which potentially could be used for adult cancer and pediatric cancer alike, does the Pediatric Rule apply to that classification of drugs?

DR. HIRSCHFIELD: Dr. Cohn, stay tuned for this afternoon. That is going to be their topic of discussion.

DR. CHESNEY: Thank you, Dr. Hirschfield. Dr. Weiner, any concluding comments? Questions?

DR. WEINER: Yes, just two comments to response to what Dr. Murphy had asked and also just by way of summary from our perspective, and this is a remark that I made actually in the meeting in February that Dr. Finklestein referred to which is that from our perspective time is really the issue. In implementing FDAMA and the Rule, time is really the question. How long does it actually take to Phase I and Phase II trials in kids, and what is the meaning of that in terms of "incentivizing" the pharmaceutical companies to do this in pediatrics? Will it be worth it? From our perspective, anything that really impedes the progress and the efficiency of the systems involved in evaluating agents and getting new information that is going to be useful for treatment or kids is a bad idea. That is all we have got.

The second point I really wanted to address had to do with flexibility. I think, you know, the conversation today has yielded a lot of interesting suggestions about how

greater flexibility might be brought to bear with respect to FDAMA and with respect to the implementation of the Pediatric Rule, both formal in terms of the redesign of FDAMA specific provisions for cancer perhaps and, in addition, an informal mechanism such as that which was suggested by Dr. Spielberg and by others, picking up on the notion that, yes, there are informal contacts in industry and personal contacts that, hopefully, will be of benefit but there are also opportunities to bring FDA to the table, as happened in February, so that we can come up with more creative solutions to getting new agents, evaluating new agents, as well as understanding agents that are already approved and already in use in treatment for kids so that we can have sufficient information about those as well.

DR. CHESNEY: Thank you for your very thoughtful comments, and I understand there is Valium outside for our FDA colleagues who I think have stood up extremely well to the challenges presented this morning.

I would like to reiterate what Dr. Finklestein said, that I really believe this is a "we/we" situation and not a "we/they" and, please, be back by 10:55 and we will attempt to address the question that the FDA specifically gave us. Thank you.

[Brief recess]

Open Public Hearing

DR. CHESNEY: We are past the time for the open public hearing and nobody has signed up but if there is anybody here today that would like to make a comment at the microphone, this would be a good time to do so. Yes?

DR. REAMAN: I would just like to make a comment because, as Dr. Finklestein referred to earlier, I was at this meeting in February where there was a great deal of discussion, and certainly the end result of that meeting was that this is a "we/we" situation and we are working together very collaboratively.

Subsequent to that, in review of the guidance that was put forth from the FDA there were some concerns as related to flexibility to some of the interpretation, but I must say from my perspective now, being responsible for developmental therapeutics and sharing that responsibility in the Children's Oncology Group, I see absolutely nothing about the guidance which would limit the early access to new agents for children with cancer, and I would really applaud the FDA in everything that they have done to interpret and to remove any obstacles from the Pediatric Rule and FDAMA in ensuring this. Thank you.

DR. CHESNEY: Thank you, Dr. Reaman. Any other comments? If not, we need then to go on to the question to the committee, and I wondered if Dr. Hirschfield, Dr. Pazdur or Dr. Murphy would like to read it or interpret it for us,

or do we take it as written?

DR. HIRSCHFIELD: I think you could take it as written. I could just read it out loud for those who may not have a copy of the question: Special characteristics of pediatric oncology necessitated a more general drug development plan to qualify for the FDAMA pediatric exclusivity incentive. These characteristics are rarity of the diseases, life-threatening natural history of the diseases, biological differences between adult and pediatric tumors, the existence of established cooperative groups, and research protocols as the standard of care. Are there other areas of pediatrics that have similar characteristics that may benefit from a similar approach?

Discussion

DR. CHESNEY: Thank you. Comments from the committee? Yes?

DR. PRZEPIORKA: The information that we have been given so far yesterday and today indicates that extension of exclusivity is for drugs and biologics, and I was wondering if this is also true for devices, such as catheters or transdermal delivery systems, or diagnostics for pediatric diseases.

