SCIENCE ADVISORY BOARD (SAB) MEETING
JUNE 11, 2001
National Center for Toxicological Research

Casciano: Good afternoon. I would like to introduce Dan Acosta who is the new chairman of the Science Advisory Board and he will start the meeting off. Thank you

Acosta: Thank you. I would like to call to order the NCTR Science Advisory Board meeting. Thank you Dan. I'm glad to be here. I would like also for the records I would like to introduce the new members to the Science Advisory Board and we will go around the table and introduce each other to the whole group in just a second but let me for the record introduce the new members. Jerry Kaplan from the University of Utah School of Medicine, Jerry, welcome. Kenneth Tindall from NC Geonomics and Biopharmatics Consortion. Ken, nice seeing you. We have a third member who is ill and can not make it; her name is Elizabeth Barbehenn. She is a research analyst at Public Citizen and she is the consumer representative to SAB. And finally we do have another member who is not so new but she has agreed to continue for another two years, Marcy Rosenkrantz. So thank you Marcy. Let me also introduce, it is my understanding, we also have Len Schechtman who is the Associate Deputy Director for Washington Operations who is the new executive secretary for SAB. And we also have here Jim MacGregor, Deputy Director for all Washington Operations. So why don't we go around. I will start. My name is Dan Acosta and I am at the University of Cincinnati Medical Center. I'm the Dean of the College of Pharmacy there. Marcy Rosenkrantz of Cornell University, Jerry Kaplan of the University of Utah School of Medicine, Catherine Donnelly University of Vermont, Nancy Gillett I'm the general manager at Sierra Biomedical, unintelligible, Jeanne Anson Associate Director for Planning, my name is Meredith Grahn. I'm the Director of the Arkansas Regional Laboratory and Office of Regulatory Affairs of FDA, unintelligible, Jim MacGregor, I'm Deputy Director for NCTR Washington Operations, Bern Schwetz Office of Commissioner, FDA, Len Schechtman Associate Deputy Director for Washington Operations, NCTR and your exec sec. Dan Casciano NCTR.

Acosta: Fine we will have Dan introduce our next speaker.

Casciano: Yes, we are very fortunate to have Dr. Bern Schwetz here who earlier gave a very nice talk to the All Hands meeting. Bern is a long standing supporter of the science in the Agency and a long time supporter of the National Center for Toxicological Research and he is presently, he is a former Director of NCTR and is presently the Acting Principal Deputy Commissioner, that's a crazy acronym too, any way we in the FDA and I hope I don't embarrass you Bern, but we in the FDA thank you for the hard work and the effort that you have made on behalf of the employees of the FDA and we welcome you back to Jefferson, Arkansas.

Schwetz: Thank you Dan, I don't use that title either. It doesn't make a lot of sense. It does not say what I do either. So Acting Commissioner makes more sense. I want to extend my thanks to those of you who are new to the board, Ken and Jerry and Marcy for coming back and helping us for another term and Dan thank you for agreeing to serve as the Chair. I also want to thank in particular the liaisons to our other product Centers in ORA and to UAMS. That makes this board I think more useful from the standpoint of surfacing information to have the kind of

