70s the agency established a pediatric use subsection of the label. The history of this is very interesting because it is in the precautions section of the label so, you know, there is a specific section

that talks about indications and sometimes the indication is age specific. Sometimes it is not. Sometimes it will say it is indicated for adults 18 and over with X disease. Sometimes it is silent about the age and just says it is indicated for, you know, patients with Ph-positive CML and blast crisis or whatever. It doesn't specifically address the age.

In the old labeling, if you wanted to find out specific pediatric information you would go to the pediatric use subsection of the label and that might describe the effectiveness data for pediatrics and might describe some clinical pharmacology information. It might describe the statement that Peter hates so much. That would be in there. The new physician's labeling rule actually has changed all that so there is a specific pediatric part of the label but it is not in the precautions section, and it actually is definitely much more user friendly.

But in terms of what we put in the label, you know, there are no specific rules. Generally

it is supposed to be information that is important for prescribers to be able to use the drug. So, there are times when, in fact, negative information is put into the label, particularly if there are important safety concerns, if it is off-label use that is commonly used but maybe has led to important safety information, for instance, that commonly nowadays goes into the label.

In the pediatric sections we haveB-I don't think we asked a specific question about that, but that is sort of wrapped into a lot of BPCA information that goes in the label, what kinds of things that, you know, you as clinicians would find useful and helpful to the label to inform you and the patient community, you know, as you consider use of these medications. I don't know if that is helpful or more confusing.

DR. LINK: Well, besides toxicity information, if data on efficacy becomes available that does not necessarily seem to make it into the revised version of the label.

DR. WEISS: Well, the other thing though is

thatB-you know, that is interesting and the adult colleagues that are sitting here at the table I know can also comment on that. Oncology is a field that is so rapidly changing and evolving that, in fact, the labels are almost never consistent with what is known in practice. Dr. Mortimer is shaking her head with that as well. You know, the whole field of oncology and clinical trials to advance the field is oftentimes far ahead of the label. The label is a dynamic process but it is a process that really lags behind what clinical research and publications tell us.

In terms of putting information also in the label, particularly things like new indications, I mean, that has been an issue very much in the adult world. When Dr. Kessler was still commissioner he put out a call for the off-label initiative to actually get things that are widely used off-label back onto the label. I think Ramzi mentioned earlier that generally we actually rely on not just published reports, though you can rely on that, but we generally like to see

the actual data. And, oftentimes the people who do these studies, the sponsor, the manufacturer of the drug is really the one who is owner, if you will, of the label. It is really their initiative to submit the data to the agency for labeling changes, for the most part.

So, you know, if there are studies that are done other places where they don't have access to the data or there just isn't really a lot of incentive to get, you know, things that are off-patent and a lot of these older drugs, you know there is a lot of information that is just not on the label because there has just not really been an incentive. We can encourage that and ask for that and make recommendations and suggestions, but we don't really necessarily have the authority to unilaterally change a label. Only in rare conditions. If we think that a drug is misbranded we can do something but we don't really have a lot of authority. It tends to be much more of a voluntary process. And, the minute you change a labelB-it is like the minute you buy a computer it

is out of dateB-the minute you change a label it is also, you know out of date because of the way this field is moving.

DR. LINK: Naomi?

DR. WINICK: Just putting together some of the comments, you must made a comment about the literature moving forward and Michael made a comment much earlier that the literature always trumps the label so I guess my question has multiple parts. Are there ways of changing the label that are faster than perhaps others if the change is only to reference a new study? Pediatrics is unique in that there is only one cooperative group. In Dr. Santana's review which, to add to everybody else's comments, was marvelous, and Peter's comments afterwards pointed out the fact that many of the trials that have been used in developing the label are from cooperative group settings or, even if not cooperative group settings, subsets of pediatric institutions that are used to the notion of data submission. A lot of the efficacy data is beyond the sponsor level.

A lot of the efficacy data is when a drug is FDA approved, perhaps not for that indication or in that circumstance but available so we use it. So, the question is, is there a better way or is there a way to expedite labeling changes directed towards efficacy where you wouldn't add a lot of text but where you would add a reference? I appreciate the fact that you need to see the data but if there is a large cooperative group mechanism and that is the way that most of the data comes to pass, realizing that there is no money for this, is there a way for COG to work in closer partnership with the FDA so that you can see the raw data?

DR. DAGHER: Well, in the off-patent process, which we didn't spend a lot of time on and will be more of a focus in the afternoon, in that mechanism the answer is, yes, there is currently a mechanism for doing so. In the on-patent part of this, as was mentioned this morning, one of the current limitations or the way it is set up right now is that exclusivity is linked to a sponsor submitting either a labeling supplement in the case

when a drug is already approved or a new drug application in the case when there is no current submission.

Now, the other kind of part of this, and I don't know whether this was part of your intent or not but because this has been raised also and we discussed this before, aside from those limitations another part of the mechanism right now in the on-patent Written Request process is that when the agency decides that you have or have not met the terms of the letter and you get or don't get exclusivity, that is based on having submitted all that was asked for in the Written Request all at once.

So, another way to potentially discuss this, although right now as far as I know that is one of the limitations that we have in the mechanism right now, is could there be, down the road, a modification so that you don't have that. You know, if you are asking for an extensive body of work as part of a Written Request, what we have now or maybe more, and you have a mechanism by

which maybe not all of those data from the completed studies would be needed at the initial exclusivity determination, that might be something else to discuss. Again, as Dr. Smith and the presenters mentioned this morning, you know, we don't have a role in actually the legislation itself but that is another component of this right now, that the way the Written Request and exclusivity determination works is that you have to submit whatever was asked for in the Written Request. All of that has to be submitted all at once when two things are being done when that NDA or supplement is being submitted. That is number one. Number two, when the determination of exclusivity is made and, number three, when we are making decisions about whether some of that information is going to end up in the labeling or not. And as you saw this morning, we are variable so far in terms of what we have added and we have not added.

DR. MATHIS: I just wanted to comment briefly on the literature. I have heard a lot of

people today say that the literature trumps the label, and I do want to add a precautionary statement here. The Duke researchers put out a paper this last year that demonstrated the lack of publication of negative studies. So, if you are relying wholly on the literature you are relying on only a partial piece of the evidence. When information comes into the FDA we don't only evaluate those centers which were positive. We look at those centers which were positive and negative. We look at the totality of the data.

