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FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ONCOLOGY SUBCOMMITTEE
OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE

SESSIONS I & II

Wednesday, June 27, 2007

8:20 a.m.

5630 Fishers Lane
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PAPER MILL REPORTING
Email: atoigo1@verizon.net
(301) 495-5831

PARTICIPANTS

SESSION I:

Michael P. Link, M.D., Acting Chair
Mimi Phan, Pharm.D., R.Ph.
Designated Federal Official

Samuel Maldonado, M.D., Industry Representative
Pamela Haylock, M.A., R.N.
Consumer Representative
Neil A. Hutchison, M.B.A.,
Patient Representative
Loice A. Swisher, M.D., Patient Representative
Cindy L. Schwartz, M.D.
Ronald L. Richardson, M.D.
Joanne E. Mortimer, M.D., F.A.C.P.
Malcolm Smith, M.D., Ph.D.
Naomi J. Winick, M.D.
Jerry Z. Finkelstein, M.D.
Peter Adamson, M.D.
Susan Blaney, M.D.
C. Patrick Reynolds, M.D., Ph.D.

FDA STAFF:

Victor Santana, M.D.
Karen Weiss, M.D.
Lisa L. Mathis, M.D.
Ramzi Dagher, M.D.

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SESSION II:

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Jerry Z. Finkelstein, M.D.

FDA STAFF:

Victor Santana, M.D.
Karen Weiss, M.D.
Richard Pazdur, M.D.
Ramzi Dagher, M.D.
Anne Zajicek, M.D., Pharm. D.

C O N T E N T S

SESSION I

C O N T E N T S (Continued)

SESSION II

P R O C E E D I N G S

SESSION I

Call to Order and Introduction of Committee

DR. LINK: Let me call the meeting to order. We are missing a couple of people but I hope that they will show up in short order but I would like to get going. Let me begin by having Mimi sort of read the conflict of interest statement. Before we do that, let's go around the room and have everybody introduce themselves. Ramsey, do you want to start?

DR. DAGHER: I am Ramzi Dagher. I am Medical Team Leader in the Division of Drug Oncology Products at FDA and I am a pediatric oncologist by training.

DR. MATHIS: I am Lisa Mathis. I am in the Office of New Drugs at CDER and I am Associate Director for the Pediatric and Maternal Health Staff. I am a general pediatrician.

DR. WEISS: I am Karen Weiss. I am the Deputy Director of the Office of Oncology Drug Products at CDER, FDA and I am also a pediatric

oncologist.

DR. SANTANA: Good morning. I am Victor Santana, a pediatric oncologist from St. Jude, in Memphis, and I have been a Washingtonian this past year.

DR. FINKELSTEIN: Good morning. I am Jerry Finkelstein. I am a pediatric hematologist/oncologist from the LA area and UCLA. I am also probably the senior person here because I think I was here for the very first meeting and most of them ever since.

DR. SMITH: Malcolm Smith, from the National Cancer Institute and a pediatric oncologist.

DR. Swisher: I am Loice Swisher, one of the patient representatives. My daughter a medulloblastoma back in December, 1999.

DR. LINK: I am Michael Link. I am from Stanford.

DR. PHAN: Mimi Phan, designated federal official.

DR. MORTIMER: Joanne Mortimer, University

of California San Diego, medical oncologist.

MR. HUTCHISON: Neil Hutchison, San Diego, California. I am the parent of a child with relapsed neuroblastoma who is currently doing well. Thanks.

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

DR. ADAMSON: Peter Adamson, the Children's Hospital of Philadelphia, pediatric oncologist and clinical pharmacologist.

MS. HAYLOCK: Pamela Haylock, oncology nurse, University of Texas Medical Branch, and I am the consumer representative.

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

DR. SCHWARTZ: Cindy Schwartz, pediatric oncologist at Brown University and Hasbro Children's.

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

DR. MALDONADO: Sam Maldonado, pediatric drug development at Johnson & Johnson and the industry representative.

DR. LINK: Thank you very much. Is there somebody on the phone now? Sometimes there is, and they can only hear you if you use your microphone so, please do so and make sure your red light is on. Make sure you tap it and make it work. Now we will have the conflict of interest statement.

Conflict of Interest Statement

DR. PHAN: The conflict of interest statement for the meeting of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee today, June 27, 2007. 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. This meeting is being held by the Center for Drug Evaluation and Research. The Pediatric Subcommittee of the Oncologic Drugs Advisory Committee will meet in an open session to discuss a review of oncology products granted pediatric

exclusivity under the Best Pharmaceuticals for Children Act.

Unlike issues before a committee in which a particular product is discussed, issues of broader applicability, such as the topic of today's meeting, involve many industrial sponsors and academic institutions. The committee members have been screened for their financial interests as they may apply to the general topic at hand. Because general topics impact so many institutions, it is not practical to recite all potential conflicts of interest as they may apply to each member.

In accordance with 18 U.S.S. 208(b)(3), full waivers have been granted to Dr. Joanne Mortimer and Dr. Peter Adamson.

Waiver documents are available at the FDA's dockets web page. Specific instructions as to how to access the web page are available outside today's meeting room at the FDA information table. In addition, copies of all the waivers can be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30

of the Parklawn Building.

FDA acknowledges that there may be potential conflicts of interest but, because of the general nature of the discussions before the committee, these potential conflicts are mitigate.

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 FDA participants have a financial interest, the participant's involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with

any firm whose product they may wish to comment upon.

DR. LINK: We will proceed now with opening remarks by Dr. Weiss.

Opening Remarks

DR. WEISS: First of all, I want to thank everybody for coming, and I really apologize for the heat and humidity. I had nothing to do with it. It was really beautiful last week but this is very oppressive. Those of you, I guess, who are from Texas and other places south probably this is no big deal, but this is miserable and I am sorry for that, and I am glad you are all here anyway and, hopefully, will be cooled off.

This morning's discussion is going to be on BPCA. First you will hear an overview of the legislation from Dr. Lisa Mathis, in the Office of Pediatrics. It is sometimes a little confusing and I know people have lots of questions not only about BPCA versus PREA, etc. so there should be opportunity to ask questions and try to clarify this if there are still outstanding questions after

the presentations.

But we chose the topic of BPCA for pediatric oncology specifically because it has been ten years since exclusivity provisions first came into effect, probably a little less than ten years though since we really started gearing up for pediatric oncology-related exclusivity and tried to really articulate I think what we would like our companies to do with respect to studies that might be appropriate for exclusivity. But it seemed like an opportune time to review BPCA, particularly as new legislation is going on currently in Congress for re-authorization.

So, we would really like your input, once you hear the overview about the legislation and then a more detailed discussion from Dr. Victor Santana who, as you heard, is a pediatric oncologist but has been a visiting scientist guest worker with the FDA for this past year and has been extensively looking at those drugs that have been granted exclusivity for pediatric oncology indications. Once you hear those presentations, we

would then like your feedback and input to what you think of the process thus far; how you consider success; and your suggestions for how FDA could think about making this better as we move forward in the next sort of rounds of exclusivity.

With that, I will turn this back over to Dr. Link to begin the meeting. Thank you very much.

DR. LINK: I think you have heard our charge, which is to talk about some of what has happened under the exclusivity, and you can maybe perhaps turn to the questions on the page after the agenda just to get an idea of what is expected in terms of what we would like to focus on, as you can see, looking for limitations for strengths and weaknesses of approaches thus far under the BPCA. Again, as you have heard from Karen, what are the things we view, particularly as pediatric oncologists, but as advisors here as ways that this could be improved. Of course, this is really important timing because of the fact that this is being negotiated now as the legislation is going

forward.

So, perhaps we can hear an overview of the legislation as it stands from Dr. Mathis.

Pediatric Oncology and the Best Pharmaceuticals for Children Act

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DR. MATHIS: As we mentioned earlier, we are going to talk about the Best Pharmaceuticals for Children Act this morning. It is impossible to talk about the BPCA without also talking about the Pediatric Research Equity Act. Those are two pieces of legislation that are really the pillars that hold up drug development for the FDA and for the United States, and we are actually very fortunate that we have these two pieces of legislation because they have done a tremendous amount for drug development and pediatrics.

As Dr. Weiss mentioned, these two pieces of legislation are sunsetting or ending October 1st, 2007 so we are in the process of re-authorization and it has been a very complicated process for both industry and FDA, as I am sure Sam can attest to.

So, as we move forward, one thing that we really want to do is to get some input from this community about how to make things better. We have actually been able to touch base with people who have their hands in the research, like Dr. Smith and other people who have some ideas about how to improve this process. And, we think we already have a couple of key pieces of improvement in the legislation that will help us specifically with oncology.