representation that we do from all of you so thank you for being here as well. Because I talked this morning and a lot of you heard that and I took advantage of the opportunity to have lunch with our SAB members to talk about some additional things and some of our FDA people as well over lunch I will not repeat those things but there was one thing that I haven't talked about yet to any extent that I wanted to and that is the peer review process. The Agency has been moving up on formalizing peer review to a greater extent than we have before and one of the aspects of that was to do a peer review in everyone of the Centers from not the protocol level, not the laboratory level, not an office level but from this whole Center and that was done at NCTR while I was still here. Since then we have been going through the rest of the Centers of the FDA. We started with the Center for Biologics and then we did the Center for Food Safety and Applied Nutrition. The Center for Devices and Radiological Health is going through their process right now. They are half way through and I'm in the middle of discussions with other Centers. CVM is working on their review program and the Center for Drugs is working on theirs as well. So is ORA. So one by one we are making the rounds through all these operating components of the FDA to do peer review of the science at the whole level. It is not peer review of the individuals or whatever it is the whole science program within various Centers. That is something that I think is important for the whole Agency. It is something that is the beginning for those Centers that do not have a more formal program like you do here at NCTR and the Center for Biologics has one probably because they are on the NIHS campus. They started as part of NIH so they have kept up the tradition of peer review in the same sense that the peer review at NCTR was modeled after the NIH peer review. So CBER and NCTR have formal review programs from the top on down to the protocol level to a much greater extent than any of the other Centers and we continue now to work to see how we can escalate that peer review process through CFSAN and other parts of the Agency to move from the big picture to more and more levels of the Agency down or the Center down below that the big picture level. Dan one of the things I would put to you is that it is probably time for you and the SAB to consider another review of NCTR. Because it has been four or five years now and the last time we did it was very helpful. I would also comment in thanks to those of you on the SAB even more so to those who preceded you in the last seven, eight, nine years. I think one of the things that is unique about NCTR is that the Science Advisory Board has had more of an impact on what happens at the Center than the other Boards of Scientific Counselors or SABs in other Centers. And as we review Centers one by one it becomes clear that a more thorough advisory program like the SAB has provided would have been helpful if it had been in place for a long time in the other Centers as well. I think that one of the things that it has helped at NCTR is that, for example, in some of the other reviews, it is discovered that there are pockets of people who are just totally out of the loop in communicating with the rest of their Center. And they may do good work but they are not part of the process of what is going on in the Center. Or there are duplications of efforts. People working on a certain pathogen in one laboratory and there is another laboratory working on the same organism that for one reason or another has evolved but they are not working together and they just coexist and it is wasteful and they are in some cases duplicative, they are clearly not working together, it's not collaborating. I think the program through the years at NCTR has helped to surface those things and as a result you don't have pockets of people who are totally ignored. And you don't have two or three teams working on the same thing as if it is a competitive process and you are trying to find which one is best. Those kinds of things haven't happened here and maybe they did at one time and if they were brought up by the SAB they have been taken care of. So I just want to thank you for the help that I know you have already been and that those of you that have been

here before continue to be. And it kind of sets the pace for those of you coming on new to continue this tradition. But I would ask you as a board to continue to be a rigorous as you can. I would encourage and Dan you and I can talk about what this would look like. There isn't just one preconceived way of reviewing the whole Center. One of the things that we are learning is that different Centers are doing it different ways. ORA is going to pick it's own way so we need to look at how various Centers are doing it to decide do you try to look at the whole Center or do we look at some particular function as a representative of the Center. That is something that I hope you all would talk about in the future, how this would work. I can do nothing but thank you and encourage you to keep going.

Acosta: Well thank you very much. I know that you have put a lot of time and effort in the last year or so and we appreciate what you have done. Before we get to Dan Casciano's remarks we first need to get the approval of the minutes from the last meeting. Are there any corrections, additions, or revisions?

Hansen: Unintelligible…there was some extended discussion about dietary supplement work and priority setting and I guess I point out to the couple of other ends points that we can talk about…cardiotoxicity and that complicates a different…

Acosta: This was discussed at the last. Who is the one doing the minutes? I'm not sure. You will be able to put that in to the minutes? Okay, appreciate it. Thank you.

Schechtman: Could I just interrupt please and ask everybody to talk in to the microphones since we are recording this information for transcriptional purposes. Often we will try and document what we think we are hearing on the tape and it is not accurate. Thank you.

Acosta: Okay, well that's good. I think we got that on tape. Are there other additions, revisions or corrections to the minutes? If not do we have a motion for acceptance? Then approved and seconded all in favor of having the minutes approved. I. Any opposed. Okay thank you, the minutes are so approved. Before we get to Dan, Len I was told that you may have a few remarks or announcements to make at this time.

Schechtman: Okay just a couple of house keeping details. We will be departing for the hotel as soon as the meeting adjourns. We will give you about a five-minute buffer but that is about all we can spare. We want to go back to the hotel to give everybody a chance of about 60 to 120 seconds to freshen up and check in and then we will be able to recongregate in the lobby at 6:45 to gather for transportation for dinner at 7:00. We have a reservation. We ask that those of you who can recall who you came here with try and reconnect with those folks again so we can keep shuttling the same people back and forth in the same manner that we got here. Thanks very much.

Acosta: Okay, well thank you. Next on the agenda is Dan Casciano talking about the Director overview.