So, I think it is really important for all of us to recognize that the label may not have all the information but I think we have to be cautious that the literature doesn't have all the information either, and perhaps we need to figure out some way of putting all of this partial information together in a meaningful manner for patients and physicians.

Questions to the Pediatric Oncology Subcommittee and Discussion

DR. LINK: I think that is an appropriate

cautionary note. So, I think we should go ahead. We have already begun in both sessions talking about the actual questions that have been addressed to us. So, you can look at that on page one. Look it over. We have read it before. We have seen the report card and I think that the statement of how much work remains to be done is certainly paramount. We are asked to discuss some of the limitations, strengths and weaknesses of the approaches and efforts thus far, and ways in which the FDA can improve that process. And, I think we have approximately thirty minutes, let's say, to do it, a little bit more, but we will see if we can get more out there. So, you are asked to sort of free think, free associate and give them some ideas.

MR. HUTCHISON: Hi. To my understanding, BPCA and PREA address on- and off-patent drugs, with the basic change that Dr. Weiss mentioned about oncologic therapies accelerating so fast, parents see that also. So, my question is, is there a pre patent or investigational new drug

process to encourage investigational drugs for pharmaceutical companies to cooperate and study those in pediatrics? Particularly, drugs on an IND are studied first for adult cancers. Then, to my understanding, there is no obligation by the pharmaceutical company to study that in pediatrics. You are really at the good will and good grace of a pharmaceutical company to do that. So, is there an incentive program to do that? Because otherwise what is going to happen to kids with oncologicalB-they are going to have to wait until it becomes on- or off-patent and, you know, that lag time. So, how do we address that?

DR. WEISS: This is not a total response but I can tell you that under PREA, and again most of the things that are studied for adults cancers wouldn't invoke PREA even if BPCA weren't around because they are very different indications. But the good thing about PREA, having lived through the time when we didn't have it and it was just evolving, was that it actually made companies think about the pediatric-related, development-related

issues much earlier in the process. It actually required that there be a plan for what and how they would study the particular entity in pediatric patients. Most of the time, and again we are talking in general about pediatrics-in general, most of the time those studies would be deferred, as you indicated, until after the adult studies were done and potentially after the adult approval.

That probably makes sense if you are talking about new agents for non-serious diseases where you might want to use the adult guinea pigs first before you expose children to something. Now, in serious and life-threatening diseases such as pediatric cancers, HIV, etc., you know, that is why I think a lot of this legislation came along in the first place. The advocacy community, you know, was really concerned that the pace was just too slow and that you waited forever and then you didn't ever get very useful information. Things were used out there in the community but, you know, there weren't really very fully studied.

So, certainly under PREA that has effected

a big change in terms of making and requiring our drug manufacturers to actually think about a pediatric development plan much earlier in the process than normally would have happened.

Now, under BPCA, as sort of you heard, I mean, you know, if a drug has specific pediatric indications being developed for a particular pediatric oncology disease, clearly the INDs and all those studies, all that development occurs in the pediatric population. If there is some discovery during development, like in the case of imatinib that has some potential utility in pediatrics, you know, then those Written Requests potentially come in earlier in the process. And, it is very hard to do in the abstract sense, the whole issue of the timing of the Written Request. You know, in some examples Dr. Santana gave, the timing may have been in a way almost too soon because we learned a lot more information as studies were done and drugs that maybe didn't provide very useful information, and subsequently studies ended up occurring, whether just by chance,

that showed that the drug probably had some utility that, you know, we weren't either smart enough in the Written Request or the available data just weren't there to be able to help formulate a more appropriate Written Request.

DR. ADAMSON: I would like to respond with my view of that. I think we have to accept the fact right now that there is a gap between what BPCA and what PREA can do. The incentive under BPCA--Sam, you may want to comment-Bmost companies will not have a good idea of what the true value of that incentive is until they are beyond Phase 1, and often well beyond Phase 1 before they know what the true value is. So, the BPCA incentive, other than raising the importance of pediatric studies as part of the culture of drug development, it is hard for a company to say we know what the value is and we are going to start now.

Where PREA is so limiting is that we are still having drugs indicated for pathologic diagnoses and not for molecular pathways. So, if there was an indication that for tumors that are in

part dependent on angiogenesis then PREA, I would think, would be able to kick in. But right now that is not happening and maybe, Karen, you may want to comment on when you first see product labels fundamentally changing to go beyond a pathologic indication.

DR. WEISS: I think when we learn more about mechanistically, and that is all of these people here and elsewhere, all the scientific researchers that can, hopefully, with their mechanistic-related research provide clues that might give us better ideas about where to target the studies.

DR. LINK: Let me just focus on a couple of questions because I think you are asking for suggestions so I am going to at least make a couple of suggestions on topics. First of all, here is what I heard. The first thing is really something simple. Is the 90 days enough? In other words, if we are going to help you, should we say that that really isn't enough time to sort of do all of this, or maybe you said that it was sufficient. I got

from Lisa's talk that this puts us under the gun a little bit.

The second thing I would talk about is, is there any way that the FDA can mandate a pediatric formulation? So, one of the problems that we are confronting is that it is all good and well to study a drug, but I am sure that Pat will comment on the ability to dissolve, like, this giant pill in something that is palatable, but it really does inhibit the studies and if you can't mandate that it be formulated in some way that an infant can take it makes it sort of impossible to conduct the studies.

Finally, I think this is what Peter was kind of nudging around, that is, is it important to broaden PREA so that you are not confined to the indication, you know, the pathologic entity for which the drug is approved but where you can say that there is good reason to believe that there is a mechanism that is targeted by this drug that would be relevant to pediatrics and, therefore, that should be part of PREA to actually allow you

to sort of poach a little bit, or whatever the word would be, in your Requests?

So, those are things that have been percolating in my head. I don't know whether other people want to comment but those things might seem obvious to me.

DR. BLANEY: I just wanted to add one thing in trying to improve the Written Request. Sometimes the Written Requests are initiated by the FDA; sometimes they are initiated by industry. But in some circumstances, I have been in situations where dialogue hasn't occurred with the pediatric oncology community as a whole as to the feasibility of the trial conduct and then that closes down because we are going back and forth, sometimes by as much as a year or more.

DR. DAGHER: Can I clarify part of that?

DR. LINK: Go ahead.