But right now I am going to give an overview and Dr. Santana will give a more precise picture of what has been happening over the last ten years.

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Again, I am going to review the pediatric legislation. I will be focusing on the Best Pharmaceuticals for Children Act but, again, I can't talk about this piece of legislation without also addressing the Pediatric Research Equity Act. We are also going to describe the BPCA on-patent process and this afternoon Dr. Zajicek, from the

National Institute of Child Health and Human Development, will give an overview of the off-patent process. Then, we are going to talk briefly about the results from the BPCA but, again, Dr. Santana is going to give oncology-specific results.

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The BPCA is a voluntary program. It was singed into law in January of 2002 and, in essence, brought back to life the exclusivity provision that first came to be under the Food and Drug Administration Modernization Act. This exclusivity is six months of marketing protection. In essence, it blocks the generics from coming on the market. Financially it is a very good incentive for sponsors to study drugs in pediatric patients.

Our mandatory program is the Pediatric Research Equity Act which was signed into law in December of 2003. It kind of resurrected the Pediatric Rule which had been enjoined by the courts in 2002.

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Again, as I mentioned earlier, the BPCA actually renewed the exclusivity provision under FDAMA and that is a very powerful incentive for the study of drugs in pediatric patients.

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Under BPCA, if a drug has patent life or any exclusivity so it is an orphan product or a new molecular entity and has some kind of marketing protection, the FDA can issue what is called a Written Request, or you often see it abbreviated as a WR, for clinical studies. That is a key point to make. The way the legislation is written right now it has to be for clinical studies in pediatric patients. So, under the current law we cannot ask for studies in adult patients and we cannot ask for preclinical studies, although oftentimes we make preclinical studies or adult studies a prerequisite before the sponsor can move into the pediatric population.

If the requested studies are conducted in the exact manner that we request in the Written Request, then the sponsor submits the studies. We

look at the results; compare the results line by line with the Written Request and determine whether or not the sponsor met the terms. If they did, they get six months of marketing exclusivity, or blocked generics for six months.

The timelines for this exclusivity granting and approval of a product are very different. Under our regulations new drugs that come in have an approval clock of ten months unless they are qualified as priority reviews, and oftentimes oncology drugs are because they are life-threatening conditions. A priority drug review time clock is six months. Also, under the Best Pharmaceuticals for Children Act any supplement, so if there is already an approved drug and they do additional studies and they come in with a supplement, any supplement has a six-month review clock. So, exclusivity is actually granted 90 days so before we have time to do the entire review we have to make that decision about whether or not we are going to grant exclusivity. So, the exclusivity occurs at three months or 90 days and

the approval occurs at either six months or ten months.

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The BPCA also provides us a mechanism where we can work with the NIH to obtain studies for off-patent drugs, and this was an improvement over FDAMA because under FDAMA there was no incentive or path forward to study off-patent drugs and, as you know, many of the older drugs are used in oncology so it was very important for us to get some fine-tuning on dosing and administration of those drugs.

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Anne Zajicek is going to cover that stuff in detail so I am going to launch into our on-patent process. As I mentioned earlier, in order to get exclusivity a sponsor first has to obtain a Written Request. The Written Request is a legal contract in a sense and it includes different components, including an indication or condition that needs to be treated; the study types, specifically if we want it double-blind, randomized

or if it is open-label; if it is a PK study versus safety and efficacy. We also ask for specific statistical information that is appropriate for the type of study that is being requested. We tell them exactly what formulation and dosing we want them to use. Some of the times that statement just says whatever you determined in the earlier phase studies. We also ask that they monitor a specific safety signal. So, if we know a particular drug has certain problems with kidneys or liver, hearing, vision, we ask them to monitor those specific issues during the trial.

We also ask that when they submit their submission they propose labeling. This is another area where pediatric drug development under BPCA and PREA is very different than adult drug development because for adults if a sponsor does a study and does not have positive findings frequently you will never see that stuff in labeling. But it has been our experience that this may be our only chance to get studies in pediatric patients so even if studies are negative, even if

they show the drug didn't work, we include that information in labeling because we think it is critical that the only piece of pediatric information that is going to be obtained gets into labeling.

We also tell them how they need to format the studies and what time they need to submit the studies by. So, if you have a Written Request and you do the studies and you don't submit the studies until the day after the date in the letter, you missed your opportunity.

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In oncology we also have a different format for Written Requests in that we actually do Phase 1 dose-finding and pharmacokinetics in the templates. So, oftentimes what will happen is that they will do the Phase 1 studies and determine that they can't move on and the sponsor can still qualify for exclusivity. That is a little bit different than with the other drugs because often in the other drug categories we don't let them do the preliminary test first. They have to do the

whole thing. We also have Phase 2 or pilot studies in these Written Requests, which is not common for most other drug categories.

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So, this is the process for the study of on-patent drugs. First industry submits what is called the Proposed Pediatric Study Request, or a PPSR, so they get the ball rolling. They come in with their idea about what they want to have studied. Conversely, we can actually determine independently what we want studied and can issue a Written Request without the request of the sponsor.

Also, the FDA will look at the studies that have been submitted and try and determine if there is a significant public health benefit. If there is, then we will go ahead and issue a Written Request. Now, frequently the Written Request may not look like what the sponsor has submitted. The sponsor may submit the PPSR and then the FDA gets into extensive discussions with researchers and the drug company in order to figure out the best path forward and, again, that may be very different than

what the sponsor initially has proposed.

After 180 days of having a Written Request the sponsor has to let us know if they intend to do the studies or not. If they intend to do the studies they move forward. If they tell us no, then we can actually refer the Written Request to the Foundations for NIH, which is a private group associated with NIH, and they will fund these studies for the on-patent drugs. Now, the off-patent drugs, as Dr. Zajicek will tell you later today, go directly to NIH. One of the provisions in the law is that if the FNIH does not have sufficient funding to conduct these studies, they can then refer the Written Request on to NIH and that has been the way most of these have gone.

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We have had a lot of success with the Best Pharmaceuticals for Children Act, as I mentioned earlier. We have had 492 PPSRs submitted. We have issued 340 Written Requests. You can see a discrepancy in that number, and that actually has to do with a lot of PPSRs being submitted that we

don't think really address a public health concern so we will send a letter back to the sponsor saying we are not ready to issue a Written Request at this time. We have requested 793 studies in these 340 Written Requests. The key about this is that many times people have accused industry and FDA of not requesting enough studies under this program. The truth is most of our Written Requests include more than two studies so industry has really had to do a significant amount of work in order to obtain their exclusivity and FDA has not let them off the hook.

We have had 150 exclusivity determinations and we have granted 136 drugs or active moieties exclusivity. That means that in a small percentage we have not granted exclusivity so, again, we are very critical when those studies come in in looking them over to make sure that the sponsor did what they had agreed to do. And, we have 131 new labels. Of course, Victor is going to go over these labels in detail with oncology drugs-Bwell, the studies that are in there.

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I am going to touch base on our mandatory program because, again, these two laws are supposed to work together and it is impossible to talk about one without also addressing the other. I have gone into this stuff in detail so I am going to move on, just making note of one point here. That is, the Pediatric Research Equity Act only applies to the indication that is included in a submission that comes into the FDA, but the BPCA lets us study indications that are off-label and it is very important for pediatric oncology that we have the flexibility to do that. PREA only allows us to study that indication which is included in the submission. So, when think about adult oncology and pediatric oncology, they are very different animals. Pediatric cancers are very different than adult cancers so PREA really limits us in this arena.

I am going to show you in a minute some of the drugs that we have gotten postmarketing commitments for and you will see that the majority of them are supportive drugs because oncology

products for adults don't trigger PREA, for the most part, in pediatric patients.

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So, we have 55 new labels under PREA, but only 15 of those labels are actually based on clinical studies. We have 191 postmarketing commitments. Now, unlike the postmarketing commitments for other things, we actually do have the authority to enforce getting these studies done.

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The postmarketing commitments that we do have for oncology include Avastin, Erbitux and Neulasta, and forgive me for mispronouncing these products. I am much more familiar with Augmentin. So, we do have three products that have postmarketing commitments for pediatric patients under PREA.

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We also have some with supportive care, candidal infections. We have some for mucositis, and then, obviously, the anti-emetics as well.

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And this is for anemia.