Casciano: I would like to also welcome the FDA/NCTR Science Board and once again I thank you for the time that you have put in to help us in the past and for your continued support

and advise in the future. I think that Marcy can probably tell you by her acceptance of extension to this board that we listen to you. So we really do and we try to respond to the comments that you make through our site visit as well as through the comments made here on the annual Science Advisory Board. We feel that we have a strong Science Advisory Board. We have just strengthened it with several … and biotech individuals and we thank you for accepting our request to be a part of this group. So what I plan on doing today is since some of you are new and some of you are relatively new I plan on providing some information on the FDA and where we fit in the FDA. During our preliminary discussions we talked about various Centers and I will show you organizationally where we fit. I will speak a little bit about the organization of the NCTR since the majority of today and tomorrow will be spent by the Division Directors providing you with updates to their programs. They will give you status and recent accomplishments and also some discussion on where they will be going and then I will talk about the function of the SAB. So this is the structure of the FDA and as you can see on the bottom set of boxes there are six Centers associated with the FDA which four of them are product Centers and two of them are … Five are product Centers and one is a research organization and that is us and what we try to do is interact with the various Centers to attempt to utilize the basic information that is in basic science that is provided through the NIH funded mechanisms and utilize some of the information derived from NIH grants and act as fundamental research or translational research towards applications to the needs of the Food and Drug Administration. And everyone of those product Centers have different mandates so it is like working with five different planets sometimes and trying to understand what their mandates are. I can see Meredith is smiling over there. She understands being a part of the Office of Regulatory Affairs. She has to understand their mandates and then respond to them. Bern is the individual sitting at the top in the Office of the Commissioner so he has not only the product centers but also the huge Administration Infrastructure that he has to over see. I'll just spend a couple of minutes talking about each of the Center's mission and where we think we interface with the various Centers. The first one of the Center for Drug Evaluation and Research and the Center assures the safe and effective drugs are available to the American people. And you can read their issues as well as I can and the areas that we interact with the Center for Drugs is mainly in premarket evaluation as far as drug safety. So we interact with them by helping develop new methods by which drugs can be evaluated for their safety where we have interest in their efficacy but we don't interact at that level and we provide methods and we provide data so that risk assessment can be developed to understand potential safety of drugs to the public. And Center for Foods, they have a huge mandate and are responsible for promoting and protecting the public health and economic interest by insuring that the nations food supply is safe. We interact with these various issues either at the food safety level, the Division of Microbiology, will tell you some of the activities that they have relative to food safety. Earlier we were discussing the potential for development of patents and therefore generating a revenue for foundations and for the individual scientist and we have interacted and developed a method to detect seafood decomposition and the process started out several years ago with a machine that was the size of this table and our researcher has reduced it to a dip stick and it is the size of a toothpick that can then be determined whether or not the seafood that we purchase from the store is fresh or is on it's way toward decomposition. And, I'm assuming, you will hear from Bill Allaben or Dr. Fred Beland on our interactions with Phototoxicity and understanding the safety of Alpha and Beta Hydroxy Acids that are components in cosmetics. Center for Veterinary Medicine is responsible for assuring the animal drug and medical feeds are safe and their issues are food safety antibiotic resistance and

Aquaculture. I mentioned our work with Food Safety. Our Microbiology Department will also tell you something about their efforts in Antibiotic Resistance and we will also talk about some of the work we have going on evaluating the safety of antifungal agents that are used in the Aquaculture industry. Center for Devices and Radiological Health is their mandate is to protect the public health by providing reasonable assurance of the safety and effectiveness of medical devices. We are developing protocols of tissue based products to evaluate/develop methods that will help us detect proems or surrogates of proems and this organization also is responsible for evaluation of genetic assay kits and we are developing gene chips that detect polymorphism in the human population and we will be used as a guinea pig for going through their mechanism. And we are just now doing some talking with the National Institute of Health and perhaps enhancing their phototox facility so that we can also evaluate electro magnetic radiation. The Center for Biologics. This is the, as Bern mentioned, this is the organization that is most like us. They have hypothesis generating scientist who also have a duel responsibility of review and their mission is to protect the public health as far as bioglical and related products including blood, vaccines, etc. And we are interacting with them in developing technology to antiterrorism activities and also they have a rather successful research program in the porteomics area that is in full collaboration with Lance Leota at NCI and we are collaborating with them in this specific area. And of course the Office of Regulatory Affairs is the lead office for all field activities of the Food and Drug Administration. We have a laboratory located on site that is a rather large responsibility in this region and we participate with them in bacterial contamination issues and seafood decomposition and other international harmonization. This is what the organizational chart looks like here at the NCTR. We have an Office of Research and an Office of Management and we will be hearing from each of these Division Directors except for Veterinary Services today on updates of their particular activities. We have the Division of Microbiology and Carl Cerniglia is the Division Director of this group. Unfortunately he is not here today and this group will be represented by Dr. Saeed Khan. Right. I was thinking Dr. Mohammed Nawaz and I'm sorry Saeed Khan. He will provide the effort that is occurring in that division. We will be hearing from an overview from the Division of Molecular Epidemiology and unfortunately Fred Kadlubar is not here. He is south of the equator. He is in Australia on a three month sabbatical and Lionel Poirier will be telling us about the activities that are occurring in that particular group. Dr. Fred Beland is here. When we allow him to leave we send him to Hot Springs Arkansas so he decided that he would rather be here and tell you about what is going on in his division and he is the Division Director for Biochemical Toxicology and he wears multiple hats and I am assuming he will talk about the Biochem Tox area and maybe part of the NTP and I think that Bill Allaben will be telling us more about our interagency agreement. We have a brand new Division Director for Genetic and Reproductive Toxicology, Dr. Martha Moore, and she was hired about this time last year I think and she came in late summer and she hit the ground running and she will tell you about the efforts going on in that group. And Bill Slikker, as many of you know, will give us an upgrade on the Division of Neurotoxicology. Ralph Kodell will tell us about some of the exciting activities going on with data base development and also statistical evaluation. And we have a second brand new Division Director. Rob Turesky. He recently joined us from Nestle's in Switzerland and Rob was trained at MIT and he will tell us about his efforts and Bill Witt, I'm not sure if Bill is here and will make a presentation but he is the Division Director for Veterinary Services and it is his function to maintain the health and welfare and production of the animals and utilizing our various protocols. Bill Allaben will provide us with some historical information on sharing some of our recent efforts we have had in