DR. DAGHER: You are absolutely right. About the first point, just to clarify that, when the program started we probably were doing more of the scenario where we were issuing some of them

even when we didn't have an indication that the sponsors were necessarily interested or had submitted a PPSR. With the evolution we have tended more to wait until we had a PPSR from the sponsors. The further reality is we can issue as many sort of self-generated ones as we want but if the industry is not interested either because of the feasibility or other issues, you know, they are going to decline as part of that program.

The other point that you made, I absolutely agree that we have to find better ways to have the discussion because what is happening now is that because of the limitations of this discussion being proprietary; part of discussions sometimes about an IND process, sometimes an NDA supplement process, unless we have time and resources to actually get outside consultants ourselves directly for us to get input from them, you know, separate from the company perspective, we to rely on the sponsors having that interaction with COG or individual investigators and having them, you know, involved directly in discussion

with us.

DR. REYNOLDS: Mike, I think you raised a good point about the formulations. I don't know if it is permissible for us to discuss this in the context of not just what the agency could do but we are now seeing a re-authorization being developed. Can we comment on what might help in that process? I am seeing "yeses."

I could be wrong but I get the idea that when we are asking the pharmaceutical companies to come forward in exchange for six months of exclusivity and conduct clinical trials, if those clinical trials, in order to be really effective, require a specific pediatric formulation, that is asking just too much in the context of six months of exclusivity. I could be wrong and maybe the pharmaceutical representative can comment on that. But I am wondering if there isn't an opportunity in the context of the re-authorization-Band I have seen tossed out the concept of dropping exclusivity from six months to three months, which I will just state I don't think is a good idea but Congress

will tell us what they want to do, but I wonder if there couldn't be a staged process whereby, if the pediatric Written Request really recognizes the necessity for a formulation that doesn't exist to be developed in order for this drug to be effectively studied in children, that an additional exclusivity could be granted on the basis of that.

DR. LINK: I think Dr. Maldonado should comment. I think that six months to three months had to do with the magnitude of how much money was being made per year on the drug. So, if it was a blockbuster it was cut to three. Is that correct?

DR. MALDONADO: Yes, that is what the Senate Bill says. The House Bill is straight re-authorization in that regard so they have to be reconciles.

I think the issue of formulation is very important. As you probably all know, the FDA doesn't approve drugs; it approves drug products so it approves formulations and they are vital for pediatrics for compliance. Unfortunately, the science of formulations, liquid formulations for

children is in its infancy. Talking to one of my chemists, he said, you know, there is only water and alcohol and alcohol has its limitations so we are left with water. So, we need to do a lot of research still in formulations.

One of the complaints that I actually heard since I was a medical officer at the FDA when we were dealing with HIV drugs to be developed in children is that a lot of these companies who develop special formulations for children have more formulations on the shelves waiting for the stability data that the FDA requires that they can sell in a year. So, somebody has to pay for it and typically industry does. I wouldn't even go as far as to say is that an incentive. I am, and a lot of others who are pediatric advocates, all for creating formulations but those are tremendous expenses, not only the creation but the maintenance of that formulation over timeB-years. So, they never pay-BI shouldn't say never, the antibiotics probably do but a lot of them don't pay by themselves.

DR. ADAMSON: A quick response to Pat and I want to talk about other limitations, I have found through the COG Phase 1 experience that the BPCA has been helpful in leveraging new formulations in certain instances. I think we, as pediatricians and certainly as pediatric oncologists, have a long history of being used to begging as the only way to get something done and that is actually changing. And, it is changing because there is a lot of competition right now. The landscape is changing rapidly. There are a lot of anti-VEGF agents out there. There are a lot of anti-EGFR agents out there. What we have successfully done, what gets a company a leg up with us is that they commit to try to make a formulation. As Sam has sad, it is not trivial and, you know, there are some remarkably insoluble drugs that are out there. But when a company makes a commitment and actually does it, in my view, that is a real incentive for us to meet our obligations to that. So, the BPCA has clearly helped us when it comes to formulations when there has been a competitive market, and that is true in

oncology right now in certain areas.

Coming back to the questions, Mike, and to follow-up on what I think Lisa said, when it comes to the label we have a body of knowledge and certainly the label is not going to reflect the entire body of knowledge, nor do we want it to reflect the entire body of knowledge. But it would seem that we should be able to look at the experience that Victor so nicely laid out and say, okay, what are we really saying is a sufficient piece of information to add in the label that is going to lead to exclusivity? Some safety data, some PK data, and some efficacy data and analyze what we really mean by that.

I think in the label we are beyond the PK and safety and we should just have a very standardized way of saying if we are going to use this, what is a reasonable dose to use in a child. You shouldn't have to dig through the label to figure that out. Once we do that, when it comes to efficacy everyone will go to the literature. What we want to know is, is there data out there to

suggest that this is not a good idea, the negative studies. You know, what has been done? If it is positive, great. We are going to find it in the literature. But what is the counterbalance to that because, again, when we submit manuscripts to journals everyone knows if you want to get in a good journal you need a positive study. If you have a negative study you are much lower down on the food chain and sometimes you are off the food chain. So, if there is, indeed, a publication bias, I think PREA and the BPCA can bridge a gap in our knowledge and we just have to think of a way of getting that in a usable and not lengthy format.

DR. LINK: First of all, you know, there is clinicaltrials.gov now so there should be some data available for trolling. I don't know how easy it is to use.

DR. ADAMSON: That is for Phase 3 in general.

DR. LINK: And Phase 2 also.

DR. ADAMSON: But Phase 1--

DR. LINK: Oh, not for Phase 1. The most

common drug we use is 6MP. You know, there is a liquid formulation in Europe that is actually very convenient. Not only is it tolerated well but you don't have to divide pills in half and multiply it by, you know, seven days a week and divide itB-you know. And, I don't understand why we can't get it. What I am saying is I don't know what the incentive would have to be, and I agree that some of this stuff is hard to do. If you could make prednisone in a liquid form and tasty, that would be like a major plus for all of pediatrics because it tastes terrible. But how can we get the stuff that has been done or that is not so hard available to children here, in the United States? I think that would be a big plus. Or, how can we get you to mandate it?

DR. WEISS: A quick commentary on that, 6MP is an old drug so it is off-patent so there wouldn't be any real incentive for whoever makes 6MP or countries that make it. It is potentially something that maybe could be addressed in the early afternoon when Anne Zajicek is up here.