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So, we have obtained some postmarketing commitments under PREA for oncology. So, just comparing and contrasting the two pieces of legislation, BPCA is voluntary while PREA is required. BPCA covers orphan indications and PREA orphans are exempt. So, we can't require rare conditions to be studied under PREA. For BPCA the exclusivity goes to the whole moiety so the active drug product. The example I always use is fluticasone which is included in a nasal spray, a topical cream for eczema and an inhaler for asthma. So, when the drug company had to study that product they had to study all of their different products containing fluticasone and they got exclusivity that covered the entire product line. So, under BPCA that exclusivity covers the entire product line and that is really where the incentive is because it blocks generics for all the adult indications as well, because the pediatric market

is so small it wouldn't be financially feasible to do it if it was only going to protect the pediatric market.

For PREA the studies are limited only to that specific drug that is submitted. Under BPCA we have a mechanism for funding studies of off-patent moieties and under BPCS we also have a mechanism where we specifically look at the safety for one year post-exclusivity. That might not seem like a lot but when you think about pediatric adverse events, there are only a few of them in an ocean of adult adverse events. So, if you look at things more generally, the pediatric adverse events do have a tendency to get washed out, to get lost in that sea of adult adverse events. So, requiring us to go in and look at the specific pediatric adverse events for one year following exclusivity has really allowed us to identify some safety signals that we probably otherwise would not have picked up.

It also allows us to post the summaries of the clinical studies up on our website so it grants

us the permission to be a lot more transparent. Again, when drugs are approved under the normal process or not approved we don't have the authority to post the reviews up on our web site, but under BPCA for pediatrics we do have that authority. So, we hope that that helps us disseminate the information to the public a little bit better.

Of course, the one big thing is that on October 1st of this year both of these pieces of legislation sunset or expire and we are currently working on re-authorization and we would love to hear your input about how we could make that better. One thing that may have happened, and I don't know what will ultimately come out at the back end but in the Senate Bill it actually does allow us to include preclinical studies, and if that ends up going all the way through and getting passed as law, that would be a big improvement, especially for oncology, if we could require preclinical studies in the Written Request.

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In conclusion, the BPCA and PREA have had

a powerful impact on providing important safety, efficacy and dosing information for drugs used in kids. And, oncology products have been studied and we have learned a lot about these products for pediatrics. We hope that scientific advancements can be incorporated into future studies of oncology drugs for kids, and incorporated under the legislation so that way we can enforce some of that. And, the new legislation being crafted is being supported by many interest groups and advocacy groups, as well as research for oncology. So, we are really hoping for great improvements in the new piece of legislation.

Questions from the Committee

DR. LINK: Thanks. Are there any questions for Dr. Mathis? We finally understand the two.

MR. HUTCHISON: Just out of curiosity, are the only two oncology drugs that are actually anti-tumor that have been studied are just Avastin and Erbitux? Are those the only two? I am just curious how many.

DR. MATHIS: No, we actually have many more

and Dr. Santana is going to go into that in detail. Those are the two drugs that, under the Pediatric Research Equity Act, are going to be required to do pediatric studies. So, those studies may be ongoing.

DR. WEISS: I could just clarify. Avastin and Erbitux are biologics. Biologicals are not included as part of exclusivity. The reason why is very simple, there are no generic biologics. Therefore, there is no patent protection to attach to for biologics so there is no incentive to attach for a biologic, you know, to keep basically the generics at bay for six months.

So, the only way is that there is either an interest in studying a biologic because it has some pediatric utility or it can be required, as Dr. Mathis said, under PREA. You know, for instance, for Avastin and Erbitux the primary indications are for a lot of the adult tumors, the very common adult tumors that don't occur in children. Somewhere down the road, in some of the work that Wellcome and other people are looking

into with respect to mechanistically if we know, for instance, that there are pediatric tumors that are EGFR overexpression, if we know more about the molecular mechanisms for cancers we might be able to see whether or not there is more appropriate rationale for studying some of these tumors in children and, you know, more incentive to request this as part of PREA. I hope I didn't confuse you further.

MR. HUTCHISON: No, it is fine. Thanks.

DR. ADAMSON: Maybe you did confuse me, Karen or Lisa. Under PREA you can only require studies if the indication is the same. But for bevacizumab and cetuximabB-the bevacizumab first indication was--what?B-in second-line colon cancer. So, how are you requiring studies for bevacizumab?

DR. MATHIS: I should make Karen answer this because I have no idea how they got away with that.

DR. ADAMSON: I think it is great, but if it is great we can apply it well beyond bevacizumab.

DR. WEISS: In fact, I think this probably is a discussion we should probably take up maybe afterwards because we could spend all morning on this kind of topic. I think it is more based mechanistically because the mechanism of Avastin may not be specifically, you know, tumor specific, you know, in terms of its anti-angiogenesis properties. So, I think there is some thought that it might have some more broad applicability across a number of different tumor types. But I think we could debate whether or notB-I think a better example might be with Erbitux where there is an interest in looking at pediatric tumors that might have the appropriate molecular targets, the EGFR type of expression, and if there aren't any, then there may not be a real rationale for going further in evaluating that particular molecule in pediatric tumors.

DR. SMITH: That is a question that I wanted to ask about. What are the ways that you can ask for rationale for an agent as part of a Written Request? For example, when you do have a

targeted agent one approach would be to study it against everything because maybe we don't understand the agent perfectly. The other approach would say, well, we don't understand everything but we understand some things. So, what is the biological basis for thinking that your targeted agent might work against certain pediatric cancers?

DR. WEISS: I would say that is an excellent question that will probably be relevant for the specific questions FDA is posing to this panel that might be somewhat better informed after the next presentation. I think those are absolutely critical in trying to figure out how best to utilize the products and the patient resources that are very limited in terms of making the most appropriate recommendations for studies.

DR. LINK: I have one follow-on question. Let's take a non-biologic. Could you just explain to us a little bit and make it crystal clear about when you can actually mandate a study of a drug? So, you have a drug that is approved for colon cancer, and take irinotecan, is there any mechanism

that you have to require studies in pediatric tumors, obviously not colon cancer?

DR. MATHIS: Under the Pediatric Research Equity Act we could not study irinotecan for that indication. It would be waived. Fortunately though, we have the other pillar, the Best Pharmaceuticals for Children Act, which allows us to then address that scientific need. So, we don't have a mandatory ability to make those studies done.

DR. ADAMSON: I am sorry, Lisa, can you then clarify the postmarketing commitment for Avastin and cetuximab? Was it under BPCA or was it under PREA?

DR. MATHIS: Under PREA.

DR. ADAMSON: Okay, so I don't understand. Again, I fully support; I think it is great--

DR. MATHIS: Right.

DR. ADAMSON: It is exactly what we should be doing, but the indication is in colon cancer.

DR. MATHIS: I was actually surprised when I went back through the postmarketing commitments

to find those, but we did it and the sponsor agreed to the postmarketing commitment.

DR. ADAMSON: So keep doing it.

DR. WEISS: This is probably not as relevant for this particular topic but I want to ask if Dr. Joe Gutenberg, from the Biologics Oncology Group who was involved, could just clarify this issue for Dr. Adamson.

DR. GUTENBERG: The postmarketing commitments being discussed here are voluntary postmarketing commitments being done by the drug companies voluntarily. They are not mandatory under PREA because PREA, as it is written today, specifies that you cannot ask mechanistically. You can only ask for that indication. If it is second-line colon cancer, it is just second-line colon cancer.

So, we have, because of cooperating drug companies, postmarketing commitments to study Avastin in PK studies in children. Also, you should know Nelasta which is a supportive drug; Kapivance which is a supportive drug. Those two

are PREA because those do exist and cetuximab would be voluntary.

DR. LINK: Identify yourself.

DR. GUTENBERG: Oh, I am Joe Gutenberg.

DR. MATHIS: I will say though that those postmarketing commitments got recaptured under the Pediatric Research Equity Act when it was enacted because it is retroactive to April 1st of 1999 and those studies are required under PREA. So, postmarketing studies that fall under PREA are required. The sponsor did agree to do them though so I think that is a very good point that Dr. Gutenberg made. Yes, there are postmarketing commitments required under PREA but it had a lot to do with the fact that the drug company was very cooperative and helpful and wanted to move forward to do the right thing.

DR. FINKELSTEIN: If you could in general terms indicate who is working with you in the re-authorization process?

DR. MATHIS: Well, you know, HHS operates by helping inform Congress when they come to us and

ask us questions about our experience with the Best Pharmaceuticals for Children Act as well as the Pediatric Research Equity Act. Outside of that, PhRMA, the drug industry--and maybe Sam can probably provide more information-BI know that they have been working with Congress as well. The American Academy of Pediatrics has been very active in helping with the re-authorization and they have been listening to their different members and trying to move things forward based on their members' experience. The Elizabeth Glaser Foundation has been very active. Actually, there have been some groups from NIH that have been very active, again, because NIH falls under HHS. They have been more responsive to questions from Congress rather than lobbying efforts.