DR. MURPHY: The rule includes biologics. Now, if you look at the list that we did publish under the FDAMA requirement, it did include some biologics because we did

not look at whether something had a patent or exclusivity, and because biologics normally don't have patents -- that is why exclusivity is not usually including those. So, I am just trying to recognize that there is a little bit of confusion about the fact that we did have some biologics on that list. We were trying to look at products that we thought would have a public health benefit potentially if they were labeled so they were on the list. But, again, as Dr. Pazdur said, you have to have something to attach it to for exclusivity to work. So, that is a problem in that most biologics are not approved where they have that patent mechanism. So. Devices -- no. It does not apply to that either.

DR. CHESNEY: Other conditions which might qualify as pediatric oncology has? Dr. Fink?

DR. FINK: Well, the two groups that I deal with, cystic fibrosis, although there is a strong national organization there, and the other would be the neuromuscular disorders and, again, there is a strong voluntary health agency that has somewhat taken leadership in those two diseases, but they are similar in that they are life-threatening; they are orphan diseases; and there are care networks through the CF centers and the NMDA centers.

DR. CHESNEY: Dr. Luban?

DR. LUBAN: I would like to add to that group

sickle cell disease. Now, while it might not be life-threatening it certainly is quite morbid and there is, through the sickle cell centers sponsored by NHLBI, a growing clinical trials network.

DR. CHESNEY: Maybe I could add one group. I don't think we have any pediatric nephrologists in the room, but having lived with one for 30-plus years --

[Laughter]

-- who has devoted his career to trying to bring rare pediatric diseases to the attention of Congress, and their needs, I would just like to say that there are many renal diseases that also fall into the same category as Dr. Fink just mentioned. They are relatively rare. They have very strong support groups, and I can't elaborate on them but maybe somebody else in the room can but there is a very elaborate nephrotic syndrome network of investigators that would be similar to some of the pediatric oncology groups. Yes, Dr. Luban?

DR. LUBAN: Perhaps Dr. Hudak or Ward could comment on the use of the neonatal networks for some clinical trials, particularly in prematures.

DR. HUDAK: Sure, the neonatal network is an NIH sponsored group of study centers for which there is competitive application by sites. It is headed up under NIH CD. I think it has been in existence now for 15 years, and

the network I think is a good example of how cooperation between NIH and academic centers can produce some meaningful and important results, and it also illustrates, frankly, some of the perils of doing large, multi-center trials where there is a significant lag phase in terms of an idea gets developed and when it gets implemented, and what happens in the interim in the clinical centers. But, this has led to some important information and clarification of therapies in neonatology, and that is a little bit different model than the orphan type diseases because we are never at a dearth of neonates, and it does target some of the important morbidities that we see in premature babies.

DR. WARD: I think the other area that is actively involved in multicenter trials is that of the pediatric pharmacology research units. Dr. Kauffman wanted to comment about it, but that has allowed also multicenter trials to proceed in areas of very important aspects of pediatric therapeutics, and to proceed fairly efficiently.

DR. CHESNEY: Yes, Dr. Balis?

DR. BALIS: The other disease I want to raise is neurofibromatosis, which is a disease that shares a lot in common with cancer and which many of the new agents that we are developing that are molecularly targeted may have application, but at this point there really is no other standard therapy, other than surgery.

DR. CHESNEY: Several other categories that have occurred to me are the immune deficiency diseases; chronic granulomatous disease, very small numbers of patients, inevitably fatal, and I don't know about their support group but certainly SCIDs and some of the other better defined genetic immunodeficiency diseases have very elaborate support groups and networks. Then, the whole area of genetic and metabolic diseases, again, cystinosis falls in that category but probably other people here can think of many more of those. Dr. Danford?

DR. DANFORD: I wish I could say that pediatric cardiology and heart disease had things in common with the research protocols and networks available in oncology but, unfortunately, I can't. There are scattered examples of multicenter trials but, by no stretch of the imagination, can we say the standard of care equals Phase III trials even in cardiology conditions that are treated with medicines rather than surgeries.

The one place where we could say that there might be that kind of a situation would be in devices, and there the interventional cardiologists do have a well-developed nationwide network. Unfortunately, we just heard that FDAMA and the Pediatric Rule don't apply in those situations.

DR. CHESNEY: Dr. Luban?