Because, you know, there are these older drugs that are added to this priority list and the criteria for putting it on the list is basically what studies of these drugs would lead to health benefits in children? It is fairly broad kind of criteria or bar. So, you know, things like even the development of the formulations, but then the question would be who would do it and, of course, if it is no longer an incentive for the company then it would fall to, you know, writing up grants and having--

DR. LINK: It is already done. The drug exists. I am not talking about inventing something. I am talking about just like I don't know if we can import it from Canada-BI don't want to mention that here but, you know, we could it import it from somewhere. Are our European colleagues on the phone? Maybe they could help us.

DR. MATHIS: The European legislation, the pediatric legislation actually does address formulations, and their take on the whole issue is that if they require the formulations then they are

going to encourage companies that might specialize in making pediatric formulations to focus on that. It would actually be nice if in the States we saw companies, and there are a couple, who want to have a niche in making pediatric formulations. That would be particularly important for off-patent drugs. Again, NIH isn't a drug company. They can do the research. They can support the development of a pediatric formulation but they can't ramp up and maintain a product line. So, it may be an interesting idea to look at smaller companies and, like I said, there are some in the States that work specifically to make pediatric-friendly formulations.

DR. MALDONADO: In terms of formulations, that would be a good idea and actually there was a company, Ascent Pediatrics, that went after prednisone and other drugs and they went out of business. The reason they went out of business was because they couldn't compete, even trying to do formulations, without having enough intellectual protection. They just lacked intellectual

protection. That is what they wanted. They said because we develop these formulation any generics come along and just scoop it from us. That intellectual protection was introduced in Congress and never went anywhere.

DR. REYNOLDS: That speaks to the issue that I was addressing basically, and we have heard from multiple friends here that this is a costly process and we need to provide some advice to those peopleB-it is not just the agency here, it is really Congress-Bto address this costly process and see what can be done. Small companies are not going to be the solution to this. As you point out, I don't think they can survive.

The other problem with this is that a few years ago when Steve Hirschfeld gathered together those people who really worked in the area of pediatric formulations to talk to this committee, he had a hard time finding more than three. The fourth one we finally got at a COG meeting was from O'Neal. And, the number of people who are experts in this area are far and few between. So, we need

something from the governmental side to stimulate this process because it is a difficult one but one that can be solved.

DR. SMITH: Yes, I certainly support the need for formulations and anything we can do through BPCA or PREA for that.

I would like to get back to the issue of the Written Request and how they are prioritized that a Written Request will be accepted and the negotiation process for the details of what will be in that and the question of how you say that this agent really is a promising agent for all pediatric cancers or a subset of pediatric cancer, and what are the criteria that will be used in reviewing the Written Request that would allow you to say, yes, we approve this Written Request versus, no, there is not a public health concern that is really addressed by this Written Request that is sufficient to provide that exclusivity benefit to the company.

We could talk for hours about what is the target validation, and so on, that would give you

confidence that something really is important for a particular type of cancer, but I think some clarity about what the expectations are for a targeted agent in particular being considered important for one pediatric cancer or more pediatric cancers.

The other area related to that prioritization process to put on the table is at what point do we stop addressing a public health concern when we study a third, or fourth, or fifth, or sixth agent in a class that is addressing VEGF or VEGFR2 or EGF or EGFR? You know, since with almost every target that I am aware of, you know, there are anywhere from several to a dozen companies that have agents addressing that particular class, what are the criteria there for approving the third, or fourth, or fith, or sixth Written Request? Because it is getting to be a real challenge in the pediatric oncology setting of how many VEGF targeted agents can we actually study--I mean, can or should are two different questions. So, those two questions that relate to prioritization I think are ones that will really be

important to address because more than perhaps anywhere else you get what you ask for so it really is important, these prioritization questions.

DR. MATHIS: Just in respect to how many "me-too's" do we look at, we definitely have faced that with other therapeutic categories. I will reflect on the HIV experience for you because initially, of course, we wanted to get as many of these drugs studied as we could but ultimately it turned out that we didn't have enough newborns in the States with HIV to study any longer. We had run out of patients. And, when you divide the patient population up so much with these different drugs, especially when they are "me-too's," you don't ever have one study that is sufficient to determine safety and efficacy. So, I think that it is critical when we are looking at the "me-too's" that we look at particular advantages. Is there an advantage to dosing or side effects? Is there some reason why we have to be compelled to study this "me-too" product in pediatric patients? I think that information is going to have to come from the

oncology community who has experience with these products.

DR. LINK: To return to my list, the timeline, is that appropriate for you? That is okay for you? You don't need help there? Okay.

DR. MATHIS: Yes.

DR. LINK: And could you have help in terms of expanding PREA? Because I view that as a very important way of actually addressing some of our concerns, which is, you know, how do you get the authority? This seems to be the only stick, sort of, that you have. How do you get them to study things which could be and would be important, especially, as was talked about, early phase where you have some clue from a preclinical thing that it might be particularly relevant in pediatric tumor but you would like to get the early phase studies sort of launched in kids sooner? How can that be changed or what can we do to suggest or help that? We have to call our congressman?

DR. DAGHER: I would only want to remind about another aspect that Lisa mentioned in her

talk comparing the two components. In the mandatory component one key exception is orphan designation. So, if you have orphan designation, regardless of whether we can make a scientific determination that the disease exists in both adults and children, regardless of whether we are talking about mechanistic or even histopathologic or combining those criteria, we cannot invoke PREA when there is orphan designation. It is very obvious that in oncology, very appropriately, many of the drugs that are in clinical investigation do at one point in their investigation receive orphan designation for particular populations or indications that are being studied. So, again, we can't comment on what to change or what to change but I am just pointing out another aspect of what the current paradigm is.

MR. HUTCHISON: I am not sure if this appropriate for this conversation but you guys mentioned clnicaltrials.gov. Just from a parent's perspective, I think registration of trials should be mandatory. I think right now it is voluntary

and, as a parent shopping around for clinical trials, it is very tough to figure out what is open and what is not. You go to the major centers, you look at the Texas Children; you look at the CHOP site; you look at Sloan-Kettering. I don't know if that is in the purview of this meeting but I want to mention it. So.

DR. LINK: What I am talking about is that in order to get your paper published now, most journals are sort of mandating that the trial at its inception be registered. So, that is the incentive for the investigator because otherwise most of the major journals will not accept it. I don't think it is a good way of finding a clinical trial for a parent or for a patient. It is just a matter of registering the trial so you can get it published.