DR. FINKELSTEIN: The reason I ask that question is because the initially the American Academy of Pediatrics played a very strong role in conjunction with PhRMA, and the FDA was of great help. They all went hand-in-hand with some great help with some of the senators in the U.S. Senate.

I am assuming the same ball is being played this time with the same game, but I may want to hear from PhRMA because they are very important in this, and they were very supportive originally.

DR. MALDONADO: This is Sam Maldonado. The same is happening. We are working with the AAP and the Pediatric Glaser Foundation. They are really the pillars of the people that are sponsoring or lobbying for this law but we are working with them too.

DR. SMITH: I am sure those things are happening. As Lisa said, you know, FDA and NIH can provide information to Congress in support of their legislative efforts. That is the role that the NIH and FDA staff can play in that.

DR. LINK: Other questions or comments? As promised, we will get sort of a report card from Dr. Santana on how legislation has affected oncologic drugs.

BPCA Experience with Oncology Drugs

[Slide]

DR. SANTANA: What I am going to do over

the next 45 minutes or so is kind of give you like, as alluded to, a report card of what has been happening with oncology drugs in relation to BPCA only. I am not going to talk about anything related to PREA. So, let's just put everything in their little boxes and we are just going to talk about BPCA.

[Slide]

What I am going to do is I am going to review the 11 oncology drugs that have been granted exclusivity. Those are listed in alphabetical order on the right-hand of the slide. For each drug we will review the regulatory history of the Written Request, the populations that were What I want to do in the first five minutes or so is kind of give you, like Mike alluded to, a report card of what has been happening with oncology drugs in relation to BPCA only. I am not going to talk about anything related to PREA, so let's just put everything in their little boxes. We are just going to talk about BPCA.

What I am going to do is I am going to

review the 11 oncology drugs that have been granted exclusivity. Those are listed in alphabetical order on the right hand of the slide. For each drug, we will review the regulatory history of the written request, the populations that were studied, and give you some brief study results and label changes that have resulted from the studies that have been submitted in regards to the written request.

I have to note here that, as has been mentioned before, there are a number of drugs, primarily supportive care drugs, that have also been approved in oncology through BPCA but I am not going to talk about those. I am going to talk specifically about oncology drugs.

There is a lot of data here, as you will see as we go through this, and I am going to try to give you at the end some summary of some of the highlights as I see them, and then give you some concluding comments on my impressions of this process that I think will be fodder for the discussion later on in the morning. So, let's go

ahead and get started.

[Slide]

The first drug is busulfan. It was first approved in 1999 for use in combination chemotherapy with cyclophosphamide as a preparative regimen for patients undergoing allogeneic stem cell transplantation for CML. I will pause here just to note that the indication for the drug was not adult specific. There is no mention of adults in this indication. If you actually read that original label, it was silent in relation to pediatrics although we know that CML occurs in children. So, keep that in the back of your mind as we go through this presentation for this particular drug.

The Written Request was issued in 2000 and exclusivity was granted approximately two years later, in 2002. The Written Request studies were for children that were undergoing a preparatory regimen for allogeneic stem cell transplantation. There was a single study that was requested in this Written Request and it was a Phase 2 multicenter,

open-label pharmacokinetic study. It was done in the United States in ten centers. It included a broad range of patients, as you can see in the age groups, for a total of 24 patients.

[Slide]

I think this drug, although it is the first one in alphabetic order, is also a very good example because there was important information from this single study that resulted in data that was used to change the label in terms of dosing, in terms of pharmacokinetics and in terms of safety. I have kind of outlined for you in bullet format some of those comments that are currently in the label based on this data. It talks about the clearance and volume of distribution. It talks about the study population in terms of ages. Importantly, it also talks about type of patients, both malignant and non-malignant patients.

Then, in the second bullet that is included in the label, it gives information about issues regarding systemic exposure and how important it is both for efficacy and safety for

this particular drug.

[Slide]

More importantly, based on this study, the label was changed to actually include a dosing nomogram based on the patient's actual body weight. I think this is important because it really distinguishes that different doses need to be used for different patients. Then the label also goes on to mention issues about monitoring for systemic exposure and how that relates to safety and efficacy. So, I think this is a good example, the first drug, of how a single study really provided some important information that was previously not there in the label.

[Slide]

The second drug is carboplatin. It was first approved in 1989, a long time ago, for advanced ovarian carcinoma. The Written Request was issued in 2002 and then this Written Request was amended in 2002 in which the sponsor requested an extension of the due date for submission of reports of data. Like Lisa mentioned, when the

Written Request is approved there is a timeline that is set of when those reports have to be sent back to the agency and that clock is determined when the exclusivity or the patent of that drug expires. So, those dates are included in the Written Request and they constitute part of that official document. So, those can be amended and you will see in various examples how those are amended as we go through these.

So, approximately three years later the drug was granted exclusivity, in 2004, and it was a very general population of interest, relapsed and pediatric malignancies. There were two studies included or requested in this Written Request. One was a traditional Phase 1 study in which carboplatin was studied in the context of irinotecan. Then there was a Phase 2 study in which a similar combination was studied of carboplatin and irinotecan. This included a broad range of pediatric patients. Of interest, there were 28 patients in the Phase 1 study and there were 151 patients in the Phase 2 study. It was a

very large study.

[Slide]

I have summarized for you in this slide on this table the results of those studies. If you look at the top of the slide, you will see that the combinations that were used were carboplatin and irinotecan or irinotecan alone. Then the study was stratified for patients with CNS tumors in contrast to patients with non-CNS tumors. You will see the response rates and the 95 percent confidence intervals in the second line, the second row. You can see that across the board there were some responses seen, and the types of tumors that responded to these agents are detailed in the third row. And, you can see that there were some partial responses. The majority of cases were partial responses.

So, based on this data a conclusion was reached that responses were seen across all the treatment arms but it was difficult to quantify the contribution of carboplatin to those responses. In addition, although there was pediatric

pharmacokinetic data, data was inconclusive as only 33 percent of the patients were within the target systemic exposure of carboplatin that the study mandated. So, based on the data that was submitted in response to this Written Request, no action was taken on the label. That is, no information was added to the label. Suffice it to say that although there was no action, exclusivity was granted because, remember, the exclusivity is not dependent on the results; it is dependent on the submission of the results. Okay?

[Slide]

The third drug is clofarabine and this is an interesting example, as you will see in a minute, because it is a pediatric specific drug. It was approved in 2004 for the treatment of children with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens. The Written Request was issued in 2003 and it was also amended in 2003, about seven months after it was issued, to include only studies with hematologic malignancies and to define the primary

endpoint for the studies as complete response and durable remission for the Phase 2 studies. The original Written Request requested solid tumors but it was very evident that this drug's activity was probably in the hematologic arena so that is why subsequently there was an amendment to define the population as children with acute lymphoblastic leukemia.

There were three studies requested and submitted in the Written Request. One was a Phase 1 study to determine the MTD and the toxicity profile. This was conducted at MD Anderson as a single-center study. Then there were two Phase 2 studies. One was in children with ALL and one was in children with AML. As you can see in the last bullet, there were a total of 25 patients in the Phase 1 and there were a total of 84 patients in the Phase 2 studies.

[Slide]

These were the results of those studies in terms of the response rates. In acute lymphoblastic leukemia population there was a 20.4

percent response rate. That is, 10 out of 49 patients had complete remissions or complete remissions with some platelet recovery. In the AML population, unfortunately, there was only a response of 2.9 percent in that only 1 out of 35 patients responded.

Based on the results of the Phase 1 and the two Phase 2 studies, this drug was granted approval through the accelerated approval mechanism and exclusivity was also granted. So, the label for this drug is pediatric specific because there is really no adult data of studies that have been conducted. So, this is the first complete label for this drug and it is a pediatric specific label and, as any label, it includes issues of indication, pharmacokinetics, safety profile, how to give it, and so on and so forth. So, this is a good example of a drug that was specifically developed and got exclusivity through all the pediatric studies that were submitted.

[Slide]

The next agent is fludarabine that was

first approved in 1991 for B-cell chronic lymphocytic leukemia. The Written Request was issued in 2001 and exclusivity was granted a little bit after two years after that, in 2003. The population of interest were refractory or relapsed aute leukemia pediatric patients.

There were two studies that were part of this Written Request. Both of these studies were conducted by the cooperative group, the CCG. The first was a dose-finding PK study and the second was a clinical study looking at activity but it also had pharmacokinetics included in it. You can see that a total of 62 patients contributed to these two studies.