DR. LUBAN: I would like to propose not a group

but, rather, a disease phenomenon that crosses groups, that is very, very common and requires a potential application of the rule, and that is in thrombosis, childhood thrombosis -- very, very common; unfortunately, poorly treated. At this point, no organized clinical trials, although there have been some moves through the hemophilia treatment centers to incorporate thrombosis trials in those groups. And, with the advent of all of the new low molecular weight heparins, it is potentially an important avenue to explore.

DR. CHESNEY: Dr. Fink, I wonder if you could elaborate or tell us a little bit more about the cystic fibrosis situation, which I thought was very analogous to the oncology example.

DR. FINK: Well, there are 125 centers that are partially funded by the National CF Foundation that participate in collaborative Phase I, Phase II and Phase III trials, and recently the National Foundation has even gone a step further and developed eight therapeutic development network centers that take care of the Phase I and Phase II trials and to use the entire network for the Phase III trials, so that there is even a gradation, and centering Phase I and Phase II trials in larger academic centers that have a large population and heavy research support has led to more efficient production of Phase I and Phase II trials, and then the Phase III trials obviously, because of patient

needs, are spread to the wider network. That has been a combined effort that really has both federal and private funding.

DR. CHESNEY: Dr. Luban, could you tell us more about the sickle cell networks?

DR. LUBAN: The National Hearth, Blood and Lung Institute has for years funded sickle cell centers which are a combination of both basic science as well as clinical research. For many years the clinical research was very single-institution directed, and it has just been within the last three or four years that there has been more of an attempt to bring those centers together and have them do cooperative clinical investigations and the initiation now of hydroxyurea trials.

My understanding from the Branch is that they would like to do more and more clinical trials and, of course, the infrastructure is all paid for already by NIH, with nurse practitioners, data monitors, in a similar way although clearly in a much lower scaled way than the cancer cooperative groups. Certainly, also from a biological perspective, lots of animal models, SCID mouse particularly, as well as pharmacologic manipulation so that as drugs can be developed, and are being developed, there should be a mechanism to do some translational clinical trials.

DR. CHESNEY: Yes, Dr. O'Fallon?

DR. O'FALLON: I believe there is an AIDS cooperative group for children.

DR. CHESNEY: Very active network of AIDS clinical treatment units, of which we have one at St. Jude, very actively involved in sharing data and comparing notes. Yes, Dr. Fink?

DR. FINK: Yes, one of the things that occurred to me yesterday when we were talking about psychoactive drugs is that almost all of the diseases and groups we are talking about share the issues of how do you cope at a family level with chronic disease? How do you administer chronic medications, and what do you do with the adolescent with a chronic disease? And, yet, none of the groups probably have the psychiatric expertise or maybe the number of patients to take on that issue, and there clearly is a need across pediatrics to try and understand family and individual coping and growing up with a chronic medical disability.

DR. CHESNEY: Thank you. I think we heard about autism yesterday which also very much falls into this category of relatively rare disease with a bad need for new drugs, new approaches. Dr. Ward?

DR. WARD: I would like to just provide something of an overview. I think we have just heard of multiple areas in pediatric medicine and pediatric problems that need additional therapeutic research. I think FDAMA can work,

and is working in many of these. And, from the February meeting, the FDA proposed mechanism by which trials at Phase I and Phase II level could qualify for exclusivity -- we heard it in its application to oncology drugs, but there are probably many other areas of therapeutics, from cystic fibrosis to cystinosis to other inborn errors of metabolism, that may benefit from that process.

When it comes time for renewal, I have concerns about trying to create carve-outs for specific clinical areas, especially if we have a process that can serve all areas of pediatrics effectively, because if one area is carved out and identified as unique many other areas will feel they are also unique, and the potential effect could be an unwinding of congressional support for renewal. And, I think we have to be very cautious in how we proceed over the next 18 months as this comes up for a great deal of debate and discussion.

DR. CHESNEY: Thank you. Any other comments? Suggestions for other diseases which the FDA has asked for? I guess, not having been at the February meeting but having worked with our pediatric subcommittee for sometime, I would also like to emphasize what Dr. Ward just said so articulately. I think many of us in the room have disabled children or children with a limited life span, including myself, and I think we would all like a carve-out, if you

will, but I think that it is important that we try in every possible way to support FDAMA, and I am very impressed at what the Oncology Group has done at the FDA -- Dr. Pazdur's presentation today -- to work with FDAMA, and I just would like to reiterate what Dr. Ward said, that we should all try at every level to support what has been a historic contribution to pediatric care.