DR. SANTANA: Neil, can I add to that and maybe ask colleagues to comment on it, but I thought there were restrictions in terms that when a sponsorB-let's not talk about pediatric studies for a minute, but when a sponsor is doing trials,

seeking an indication, that is all confidential information. Those trials are not disclosed until the drug is approved for the indication. So, aren't there confidentiality issues of tying studies to publicly designated Written Request studies that the public could have access to?

DR. MALDONADO: Actually, I cannot speak for the entire industry but I know that PhRMA has advised companies to make it public. Some companies, including J&J, have made it a policy that all our trialsB-allB-will be published.

DR. SANTANA: Correct, but what I am addressing is the issue that this is a BPCA Written Request sponsored trial, that designation, so that people can search and find those trials specifically that are tied to a Written Request. See what I am saying? You are publishing everything. I am trying to address the issue of identifying those trials that are part of this process.

DR. MALDONADO: Yes, I am not aware that they identify.

DR. MATHIS: Yes, I don't know how you would specifically identify it either, but I do know that in our template language of the portions of the Written Request that are consistent, at the end of the Written Request it does notify the sponsor that if the drug is being used for a life-threatening condition it must be registered with clinicaltrials.gov. But, again, I don't know that there is any way to search for those specifically.

DR. WEISS: Mike, your comment about expanding PREA is very interesting. When this legislation was being proposed in the late '90s there were these two very polarized camps where the industry group felt that the agency was way overstepping our bounds in mandating studies. You know, that it was just completely inappropriate and it was going to lead to all sorts of liability issues, etc. Then, in the other camp, the advocacy community basically said this legislation didn't go far enough. So, it is typical, you know, of anything in government. Things are oftentimes a

compromise between two very polarized camps.

So, I mean, I think your comments are very interesting and certainly, you know, I am sure that there are groups that are very interested in looking to see. I mean, I have heard the comment that PREA hasn't gone far enough in terms of what is being mandated. So, you know, just a comment sort of on the history of how this all evolved over ten years ago. There were these huge knock-down, drag-out fights between very opposing groups on this legislation.

DR. SMITH: Just in terms of early access and something that was said earlier, I think just the BPCA and PREA as they exist now and putting pediatrics on the radar screen early really has made a huge difference. So, you know, there clearly can be advantages to some of the things that have been discussed today but I think there has been a huge difference in terms of access. Just as an example of that, I am the project officer at NCI for the pediatric preclinical testing program, and we have companies now call us

with agents that are early in development, and we can do preclinical testing while the agent is going through its initial adult Phase 1 studies and really be planning to have a pediatric study ready to open when there is a dose and schedule that is sufficient, when there is enough safety data to proceed with that.

So, I think, you know, there will be more than one example of that process of playing out and I think it is in a large measure the result of pediatrics getting on the radar screen from BPCA and PREA that we are getting those kinds of calls and getting that kind of interest in the program.

DR. LINK: Peter?

DR. ADAMSON: Yes, I wanted to follow-up on what Susan brought up a little bit earlier as far as how we can improve the process. I think formally setting up a process that is going to address, one, feasibility and, two, importance would be helpful. I think you need a small working group of people who know the specific area before you issue a final Written Request as part of that

process. I am not saying it is the same group of people for every Written Request, by any means, but people who know, okay, this is the landscape. What you are asking for should be feasible and, secondarily, we agree it is important. I think we can learn from the carboplatin experience that we don't want to repeat-Bagain, I don't want to put that out there, you know, hindsight is 20/20; I recognize that. We want to learn from that experience and other experiences. But I don't think we would expect the agency to do that independently. I mean, there are a lot of factors that come into play and you have a pediatric oncology community that wants to act in the best interests of children. Let's leverage that relationship and we want to work closely with industry too.

DR. LINK: Have we given you any help? Go ahead, Naomi.

DR. WINICK: Just a quick comment. In Dr. Santana's presentation he mentioned, with respect to carboplatin and perhaps another agent, that

exclusivity was granted because data were submitted even if the data weren't particularly perfect. Is there an additional incentive that could be awarded if the data are usable? Forgive my use of that word.

DR. DAGHER: The current mechanism is obviously limited to just whether or not you have submitted the data and the reports based on what the letter outlined. Now, in the case of carbo, Dr. Santana mentioned the issue about the AUC and how many patients did not achieve the target AUC. I am not even sure, given that 90-day time frame, whether we knew at the time of the exclusivity determinationB-we also had not come to all those conclusions about the interpretation of the data at that point. That happened as the review was ongoing.

Now, can I say that the exclusivity determination would have been different if all the review processes had been completed? We don't know that. The other point here is that the body within FDA that makes the determination about exclusivity

is not the division that is going to make the decision about what goes in the label or not. So, the particular division that is reviewing the information and the office involved will make the decision about the ultimate labeling. But the exclusivity determination is made by a body within FDA, called the Exclusivity Board, and Dr. Mathis can tell you more about that. Of course, they make that determination based on our recommendation and, again, our recommendation is based on everything we know at the 90 days. So, maybe you want to talk more about the Board.

DR. MATHIS: People keep bringing up the time frame for determining exclusivity versus how much time we have for approval and I think both industry and FDA have said we wouldn't be bothered if we had more time. I will just put it that way. Industry really doesn't mind one way or another because the exclusivity attaches to the end of whatever they have existing anyway so they don't necessarily need to have it by three months.

That being said, just talking about the

process, the way the system is set up now the responsibility of asking for and obtaining good studies is on the FDA. We issue the Written Request and we are getting better. Initially we were new at the process, as was everybody else, and we maybe asked for things more vaguely or imprecisely or didn't understand the pitfalls. So, some of the earlier studies that did come in, many did meet our expectations; some fell short of our expectations because we didn't clearly iterate exactly what we needed. Again, we are learning from that process. And, I think at this point in the game, rather than looking towards legislation to improve the process, I think that we need to look internally and I think it is a great idea that we involve other experts. We have to look at ways for improving our process because I don't know that increased legislation would make the process work better. We have to improve our process, and that is really why it is so critical that we get your input.

DR. LINK: We do need to break for lunch.

Is this a short comment, I hope?

DR. FINKELSTEIN: A short comment, getting back to labeling. It seems to me that in the pediatric oncology arena we are concerned that our studies are ongoing. I heard a statement saying that the owner of the label is really the industry. So, my question is between FDA, maybe the community and industry can we not have a phrase in there indicating that ongoing studies may actually either show efficacy, or there are ongoing studies regarding this agent that leaves it open to the fact that life is changing all the time versus closing, say, a door on topotecan?