[Slide]

I have kind of summarized for you the results of those two studies. In the top line is the Phase 1 study in which the drug was given as a single agent, initially as a bolus and then as a continuous infusion. It included 9 children with AML, 36 children with AML and 17 solid tumor patients. Dose-limiting toxicity, defined as

myelosuppression, was established in solid tumor patients but in the leukemia population DLT could not be defined because of issues related to myelotoxicity and its relationship to residual leukemia in the marrow and trying to dissect the contribution of those two.

Of interest, there was some pharmacokinetic data that was different in children in terms of clearance of this drug used in children compared to adults. There was only one CR and three PRs in children with ALL and no responses were seen in children with AML and solid tumors within the context of this Phase 1 study.

The second study was a Phase 2 study in which fludarabine was combined with another agent, another antileukemic agent, cyterabine-ara C, in this case in 13 children with ALL and 18 children with AML. The same maximum tolerated dose defined in the Phase 1 was used. In this case there was a response rate of 9 out of 18 patients with AML who had a CR or PR and 3 out of 9 children with ALL had a CR/PR but these responses were very brief so it

is difficult to quantify the long-term contribution of this therapy to those children. This data did result in a comment in the label. The comment says that fludarabine was evaluated in 62 pediatric patients. However, the data were insufficient to establish efficacy in any childhood malignancy.

[Slide]

The fifth drug is gemcitabine and it was first approved in 1996 for locally advanced or metastatic pancreatic cancer. The Written Request was issued in 2001 and there were two amendments, in 2002 and 2003, to request a change in the time frame for submission of the study reports and the data. Exclusivity was granted about four years later, in 2005, and the patients that were studied were refractory children with ALL, AML or non-Hodgkin's lymphoma.

The two studies that comprised this Written Request were both cooperative group studies, one done through the CCG and the other one through the COG. The first one was a PK study and the second one was a Phase 2 activity study. As

you can see in the bottom, there were 14 patients in the Phase 1 and there were 32 patients in the Phase 2.

[Slide]

These results are summarized in this slide. The Phase 1 was done in children with relapsed acute leukemia. An MTD was defined based on that study. In the Phase 2 there were 20 children with ALL and 10 children with AML. Unfortunately, there was only one complete response in a child with ALL, a response of only one out of 30 patients studied. Toxicities of this drug in children were well defined and included in the study submitted in the Written Request, and are very similar to those seen in adults.

Based on this information there was a change in the label, and the statements included that effectiveness could not be established, but it went on to describe the studies that had been submitted as part of the Written Request and the exclusivity determination. Importantly, it also states that the toxicities that were seen in

children are very similar to those seen in adults.

[Slide]

The next agent is imatinib. This drug was first approved in 2001 for adults with Ph-positive CML. The Written Request was issued in 2000 and there were three amendments to this Written Request, on in 2003 and one in 2005 requesting a time change of when these study reports and the data needed to be submitted, and then in 2004 to extend the study population to newly diagnosed children with Ph-positive CML.

The issue with that last amendment was that there was emerging data in the adult population that this drug was active in newly diagnosed adults with CML. The pediatric Written Request was written originally for refractory/relapsed children with CML so it was a good move to amend it to a new population of children, children with newly diagnosed CMLB-so more specific and in parallel to what was occurring with the adult population. So, that was a clever and a very good amendment to that Written Request.

Exclusivity was granted approximately six years later, in 2006.

The population of interest was children with Philadelphia-positive leukemia. There were three studies submitted as part of this Written Request. Two of them were Phase 1 studies in children who had recurred after stem cell transplantation or who were deemed resistant to alpha interferon therapy. Both of these studies were conducted through the cooperative group. Then, there was a single Phase 2 study to evaluate the response rate and determine the survival in newly diagnosed children with CML. This was also done through COG centers and included age groups from 2 to 20. There were a total of 17 patients in the Phase 1 and there were a total of 51 patients in the Phase 2.

[Slide]

I have summarized for you those studies on this slide. For the Phase 1 studies, the first one was open-label in relapsed patients. It included 14. There was another small Phase 1 study that

only had three patients. What was determined based on the results of the Phase 1 data was that the pharmacokinetics in terms of AUCs or systemic exposures achieved in children were very similar to adults, and that the drug is also very rapidly absorbed in children, reaching its Cmax within 2-4 hours.

Of interest, because most adult drugs are dosed as single doses not adhered to a kilogram or a meter-squared, there was interest in beginning to relate the dose in adults to the dose in children, and these studies did demonstrate that a 340 mg/m^2 dose in children is comparable to the fixed dose of 600 that is commonly used in adults.

The Phase 2 was a multicenter cooperative group study. These were newly diagnosed children, previously untreated, with chronic phase CML. The dose that was used was the dose that had been established in the Phase 1 study and there were significant complete hematologic and cytogenetic responses seen in the pediatric population.

So, the results of this information led to

changes in the label that I have outlined for you at the bottom of the slide. I kind of highlighted for you some of the key features. It talks about the indication, which is newly diagnosed children. It says that it is also useful in children with relapsed or refractory CML and although there are no controlled clinical trials, there is information regarding the activity of this drug, and there is information regarding the dosing of this drug in children. Then, a very important statement is that there is no experience in dosing children less than two years of age. We will come to that at the end in some of my conclusion slides for why I have highlighted that.

[Slide]

The next drug is irinotecan. It was first approved in 1996 for metastatic colorectal cancer. A Written Request was issued in 2001, with an amendment in 2003 and exclusivity was granted about three years later, in 2004.

The population of interest were children with refractory solid tumor. This is the Written

Request that contains the largest body of data because it contains the largest number of studies. This Written Request had four Phase 1 studies submitted to it and two Phase 2 studies. I want to spend a little bit of time going through those so you can get a sense of the data that was included in these studies.

[Slide]

In this table is a summary of the Phase 1 results. If you look at the left column, there were four Phase 1 studies. Three of these studies used different schedules of administration. The first study included weekly times four. The second study had daily times five for two consecutive weeks. Then, the last two studies included daily times five for only one week, given every three weeks.

The first two Phase 1 studies were single institution studies. One was conducted by Dr. Blaney's group at Texas Children's. The other one was conducted at St. Jude. Then, the other two Phase 2 [sic] studies were conducted through the

cooperative group mechanism and included centers not only in the United States but also centers in Canada. I hope that issue of international research comes up during the discussion.

The age groups that were included are highlighted in the fourth column here, and I just want to note for you the large number of patients that were enrolled in these Phase 1 studies that actually did contribute pharmacokinetic data. The results of these studies are in the last column. You can see, with the exception of the last study, most of the studies were successful and that they did define an MTD given the schedule that was being studied. The last study, unfortunately, was closed early due to slow accrual.

[Slide]

The two Phase 2 studies for irinotecan are highlighted in this slide. The first study was a multicenter study done through the cooperative group mechanism here, in the United States, and in Canada. It was in patients with refractory solid tumors. You can see that when the different strata

of patients were evaluated the responses were seen in the relapsed rhabdomyosarcoma population and that 3 out of 19 patients had a response.

The second Phase 2 study was in children with metastatic previously undiagnosed high risk rhabdomyosarcoma. So, these are children who had not received chemotherapy before. That was also conducted in the United States through the cooperative group. The results of this study are interesting in relation to what we learned and what eventually made it to the label. So, as many of you in the audience and on the panel recall, in the original study the response rate was 42 percent in that 9 out of 21 patients had a response to single agent irinotican, but there were a number of disease progressions and there were a number of deaths when this agent was used as a single agent.

The study was subsequently revised to use the combination of irinotecan and vincristine, based on some preclinical data and in that setting of that combination there was a very important response rate observed of 70 percent, comparable to

the standard of care that is used in the United State.

Unfortunately, the data from the second combination study was not submitted at the time of the data that had been submitted for the requirements of the Written Request so that information did not make it into the label. But I encourage the sponsor and others to consider whether there should be a revision and that information should be included in the new label because it is important information.

[Slide]

Given the wealth and the depth of data that these six studies provided, the label was extensively rewritten for this drug. Although there is a statement that says effectiveness cannot be established based on these six studies, the label does go on to give some very specific data about the patients that were studied, pharmacokinetic data and adverse event data in children. So, I think this drug is a good example of how some very important information was included

subsequently in the label and potentially the label needs to be revised based on new emerging data that has resulted from the Written Request.

[Slide]

The eighth drug is oxaliplatin. This was first approved in 2002 for advanced colorectal cancer. There was a Written Request issued in 2004 and then there was an amendment again in 2005 to extend the time frame for submission of study results. Then exclusivity was granted approximately two years later, in 2006.