DR. MURPHY: I guess I want to second or third that because I think when you go to Congress you never know what you are going to come out with at the end, folks. So, we have something that is working. We are working on ways to make it work better where we have identified problems. If you tinker with it too much, you don't know that you are going to get it at all, first of all, secondly, you don't know what you are going to end up with.

It is like a new child having certain infirmities and we want to trade it in for another child, I would say let us work with this child and support developing this child, if you will, because it truly is a program in its infancy. Think about what the potential would be for moving all these various fields forward, if we could ever get to the point where we actually had products that are already out there that aren't labeled and get them studied, plus then move these developmental fields forward in all these areas of science -- we have an opportunity here, and I would

caution some restraint as we go forward and, instead of trying to fix every single problem use the tools we have been given and work with them and work to have FDAMA renewed very much in the format that it is -- not that FDA doesn't have its problems either with it, but we really believe that we are just now discovering how to work with this opportunity in the most positive way. Thank you.

DR. CHESNEY: Dr. Spielberg:

DR. SPIELBERG: I would fourth that. With the perspective of having been in pediatric pharmacology for 25 years, this really is historic. I think most of us who have been in the field for a long period of time never would have imagined that we would be in the position where we are today where a lot of the past issues are no longer issues; where drugs are being actively studied; where large numbers of compounds which had been orphan for many, many years are now being actively studied.

The renewal of the legislation really is crucial I think not only to the issue of getting drugs studied, but really also has tremendous impact on the overall activities within pediatric departments around the country. It has stimulated a great deal of translational research.

If I can be critical of departments of pediatrics because I was in them for many years, even when I was junior faculty I was told there were two things you could do,

molecular biological or patient care, and that was it, and molecular biological was too difficult for clinicians and, after all, the molecular biologists didn't understand anything about patients so they should stay away.

What this has done is revitalize the whole issue of translational research. The old model which I was taught in the '60s in medical school of bench to bedside really does have validity, of getting science to the patients who need it, and this initiative has really reawakened that in a remarkable way. It is truly critical for renewal not only for pharmacologic interventions but really for clinical investigation in pediatrics in general.

And, there are certain things that have been done around the sites independent of the FDAMA effort, and I think that is another lesson that we can take. If there are specific issues, we can go outside the legislation to try to fix certain things. One example is that we have been working on legislation to increase the number of pediatric pharmacology trainees, you know, Ralph and I -- Bob is the only one who doesn't share our hairdo -- but we all are getting old and we recognize that so many years have gone by without pediatric departments focusing on the need for translational research that the next generation of translational researchers isn't there.

But that legislation, including some clever things

that Sen. Dodd's and DeWine's office came up with of debt forgiveness of those who go into pediatric investigation and stay in that field, along with additional support for the PPRU network to actually support the training slots that are needed, is really one aspect of things that we can work on independent of FDAMA, but even that initiative is truly dependent on FDAMA renewal otherwise we are going to be training people who won't have jobs in the long run. One of the neatest things about trying to train young people is that they will have jobs, otherwise why spend all those years? And, FDAMA provides routes for pediatricians to be involved in government, to be at FDA, to be at NIH. It provides routes for them to go into industry because industry will be working on pediatric projects, and it will obviously provide routes for their careers in academia so that the studies can be carried out.

So, you know, if you look at that piece of legislation for trainees and then you look at FDAMA you say, "aha, the two work together and they really do complement each other." Similarly, I think as time goes by, I think Dianne is right, I mean we have had -- what? -- a year and a half experience with this, barely two; ten drugs getting labeled in the previous ten years for kids and eleven drugs getting labeled in the last year. I mean, that is a ten-fold increase in the rate of activity. And, obviously, from

all the compounds that are now being studied, all those things will lead into labels. We have made mistakes and we have realized knowledge gaps. Those knowledge gaps then can be turned into support for NIH funds to study those disease processes so that we can get outcome variables that we can study so that we can, in fact, get drugs properly labeled for kids. It all kind of beings to work together. But critical to the whole effort really is getting FDAMA renewed and keeping the process going.