DR. LINK: Well, I think life is always changing. We could put that on the label--

[Laughter]

DR. FINKELSTEIN: I think industry and the FDA could come up with a phrase that is comfortable for industry. Since they own the label it actually would be to their advantage.

DR. LINK: Well, that is true with adult studies too. I mean, I don't know that that is

unique to pediatrics.

DR. FINKELSTEIN: Well, it is unique to oncology in some respects.

DR. LINK: We do have to break for lunch because we have an afternoon session. So, I am supposed to summarize a couple of points here.

DR. WEISS: Can I just ask, I mean we do actually have some flexibility in time. These were just our best guesstimates but, you know, you can have a shorter lunch. Sorry!

DR. LINK: For one thing, as the chairman, I can go home and talk to my wife.

DR. WEISS: Right. I know you have been in town for a long time now. There are a couple of things that we asked in our questions, and you have addressed a good number of them. I really have taken a lot of notes about this. In terms of the types of studies, and maybe we don't have the answers yet but we have sort of one the "same old, same old." I mean, the general paradigm has been, you know, to do some Phase 1 looking at MTD, doing some Phase 2 in a number of different solid tumors

and patient groups and potentially some leukemia because you don't exactly know what you are looking for, and maybe down the road when we know better about molecular pathways that will change and be more focused, but that has been sort of the standard mantra thus far, you know, in the genesis of the Written Request and in the information that comes out. It tends to be, as I think you summarized earlier, that it hasn't led to anything in terms of meaningful in terms of showing that there is some real activity in the particular pediatric specialty.

So, I don't know, maybe this doesn't have an answer yet but, you know, I have heard some complaints that maybe we could be more clever, creative in the kinds of studies we ask for but, of course, you know, we are sort of limited by our knowledge base right now. So, anything that anybody can comment on with regard to that, that is one question.

Then let me ask this question because it is something that Victor had put up in his last

summary slides about how do we measure success. What we have now is sort of a summary of the last ten years or so where we are with oncology. We are talking about re-authorization. We all think it is, you know, happening. So, at some point, whoever is left at the agency five years from now to reassess the next five years at that point, what would you consider measures of success for going forward?

DR. SMITH: I do think one key issue is maybe it is not all of rhabdomyosarcoma; it is a subset of that, and increasingly it will be it is not all of ALL; it is a subset of ALL. Again, I think the science is driving this in adult cancers to defining populations that are more likely to be responsive and I think we should be really applying that same level of science to the pediatric populations to identify populations that are most likely to respond. So, that is a key innovation, more effectively identifying the population.

Then I think knowing the single agent activity for that population in general will still

be an important question to address, and we have Phase 2 designs for that. The randomized Phase 2 studies that we are doing more and more of can be considered but it gets to what Peter was saying earlier about feasibility. You know, there is a very limited number of randomized Phase 2 studies that we can do for any given childhood cancer in the recurrent disease setting because of patient numbers. So, I think if those are going to become part of Written Requests, then there is going to have to be close consultation about the feasibility of how many of those studies can be done.

DR. MORTIMER: I guess my concern as a purely adult person is that the endpoints in adult oncology have shifted. So, the sort of paradigm of using progression-free survival and time to disease progression no longer exists. So, I think about using drugs like cerafinib and bevacuzumab, all these new biologics, in the pediatric population and you have no idea of what the endpoints are because endpoints prolong survival without any change in tumor size. So, I guess at the heart of

this is that the Pediatric Rule does not have enough patients to answer these questions and, yes, it is great to think about biologics but we haven't done that well in adult diseases in which there are plentiful patients. So, is there a creative way to use the international community, to use Canada so that you can get the denominator because that is what you guys really need here?

DR. LINK: I think Ramzi was hinting at that earlier.

DR. ADAMSON: I can try to partly address that but then I am going to come back to Canada. That is, I think when we talk about efficacy we, as the pediatric oncology community, have to think beyond the standard CR/PR but we have to be careful, and I pointed this out before. You can always tell the difference between a pediatric Phase 3 trial and an adult Phase 3 trial. If you look at the X axis, hours in pediatrics is years; the adults are weeks. So, we do have different goals.

But I will point out I think it was

cerafimib that received approval on a Phase 2 100-something patients. Which one was it? So, we can do those studies but, you are right, we are not accustomed to doing those studies and we have to think differently.

Now let me come back to your question and the theme I think has emerged from a number of others, coming back to formulation. Should that be a part of Written Requests? One proposal might be okay, if you are second or certainly third in your class let's get a formulation out of you and, in fact, if you get a formulation and PK, well, you know, we have another agent in the class looking at Phase 2. We don't need five Phase 2 studies of "me-too's" but it would be a real advance to have a formulation. You don't want to set the field back by saying if you are first in a class we are going to wait until you have a formulation because we don't really know if it is going to be of value. But when you are second or third maybe the requirements look a little different. Get a formulation, get PK and safety. The data will

emerge from another in that class but you will get exclusivity because you went the extra step and got the formulation. That might be a way to meld some of the discussions that are going on here as far as moving forward.

DR. BLANEY: Karen, I was just going to say this isn't a measure of success that you can quantitate, but the fact that our ability to get drugs into the preclinical screens earlier and the fact that it is not always us out there begging, which we still are doing but industry is coming to us in some circumstances, and the fact that we are having discussions about "me-too's" because many "me too's" do want to be the one to have exclusivity and we are not going to be able to do all of that, so those are not measures of success that you can quantify but we have seen progress.

DR. RICHARDSON: I wanted to just comment on a couple of other remarks, some of the things that Joanne said for example. You know, if you look at the history of clinical trials, at least in the adult population, it seems to be oriented

towards identification of active drugs in patients with advanced metastatic disease and then application of these drugs to an earlier clinical setting and finally into the adjuvant setting. We are now seeing the same sort of thing happening with these targeted agents as well. We are seeing that with, for example, imatinib as an adjuvant in gastrointestinal stromal tumors. That was just approved and seemed to be quite active.

When you look at some of these comounds, these various VEGF inhibitors, tyrosine kinase inhibitors, compounds like cerafamib, and if you look at drugs like lenolinamide some of these, in theory at least, would seem to pose special problems or risks to growing children, particularly if they are given for a year or two. If one is looking at this class of compounds in this patient population, should the agency require some sort of long-term toxicity studies, and does that become a disincentive to do this type of treatment?