The population of interest was children with refractory solid tumors. There were four studies submitted as part of this Written Request. One of the Phase 1 studies was a French study that had been conducted by Vassal and his group in Europe. The other Phase 1 study was conducted at a U.S. center.

The Phase 2 studies were conducted through the cooperative group mechanism here, in the United States. As you can see at the bottom of the slide, there were 69 Phase 1 patients and there were 90

Phase 2 patients.

[Slide]

I have highlighted the results of those four studies for you on this table. In the top of the slide are the Phase 1 studies. You can see that these were relapsed solid tumor patients. In the first study there was a day 1, 8 and 15 schedule. In the second study it was just a day 1 every 3 weeks type schedule. Both of these studies identified the same DLT, which is sensory neuropathy. Also, the pharmacokinetic data was important to establish that clearance in children was very similar to adults for this particular drug.

Then, the Phase 2 studies included patients with CNS tumors and in the second study were patients with relapsed tumors, using the dose that had been identified in the Phase 1 studies. The results were that only one partial response was seen in the total of 90-plus patients that were studied.

[Slide]

Based on this data, a statement was added to the label that effectiveness had not been established based on these limited studies, and that no significant activity had been seen in the studies that had been submitted. However, some data regarding the clinical studies and a summary of the adverse events that were seen in children are now included in the label.

[Slide]

The night drug is temozolomide, which was first approved in 1999 for adults with anaplastic astrocytoma. A Written Request was issued in 2001. Then there was an amendment in 2001 requesting that data from a previous NDA that had pediatric Phase 1 data could be incorporated into the Written Request data sets, and then defining the patient population more specifically for the Phase 2 studies. Exclusivity was granted in 2002.

The population of interest were patients with malignant brain tumors. This Written Request had three studies. Two were Phase 1 studies and one was a Phase 2 study in patients with recurrent

central nervous system tumors. The number of patients that contributed to this Written Request were 90 patients in the Phase 1 studies and 122 patients in the Phase 2 studies.

[Slide]

The results of these trials are summarized in this slide. Of interest, the Cmax and systemic exposure in children for this particular drug appear to be different. They are higher and it is unclear if this is related to increased bioavailability in children or decreased clearance or other potential mechanisms that could account for these higher systemic exposures. However, the pediatric data did demonstrate that there was proportionality between the dose and the systemic exposures; that there were no issues related to age and clearance. And, a five percent response rate was observed. There was one CR and five PRs in the brain tumor patients that were studied.

So, the label has a statement that effectiveness has not been demonstrated based on this information. However, it goes on to describe

the study populations that were included in the Written Request and a statement related to the toxicity profile of this drug being similar to children compared to adults. I think it is of interest that although the studies that were part of this Written Request were not very compelling in terms of activity, this drug really has become the standard of care for patients with brainstem gliomas. It is an interesting disconnection there and may be worth discussing later on.

[Slide]

The next drug is topotecan, which was first approved in 1996 for ovarian cancer. The Written Request was issued in 2000. In 2001 there was an amendment and then exclusivity was granted about two years later, actually 18 months later, in 2002. It was studied in children with relapsed or refractory malignancies.

This Written Request included four [sic] studies, two of which were Phase 1 studies and one which was a Phase 2 study and you can see from the data that these studies were conducted through the

cooperative group mechanism and include centers both in the U.S. and Canada. The total number of patients in the Phase 1 were 52 and the total number of patients in the Phase 2 were 150. That is because there were different solid tumor strata in the Phase 2 studies and, thus, the large number of patients.

[Slide]

The results for topotecan provided pharmacokinetic data and parameters across the age groups that were studied; defined the clearance in children; the volume distribution and the half-life, all very similar to adult reported values. The overall response rate was 8 percent but, of interest, in the neuroblastoma population there was a response rate of 18 percent in 7 out of 38 children with relapsed neuroblastoma, demonstrating some level of activity. In addition, doses in relation to G-CSF support were also a part of these studies so the studies were successful in the context that they provided different dosing based on the availability of hematologic support.

No actions were taken on this label, primarily because the submitted data were not strong enough to support an indication and that safety and efficacy had not been demonstrated in these patients.

[Slide]

The last drugB-we are almost thereB-is vinorelbine. It was first approved in 1994 for unresectable non-small cell lung cancer. The Written Request was issued in 2001 and exclusivity was granted about a year later, in 2002.

The population of interest were children with leukemia, lymphoma or solid tumors. There were two studies submitted in response to this Written Request. One was a Phase 1 study conducted by the cooperative group. The other one was a Phase 2 study also conducted in U.S. centers. There were a total of 29 patients in the Phase 1 and a total of 46 patients in the Phase 2.

[Slide]

The results of those studies in summary provided an MTD defined as 33.75 mg/m^2, which is

very similar to the adult MTD. In terms of activity, in the 22 patients that were evaluable only one partial response was seen in a child with recurrent rhabdomyosarcoma.

So, the label was changed and did include new information kind of describing briefly the studies that had been conducted, and that at doses very similar to those used in adults no meaningful clinical activity was observed.

[Slide]

Now I want to kind of put all this information, which is a lot of information to digest, in some perspective. So, I have a couple of slides of some summary points and some messages I want you to remember from this big data set.

In terms of the oncology drugs that have been granted exclusivity through BPCA, there have been 31 clinical studies with over 1,300 pediatric patients participating in those studies. The median time from the issuing of a Written Request to the actual determination of exclusivity is 19 months, and you can see that the range is pretty

broad. It can be relatively quick, 12 months, or it can be relatively long, four years or 48 months. But most of them fall in the 19-month range.

You heard me talk a lot about amendments to the Written Request, which is a mechanism which I think is good because no study and no Written Request is perfect. So, the majority of Written Requests have had an amendment. Some have had no amendments and, as I mentioned to you, there was one that had up to three amendments and in the next slide we will see the reasons for those amendments.

The number of studies contained in the Written Request were a median of three studies. With the exception of busalfan that only contained one study, the majority of the other Requests contain more than one study. As you recall, the irinotecan Request was striking in that it contained a total of six data sets or studies.

The number of patients for the Phase 1 averaged about 29 and for the Phase 2 averaged about 46. Then I will highlight fo you some of the Phase 2 studies that had a large number of

patients, but that had more to do with different strata and the different groups of patients that were contained in those Phase 2 studies. They were not disease specific Phase 2 studies but they were broad Phase 2 studies with different strata.

Then, of some interest in terms of the data sources, that is, where the data was coming from and where the studies were being conducted, about two-thirds of the studies were being done through the cooperative group mechanism or through consortia and about a third of the studies were individual institution studies or studies that were conducted by the sponsors by contacting investigators on their own. As I mentioned to you during my presentation, a number of these studies were actually international studies, some having been conducted in Canada and some having been conducted in France.

[Slide]

The reasons for the amendments, the majority of the amendments occurred with a request to extend the timetable that had been set in the

Written Request of when the study reports and the data had to be submitted. However, there were other amendments that I think are important which, once again, stress the importance of this being a dynamic process in terms of amending the Written Request. Primary endpoints were clarified or were redefined; a change in the study population or the age groups that had to be studied; and then clarifying protocols or studies that would generate the data.

[Slide]

This is a visual slide that kind of presents to you the whole context of the 11 oncology drugs and the type of studies that were performed in terms of PK, safety, activity studies or a combination of PK activity and safety studies. I think you get the flavor that for the majority of the Written Requests, many of them had two, three or more studies included in the data sets.

[Slide]

Now, a very interesting focus of the Written Request data sets is to try to identify

potential differences between children and adults because I think that is part of the genesis of this whole legislation. So, in this slide I have outlined for you in different colors the different contributions of these drugs to that important comparative clinical pharmacology.

For example, for clofarabine, as I mentioned to you, this was a pediatric specific developed drug so the current label is really a pediatric label. There is no adult data in the pediatric lable.

For the four drugs that are highlighted in green, busulfan, fludarabine, temozolamide and vinorelbine, data that was generated from the Written Request studies were important to demonstrate important clinical pharmacokinetic and pharmacodynamic principles in children compared to adults. I won't go through them in detail but there are important things as we consider how to dose children and how to potentially relate clearance and exposure to toxicity and potentially to efficacy.

Then, for gemcitabine, imatinib, irionotecan and oxaliplatin and topotecan the data was very similar and I think that is also positive data, that you have important information related to pharmacokinetics in children compared to adults as being very similar. Then, for carboplatin we don't really have at present any comparative data to make any claims.

So, I think this is an important message because I think a lot of the pharmacokinetic studies and a lot of the safety studies that were done in pediatric oncology as part of the Written Request have led to some important observations.