DR. CHESNEY: If I could just make one more comment, my husband, for those of you who don't know, is the chairman of our department but if I had a dollar for every time he has come back from a meeting at the NIH or Congress and said, "I can't stand these internists; they forget that children aren't just little adults and that we absolutely need to focus on pediatric issues." And, I think there have been many positive outcomes of his work and many others, the PPRUs is just an incredible idea. Maybe, Ralph, you can tell me sometime whose idea it was, but these centers that are just devoted to studying drugs in children are just revolutionary. And, I think in so many ways FDAMA represents this major new movement in support of children that I would just add again to Dr. Spielberg's always articulate comments that it is really critical that we try to work within the system or we will be back where we were

when internists ran the show -- apologies to any internists in the room! Any other comments? Ralph?

DR. KAUFFMAN: I would just add briefly to Steve's comments, and that is we need to understand that renewal of FDAMA is not automatic. There is very powerful opposition out there that will be doing everything possible to try to see that FDAMA is not renewed, and will be lobbying whoever is in Congress next session very aggressively to try to keep this legislation from being renewed. So, it isn't going to be automatic, and all of us are going to have to engage in a concerted effort, those who have the welfare of children at heart, to make sure that this gets done because it certainly is not a sure thing.

DR. CHESNEY: Thank you. Dr. Ettinger?

MS. ETTINGER: I just feel, from the unique perspective of being at the bedside as a nurse, I can reiterate what Susan had said. It is really important that we put concrete measures from bench to bedside because it is our parents and it is the families who actually drive this including parent support groups in all of these, they are the ones who actually bring it forth and I think it is most important that we continue that.

DR. CHESNEY: Dr. Murphy, the last word.

DR. MURPHY: I just want to thank you for your thoughts and the fact that, as we move forward in each of

these areas, we will be bringing different issues to this committee, again usually supplemented with the subspecialists, as you saw yesterday with neuropharm., and actually they have been one of the more active participants in this last year and a half in trying to help us to develop priority setting in how we move forward in this area. And, we will, as always, listen to what you have said as far as some of the areas that we may need to look at in our future written requests as we try to move the science and the information that is available. Because -- it a very good point to end -- what are we trying to do? People say why is the label so important? Because that is FDA's way of providing the science and the information. Now, we are hoping to develop other mechanisms and being able to transmit the information to the public in other ways besides just the label, but for right now the label is our main say of communicating to both the professional and, through some of our package inserts and med. guides, to the patients and the families. And, that is the goal. The goal is that you will have the right information, meaning you will know how you are dosing the child. The mother and father have the expectation that when their child receives that medicine it will have been studied and we will know that it will work, and we will know how to advise them as to how the adverse effects are. So, we are expanding this spectrum of the

preclinical all the way to not just the bedside in the hospital but the bedside at home in the middle of the night when you should be able to expect something as simple and common as your anti-pruritic to have the right dose. So, thank you all very much.

DR. CHESNEY: I want to thank all of our speakers today. I want to thank Dr. Smith, Dr. Weiner, Dr. Pazdur, everybody who made contributions and comments this morning. I think this has been a very, very informative session for those of us who are not oncologists.

This meeting will reconvene at one o'clock. Yesterday lunch was in the Plaza Cafe and there was room reserved for the FDA; we are not sure if that is true today. I think our executive secretary has an announcement.

DR. TEMPLETON-SOMERS: I just want to clarify this afternoon's meeting because I think there might be some confusion. The pediatric subcommittee of oncology will convene at one o'clock in the Chesapeake Suites to talk about the extrapolation issue, and the pediatric subcommittee of the anti-infective drugs stays in this room and you will be meeting also at one o'clock.

DR. CHESNEY: Thank you very much.

[Whereupon, at 11:34 a.m., the proceedings were recessed]

CERTIFICATE

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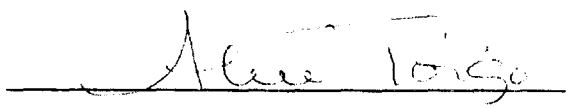

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Lawyer's Notes