DR. LINK: No answer from the FDA?

DR. WEISS: We are just saying that that is

always important and, you know, certainly in pediatrics as everybody, I am sure, at this table knows, there are all these groups that are involved in late effects, long-term effects. It is a very, very avid, busy area in pediatric oncology. But I am just sort of thinking that, you know, now everything is all kind of a one fell swoop but we need to think creatively about how to sort of separate out, as I think was mentioned earlier, different parts of the Request so that we get the primary data in first and then have some kind of follow-up information. We just have to think creatively as to sort of how to phrase those and how to collect that information.

DR. REYNOLDS: I guess the question that was sort of proposed here is what kind of metrics of success you could measure, I think is what you are looking for. I know that a couple of years ago when we were talking about the problems of getting drugs early into children, several of us all came up with the same number. I think Peter had seven years and Susan had seven years and we had the same

number ourselves. An average time of when you started in humans to when we saw it going into children was about seven years in the old days. I think we would all agree that that has gotten better. I would think that we may be able to measure that as a metric because it is a complex process, but the real question is if it is an interesting agent, if it is an agent that was useful in children, how quickly is it from when it first gets into human studies does it then enter into pediatric formal studies?

DR. WEISS: That would probably a very interesting research project when Victor comes back to do another sabbatical in a couple of years.

DR. LINK: Well, I think we are about ready for lunch. We hope we have been helpful but I think that what we have heard, at least in summary, from Victor's report card is that these two laws have been helpful; that there is a lot of information that we have learned, not efficacy necessarily but certainly how the drug should be given; and I think, more importantly perhaps, that

pediatrics is on a radar screen somewhere so people are much more attentive.

I think one of the most important things that you have heard is related to the design of the Requests, and I think that what you are hearing, hopefully loud and clear, is that there is a willingness on the part of people in the community, represented by the people at the table here, to participate or help FDA sort of figure out what should be in that; what should the design look like; what else is out there that may be relevant; what are the pathways that may be of interest. So, I think there should be some more interaction with the people that are in the field that are actually doing this.

I think we heard about formulation. I don't know what you can do but, you know, it is wonderful to tell us that you want to do a trial but it is not feasible because kids barf up pills. I am not sure I got the message about this timeline. Everybody shook their heads, no, 90 days is enough and then you went and said, well,

everybody says that a little more time would be more helpful. So, I think we should recommend that 90 days may be a little tight for you.

We all know now that what the label says is not the final word, that life is changing all the time so we have to keep that in mind, and what is on the label does not necessarily reflect the latest data and we should be aware of the fact that it certainly doesn't reflect the negative studies that don't get published. So, I think it was an appropriate word of caution. Mostly, I hope that this discussion has helped address some of those things for you.

Now we are going to adjourn for lunch and I don't know when we are coming back for session II.

DR. PHAN: Before we break for lunch, I am reminded that in the spirit of federal Advisory Committee Act and the Sunshine Amendment, we ask that the advisory committee members take care of their conversation about the topic at hand in an open forum of the meeting, and to refrain from

discussing the meeting topic during breaks or lunch.

[Whereupon, at 11:50 a.m., session I of the proceedings was adjourned for lunch, to reconvene in session II at 12:30 p.m.]

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A F T E R N O O N P R O C E E D I N G S

SESSION II

Call to Order and Introduction of Committee

DR. LINK: Let me call this session to order on the Best Pharmaceuticals for Children Act as it pertains to drugs that are off-patent, I believe. So, we are going to hear a presentation about that to educate us. I think we all learned something this morning, a lot this morning. Then we are going to actually discuss retinoic acid in that context.

We have to go around the room again and we will believe, I guess, with Patrick. Introduce yourselves and your affiliation and your specialty.

DR. REYNOLDS: Pat Reynolds, Developmental Therapeutics, Children's Hospital Los Angeles and University of Southern California.

DR. SCHWARTZ: Cindy Schwartz, pediatric oncologist from Rhode Island University and Hasbro Children's in Providence, Rhode Island.

DR. RICHARDSON: Ron Richardson, medical oncologist, May Clinic, Rochester, Minnesota.

MS. HAYLOCK: Pamela Haylock, oncology nurse, University of Texas Medical Branch in Galveston.

MR. HUTCHISON: Neil Hutchison. I am from San Diego, California and I am the parent to a relapsed neuroblastoma child.

DR. MORTIMER: Joanne Mortimer, University of California, San Diego, medical oncologist.

DR. PHAN: Mimi Phan, acting designated federal official.

DR. LINK: I am Michael Link. I am a pediatric oncologist from Stanford.

DR. SWISHER: Loice Swisher. I am a parent of a brain tumor child.

DR. SMITH: Malcolm Smith, pediatric oncologist, NCI.

DR. WINICK: Naomi Winick, pediatric oncologist, UT Southwestern.

DR. FINKELSTEIN: Jerry Finkelstein, pediatric oncologist, LA area.

DR. WEISS: Karen Weiss, pediatric oncologist, Office Director, Office of Oncology

Drug Products at FDA.

DR. DAGHER: Ramzi Dagher, a medical team leader in the Division of Oncology Drug Products, FDA. I am pediatric oncologist.

DR. ZAJICEK: Anne Zajicek, pediatric clinical pharmacologist, NIH.

Conflict of Interest Statement

DR. PHAN: Conflict of interest statement for the meeting of Pediatric Subcommittee of the Oncologic Advisory Committee: This is June 27, 2007. The topic for this afternoon session is 13-cis-retinoic acid.

The following announcement addresses the issue of 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 respect to FDA's invited industry representative, we would like to disclose that Dr. Samuel Maldonado is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Maldonado's role on this committee is to represent industry interests in general and not any one particular company. Dr. Maldonado is employed by Johnson & Johnson.

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.

DR. LINK: Dr. Pazdur, you have to introduce yourself.

DR. PAZDUR: Richard Pazdur, Office Director, Oncology Drug Products.

DR. LINK: Thank you. On the agenda today we have a presentation about the further development of drugs that are off-patent. Then we will have presentations by two investigators who are experts in the management of advanced stage neuroblastoma, particularly with the use of cis-retionoic acid. So, why don't we begin with a presentation to set the stage for this afternoon's meeting.

The Best Pharmaceuticals for Children Act

DR. ZAJICEK: Good afternoon.