[Slide]

As I mentioned to you, out of the 11 drugs, 9 drugs now have information in the label including dosing, safety and indications.

[Slide]

And, to try to summarize all that complex data into something more visual, I have done that through this table which looks at the type of information included in the new label by the nine

drugs that really have met those criteria. For example, if you focus on column one which describes expanded age to include pediatric age groups previously not included or including a new indication for the product population, you can see that clofarabine and imatinib met those criteria and now have information in the label.

If you look at the second column, which is specific pediatric dosing change or adjustment, I mentioned to you earlier that busulfan now has that based on the studies that were submitted and imatinib also has that based on the studies that were submitted.

If you look at the third column, safety new or enhanced pediatric safety information, you can see that busulvan, irinotecan and oxaliplatin now has safety information specific to pediatrics.

Then if you look at the NME, the new molecular entity column, clofarabine is a new molecular entity which is very pediatric specific.

So, there is some information that is now making it into specific sections of the label based

on the oncology drugs that have been studied.

[Slide]

So, I want to finish by kind of, I guess setting the stage is a good word to use here for the potential discussion that we could have this morning in terms of where I see some of the good things and some of the things that we have to work on as we move forward.

I think a very important point that I think was stressed this morning with BPCA is that this is a voluntary process so the agency cannot go to the sponsors and force them to do studies. That obviously creates an environment in which there has to be a lot of mutual cooperation to get these studies done and I think industry has been responsive to that. But it does provide constraints to the agency in what they can ask for and what they cannot ask for and then initiates, obviously, a mechanism that involves negotiation.

I think it is important to remember, and I am
preaching to that choir here in terms of the

audience and the table in terms of its clinical practice, and that is, that clinical research is really the cornerstone of therapy. So, the majority-Bnot all but the majority of our patients are participating in clinical research so they are not really being treated by standard of care or as medical oncologists do in many circumstances. So, that fluidity of patients participating in clinical research and how clinical research can lead us to inform the Written Request better I think is something we need to discuss.

Then, on kind of the negative side, the other side is that because pediatric oncology occurs within the context of research, how much attention do we really pay to the label, which I think is a big piece of information that is used by other healthcare providers? But within the context of clinical research, what is the value of that? And, I think that is something that we need to discuss.

The other important point is looking now at the process of how a Written Request is drafted

so that the content of the Written Request really addresses issues of clinical importance. I have to tell you, after spending 12 months this past year at the agency, I have seen an evolution of the Written Requests that are coming through the Oncology Office. Clearly, I am giving you what happened in the past and I think there has been an internal revolution, and I certainly look forward to Karen and Ramzi talking a little bit about that during the discussion.

But, clearly, this is a process that involves a lot of stakeholders. It involves the sponsors because ultimately they have to do the studies. It involves the regulators because they are the ones that legally issue the Written Requests. It is not the sponsors that issue the Written Request; it is the agency. It involves the investigators that do the studies. You have heard that two-thirds of these studies are being done by cooperative groups. We have to discuss what is the involvement of subject experts in this process, and what is the potential contribution of the patient

community in this process. I think those are all issues that I think are important to formulating a Written Request that is meaningful.

You heard Lisa talk a little bit before about the PPSR, which is the document that the sponsor can submit originally without the agency really having requested it previously. So, we have to understand how those two documents relate to each other and how the ultimate output is reached in terms of the final Written Request.

I think an important issue is the timing of the written request relative to product development. That is important so that we can learn the most once we do our studies without doing studies too early that potentially will fail and not doing studies too late in which, you know, the horse is already out of the barn. So, we have to get a better understanding of when that timing issue comes into play.

I think how we use preclinical science to better inform the questions to be answered by the Written Request, I hope that in the future the

Written Requests are more focused on specific questions that need to be answered that are better informed through preclinical questions that are coming up down the pipeline and, hopefully, with the new legislation maybe that is something that you, guys, will have a better handle on.

I think the types of studies and designs that may be the most informative. You saw that almost exclusively all the studies that I described to you are the traditional Phase 1/Phase 2 studies, maybe with the exception of irinotecan which was kind of a window study, the others were the traditional Phase 1/Phase 2 and maybe we need to look forward to new designs and new ways of doing the studies to get the most information in the shortest period of time.

Then, none of the 11 drugs that have been studied in oncology so far have had any issues of formulation studied. I mentioned to you that, you know, in the CML population there are a few patients and, clearly, if you look at the population of pediatric oncology in general about

10 or 15 percent of our patients are less than two years of age and none of these studies so far have really provided us any guidance about issues in those specific groups. Maybe that is something we should focus on in the future if those groups exist, how we can have Written Requests that address those patients.

Then, I think another important point is building flexibility in the process. It has to be a process that can be amended; that can have conversations going back and forth.

Lastly, and I want to leave you with this last point, how do we define success? I think in other areas of pediatrics maybe a label change is a success because general pediatrics is practiced in the community, you know, where parents and practitioners look at the label. But maybe pediatric oncology is different and maybe we should define success of this program a little bit differently.

[Slide]

So, I think with that I will finish by

acknowledging that the real work here was done by members of the medical review teams and pharmacokineticists and pharmacologists, and all those individuals in the Oncology Office that do this work because they were the ones that really reviewed all this Written Request data that came in. Then I want to thank Karen and Ramzi for their guidance and advice on this project. Thank you.

Questions and Discussion

DR. LINK: Thanks for that great review. Let me just summarize the way I saw it and you can tell me what you think. So, in 8 of 11 of these drugs that you studied there was really no meaningful response data that was gotten from this.

The second point which I think you made and it certainly resonates with me is that the label said, you know, these drugs have no defined efficacy in children yet the majority of these drugs have actually entered clinical practice in pediatric oncology anyway.

DR. SANTANA: Right.

DR. LINK: So, it seems to me that the

focus here, at the agency, is trying to do something about the label, and I am talking about PK only but also about, you know, the drug is good for X and not good for Y. Yet, in the community in which these drugs are being used primarily in, let's say, oncology practices which are in cooperative group settings, not necessarily on studies, we don't seem to care. So, comment a little bit about that in terms of how the program is a success or not a success.

DR. SANTANA: I think you have hit on some of the points that, hopefully, we will get more feedback during the discussion. I think one issue is that what I am presenting today has to be taken in the context of a historical perspective. These were the initial studies that were asked for in the last eight to ten years to satisfy the Written Request mechanism. You know, many of the studies, as we move forward, should be more specific for example in the populations that need to be studied. Many of the Phase 2 studies failed because there were a very large number of studies looking at, you

know, ten different strata of small populations of patients and in retrospect-this is no criticism to anybody because I participated in the studies-in retrospect, maybe some of those studies, in relation to the Written Request, should have been very focused on certain diseases where we could have gotten best mileage out of those patients in terms of defining the response and defining the safety profile, knowing that those populations potentially would be the populations that would benefit the most from that drug.

So, maybe we need to rethink as we work with the agency and with the sponsors what new studies will be fulfilled in the Written Request to make those studies more specific so that the output is more positive in its content. So, I think part of it, Mike, is the historical perspective of when this was occurring in the last ten years, and the learning curve that sponsors, that we as investigators and that the agency was having through the process.

Your last comment regarding the label I

think is an issue that is worth further discussion. I think the label is important information because it is a public health issue. I mean, that is how the agency views it, that it is informative to healthcare providers. In pediatric oncology we don't use the label that much but parents read the labels. So, I think for the parents to have access to that information that you and I may know as investigators because we read the next manuscript in JCR, or whatever-BI think for parents to have that information made available is one potential mechanism.

DR. LINK: It worries me that we are prescribing a drug that, when you pull out the label it says this thing has no activity and you just prescribed it for my kid. You know, that is what I am worried about with the labels actually.

DR. SANTANA: So, we should worry about what the label says and we should have information that is relevant, yes.

DR. LINK: Before we go on, Dr. Winick, would you introduce yourself just for the public

record, who you are. We know you.

DR. WINICK: Naomi Winick, University of Texas Southwestern.

DR. LINK: Thank you. Jerry?

DR. FINKELSTEIN: That I think was a superb presentation. I mean, I congratulate you.

DR. SANTANA: I didn't do the work. The medical teams--

DR. FINKELSTEIN: Well, whoever did the work behind the scenes, I also congratulate them.

DR. LINK: We assume you read the written materials before you got here.

DR. FINKELSTEIN: I did. I brought it along here, all this stuff here. I brought it and carried it on the plane that Mimi made sure I got on.

Given that, I have to congratulate all pediatric oncologists because despite the relative negative report you have given we continue to improve our survival rate. I think your presentation is so great that I would hope that Peter would invite you to COG because I think we

have to hear this. In some ways, you are the outside review for what is going on in pediatric oncology.

I agree with you, Michael, that some of these drugs we continue to use and maybe that is why we have to continue this forum also in COG because maybe we should ask ourselves why we continue to use them.

Lastly, I have two other things. One is addressed to you. But let me address the label part. We struggled with the label part when this whole program was initiated a long time ago. Yes, we, pediatric oncologists, don't read the label but, yes, I agree with you, the community does read the label and if the label indicates there is no indication in pediatric oncology we, who are responsible for the care of these children, better darned well know the data about why we are still using the drug. So, I think that is a good question. And, I was suspect of the label and we met originally starting this whole program, but I am not suspect anymore. I think it is an important

contribution to the community.

My last question is I am a little confused. How long does patent really last? When I looked at the exclusivity--when does it come in? When doesn't it come in? As I am listening to your presentation, there seem to be all kinds of dates here and maybe I am the only one being confused on the algorithm of progress.

DR. MATHIS: Well, first, as a general pediatrician I will tell you that pediatric oncologists are not the only people that don't read labels. I never knew how much information is in a medication label until I started working at the FDA. Now I go to the label all the time when I am practicing because I understand what is in there, but you don't really learn that in medical school in residency.

Going back to the exclusivity and patent, I always kind of describe pediatric exclusivity as the caboose on the train. It is not a stand-alone exclusivity. In other words, you can't be granted pediatric exclusivity unless you have an existing

patent to attach it to or other existing exclusivity to attach it to. When a drug is approved for use in any indication you can have anywhere from three to seven years of exclusivity, depending on if it is a new molecular entity, if it is a new population, if it is an orphan or if an exclusivity is actually the longest, being seven years. So, exclusivity is probably the most relevant thing to attach your pediatric exclusivity to.

The patents are not determined actually by us. They are determined by the Patent Office and can be very variable. In addition, they can be challenged in court. So, while the exclusivities that are granted by the FDA cannot be challenged in court, patents can be.

So, some drugs, if you go into our "Orange Book" which is, of course, where we list all of our patents and exclusivities, which nobody really cares about except probably for PhRMA, you can go in there and see that some drugs have patent and exclusivity protection out for the next 25 years

while others that are new molecular entities may only have patent and exclusivity for the next ten years. So, again, it is variable.

What we do try to do is to look at the date of exclusivity and patent that exists in the "Orange Book" and try and engage drug development against that. But we never really use that as our only landmark for the date in the Written Request. What we try to do too is figure out how long it will take for the studies to be completed and in oncology sometimes it takes a little bit longer because it takes a long time to accrue the patients. So, you will see dates all over the board and that is just the reality that we have to live in.

DR. LINK: I just want to make one thing clear. I didn't say that we are giving drugs that are not active. I was saying that the label does not necessarily reflect what we know. So, you know, topotecan doesn't show any activity in pediatrics. It says that in the label but we have plenty of data that shows that it is a very active

moiety. So, just because this is a public record I want to go on record, I wanted to go on record that we are sort of giving drugs that don't have any activity.

DR. SANTANA: But, Mike, let me try to follow-up on that. The issue for me isB-and I know that topotecan is very active in neuroblastoma because I have participated in some of those trialsB-when that new information makes it into the label so if it wasn't included as part of the Request, this is a voluntary process, the agency has no stick to force anybody to change the label. So, if it is going to come through the supplemental NDA process, or whatever process, it is the sponsor who has to take the initiative to take those studies that we have done that clearly demonstrate activity of this particular drug to make it into the label to inform it better. But BPCA can't do that because they are tied into what was put in the Written Request. The example of irinotecan I gave is a good one.

DR. LINK: Understood. I mean, we know

that the literature trumps the labels. Dr. Mortimer?

DR. MORTIMER: I expect I know the answer to this, but long-term side effects in these individuals, I suspect there aren't any for most of these drugs but there must be for imatinib and I presume there are vast differences for long-term complications for kids compared to adults.

DR. SANTANA: So, we know that outside of the context of the studies that were submitted as part of the Written Request but the only Written Request that I recall of these 11 that specifically looked at issues of survival, not really long-term effects, was the imatinib one that requested that long-term survival in the CML population be provided. But the majority of the Written Request studies did not specifically request data related to long-term effects.

DR. DAGHER: Can I just clarify? I just want to clarify that one point, if I may. In the imatinib and the clofrarabine, because these resulted in new indications specifically to

pediatric populations, some of that safety information will be obtained as part of postmarketing commitments that would have been part of the actual approval letter. So, it is not specific to the Written Request process but, because there were new indications, there would be postmarketing commitments that would include requirements for follow-up either on the same studies that were the basis for approval or additional studies that are being conducted which will provide us with more long-term information about the safety issues that you described.

The only other thing that I want to clarify vis-a-vis the last point that Dr. Link was mentioning is that Victor pointed out the limitation of the timeline that you have for, you know, submitting information. Another is you are pointing out, you know, this discrepancy between what we have available in terms of what is being submitted versus what is out there in the literature.

Another issue there is also the

availability of the actual data and not just, you know, literature or study report. So, when we are formulating the Written Request and even through the purview of being able to amend a Written Request during the process, unless the sponsor would actually have the data, not just the reports or even literature available, we have found that would be an important consideration in deciding whether to ask for those kinds of studies or have them included in the Written Request. So, aside from the fact that it is voluntary, the other issue is all these other studies that are out in the literatureB-would that data be available, the data for submission or not?

DR. LINK: So, some of them come in after the label is already made.

DR. DAGHER: Right.

DR. LINK: Understood. We are going to go in order as people raise their hands so don't be too impatient. So, Peter is next.

DR. ADAMSON: I have just a couple of comments and then a question. I think we are in a

position, Victor, from what you presented to make a report card of the Written Request process because when I look at the Written Requests and what emerged I think you can categorize it in a number of ways. The first is that the vast majority of the data that was used to support exclusivity was culled from cooperative groups or single institution data. I think that is a good thing. I think the first place you want to look at when you put out a Written Request is, well, has it already been done because you don't want to repeat it. So, I think that was a very good exercise and I think important data did emerge.

But the breakdown that you did of 21 versus 10 I think is a little misleading because, as far as I can see on this list, there are really only three drugs that required launching of a new trial that would otherwise not have been launched. Everything else--and again I may be off a little bit on the math, probably not-Beverything else the trial had already been done or was in progress.

The one that I think I would focus on most

closely is which trials were launched and how did we do that. It is another issue for the cooperative groups to say, okay, what are we really learning from our cooperative group trials that we are signaling here with a lack of label change, a lack of effectiveness label change. The one that stood out for me was carboplatin as far as what were people thinking when we put that Written Request out. What did we really think we were going to learn from this kind of randomized study that exposed 150 children?

So, I think it is a good time for us to step back and break it into those two large groupsB-how effective were we in getting information that already existed in a format that is usable? That is very important. But when we do launch new trails, how good did we do in saying, oh yeah, this was a good idea? And, it is a gap analysis saying what information do we need; what exists; is it usable; what do we have to do prospectively.

The question I had, and it follows Mike's

and others' comments, is that essentially the label changes, when it comes to effectiveness, says effectiveness in pediatric patients has not been established. Now, that is a very broad term because it might not be established because a child has never received a drug. It might not be established because the design was horrific. Or, it might not be established because the drug is ineffective. It may be an oxymoron to put this in a label but when do you put in the label the drug is ineffective?

DR. LINK: Somebody want to take that?

DR. MATHIS: These guys can give you more of an oncology-specific response to that because that is a very important point and something that we, as pediatricians, have been struggling with since we started working through this BPCA process. If you go back to older labels what you will see, after the mandate that there be a pediatric use section in the labeling, is that they almost all contain a statement that says safety and effectiveness has not been established in

pediatrics, and that means nothing to us when we are treating our patients.

So, what we have been doing, and this has been an evolution, first of all people didn't think about pediatric patients in the past. So, one of the first things that has changed over the last 10 to 15 years is that people are thinking about kids and they are realizing how meaningless that statement is. So, we all are really working on trying to provide more specific information in that section of labeling. In other words, can we just describe the study so that way people can understand what is really there rather than having to interpret a non-meaningful statement like safety and effectiveness has not been established?

So, yes, that is a huge issue. Hopefully, as you are seeing new labels you will see a change in that. Hopefully, we will be able to provide more informative data that says exactly what we know and what we don't know.

DR. ADAMSON: But to date you do not have a label that does that. Is that right?