[Slide]

I appreciate this opportunity to talk about what we are doing at the NIH.

[Slide]

I am going to skip through the first few slides but what I wanted to focus on is exactly what the NIH is doing. As Lisa Mathis had mentioned this morning, the original FDA Modernization Act did not have a role, or there

wasn't any possibility of doing anything with off-patent drugs. So, the BPCA of 2002 attempted to fix this. The NIH's role here is to not only perform the off-patent drug studies and some on-patent drug studies, but actually to prioritize drugs for listing, which is in part what we are doing here today.

[Slide]

So, the NIH is responsible for putting together a master list of all off-patent drugs which lack pediatric labeling. This tends to be in the neighborhood of somewhere around 200 drugs which don't have any exclusivity protection and which lack pediatric labeling.

The legislation was very nice in discussing exactly how we were to go about prioritizing these drugs and they had four comments to make. Number one, is there available safety/efficacy data? In other words, if the data already exists and we could get the data by some means and presented to FDA we would not have to repeat a clinical trial. So, number one,

availability of safety/efficacy data. Number two, are additional data needed? Number three, will new studies produce health benefits? Number four, will the drug need to be reformulated or does it need to be reformulated?

One of the issues about these health benefits and how we have been prioritizing is the question of severity versus frequency. For example, should we be studying drugs for very high frequency conditions only? In that case, we would only be studying drugs for otitis media. On the other hand, if we are studying drugs for severe diseases, then pediatric oncology would obviously be the choice there. So, when I go in the next few slides about the drugs that are prioritized I will show you that we sort of have a fairly large sampling of drugs for high frequency conditions, high severity conditions and somewhere in between.

The issue of reformulation has come up today. We have been talking a lot about it at NICHD as well. We have put together a pediatric formulation initiative. One thing I should

mention, which I didn't realize about the reformulation is that Dr. George Giacoia in my Branch put together this very nice meeting, about a year and a half ago, with many experts to talk about the formulation issues and, you know, as an American and as a pediatrician, I think of a liquid formulation as being great, a perfect solution but for people that were in this meeting from Third World countries, developing countries, the water is contaminated and you can't drag gallon jugs of stuff across the Sahara Desert. So, there are other issues in reformulation, aside from just trying to get something in a liquid formulation, an alcohol solution, an elixir, a water solution, meaning coming us with some sort of formulation where there might be some sort of, you know, small pellets where you would be able to make sure you had the right dose and that it was stable and didn't require refrigeration, for example. So, there are all kinds of other issues besides making things into a liquid for a formulation.

So, at the end of the day we prioritize

and publish an annual list in the Federal Register, but we do it in combination not just with people at the NIH and the FDA but in consultation with other people at the NIH. At the NIH there are 27 institutes and centers, including the National Cancer Institute, the National Heart, Lung and Blood Institute, and so on, and we talk with them, and other federal agencies. As I said, the FDA obviously, the Centers for Disease Control and Prevention, pediatric subspecialists like yourself, as well as advocacy groups. So, at the end of this meeting, if you would like to tell me about some drug that you feel strongly about should be prioritized, and this is how 13-cis-retinoic acid got on our priority list that I will get to, please let me know because we are certainly interested in knowing if you, as advocates or oncologists, have any other drugs that you feel should be developed for children.

[Slide]

I won't read through this laundry list but in the legislation we are responsible annually for

publishing this prioritization list. The original list focused a lot on neonatology so azithromycin for treatment of chlamydia; treatment of ureaplasma urealiticum and the possible cause of bronchopulmonary dysplasia was listed. BaclofenB-there is an asterisk after baclofen and the reason is that baclofen originally was off-patent. Then an immediate-release formulation became available and so the patent status was changed from off-patent back to on-patent because of this formulation change. It is my understanding, however, that this new immediate-release formulation actually is not available, and the same thing with metoclopramide, when we get there.

Other drugs listed are bumetanide for treatment of BPD, dopamine, dobutamine, furosemide also for BPD, lithium for acute mania, lorazepam, rifampin, sodium nitroprusside, spironolactone.

[Slide]

The second year, another assortment of drugs for various indications.

[Slide]

Then, in 2004 we have our first list of drugs for oncology. Here we have vincristine, actinomycin-D which we have ongoing projects with which I will explain in a minute.

[Slide]

Another list of drugs.

[Slide]

In 2006 we started thinking about this because we were coming up with drugs to study but part of the issue is you really want to see what conditions are important and then think about maybe studying drugs, maybe comparing one drug to another drug, and so on. So, we made a change. We are still listing drugs but we are taking into consideration the conditions for the drugs.

So, the first condition was for ADHD and then hypertension which has become a huge problem, parasitic diseases, influenza, cancer, methotrexate and daunomycin were listed that year, for poisonings pralidoxime and sickle cell anemia and, in particular hydroxyurea.

[Slide]

In 2007, another list of conditions including infectious diseases such as methicillin-resistant staph infections, and the drugs listed this year included clindamycin the, tetracyclines and trimethoprim-sulfamethoxazol; hypertension; neonatal research; cancer. We have listed this year 13-cis-retinoic acid which is, again, the purpose of this afternoon's conversation; and asthma.

[Slide]

Now, this is the pathway. So, once we come up with this drug list that gets published in the Federal Register, then that list comes back to the FDA and the FDA, with some comment with us, creates a Written Request which, again, is just a letter to the NDA holder explaining what kind of studies the FDA would like to see for pediatrics. The Written Request is sent to the holder of the new drug application and for on-patent drugs they have 180 days to decide whether they want to accept or decline. Then, at the end of the 180 days,

rather than this Written Request going directly to us at NICHD, it goes to the Foundation for the NIH. Now, the FNIH, the Foundation for the NIH, is not the NIH. It is an organization that collects private funds in order to fund some activities at the NIH but it is not the federal government.

[Slide]

This is in contrast to the off-patent trajectory. So, the Written Request is written by the FDA. It goes to the holders of the new drug application and/or the abbreviated new drug application, the aNDA. So, these are the primary manufacturers and the generic manufacturers. In this case, they have 30 days to accept or decline the Written Request. At the end of the 30 days the Written Request comes to us, to NICHD.

The way that we have been funding these in the current legislation is under contract. Now, the NIH has three ways to fund thingsB-well, sort of two. So, there are grants; there are contracts. There are general grants, like you are an investigator and you have a good idea; you get a