responding to the FDA's needs and respond through this interagency agreement which is also a source of revenue for us. Okay so I thought I would give you a snap shot of the NCTR Resources over the various fiscal years and you can see that in the last eight or nine years we have not had any of the, this is the FDA allocation and there has been no growth here and this is indigenous to the FDA. And we have had a variety of recommendations made earlier to try and enhance this process and perhaps some of them will …, so any way this is the FTE allocation that we have had over the last eight years as well and you can see that from FY93 to FY 99 this is representative of what is occurring in the FDA. We had a large loss in people and there has been a slight rebound and we are anticipating a continued enhancement of the slight rebound. The way we attempt to maintain a level of productivity is we have a rather successful postdoctoral program as well as utilize the on site contractors to provide a method of maintaining a certain level of productivity. Now this is another way of depicting our resources over the years. You saw the green bars and the red bars are the additional sources we received from the National Institute of Environmental Health Sciences and it is through the National Toxicology Program Interagency agreement of the FDA. These additional dollars have allowed us to maintain a critical mass of scientist here at NCTR and Bill Allaben will talk to this particular interagency agreement. For 2002 we went through a rather ambitious process of requesting additional dollars and as you can see the appropriated dollars were some of a percentage of what we had asked for but one of the increases that we have obtained, we being the FDA, for the first time in ten years is cost of living increases. It is reflected in all of the previous charts I have just shown you that when the annual salary increases incurred there were no appropriated dollars to pay for them so those dollars have come from other sources and they came from other programs and redirection of funds and this year it seems like there is a high probability that we are going to obtain cost of living increases. And hopefully when this becomes part of the base, it is a very difficult problem on the road to …. And for 2003 this is what our request looks like. Our request in the premarket review is the largest request. We are making an effort to enhance the visibility of the Proteomics in the FDA so we are requesting two and a half million additional dollars in the Proteomic/Genomic area and additional dollars in antimicrobial dietary supplements and food safety is still a high visibility in the new administration as well as the old administration so there is a potential for obtaining nice dollars there and a cost of living as well as attempting to catch up with … So here are a few areas of what impact directly on our mandate to respond to FDA needs. We provide FDA with highly credible scientific data to the National Toxicology Program Bioassay so that their risk assessment can be made more confidently. We are relatively major players in the food safety initiative. I mentioned the system that allows us to detect seafood decomposition. Our Chemistry has developed this process of attempting to revise this system to also detect decomposition in poultry and the technology that we would like to apply in the Proteomic field, the analytical technology is transferable to Bioterrorism as well as the food safety initiative and we provide an intellectual resource for the FDA. We are consultants to all of the various centers when research questions arise that need consulting to respond. We also are involved in what I call fundamental research and some of my colleagues call translational research and this is application of technology in other things of these research results to the application to the applied environment. And we are doing work in DNA adduct area and we have been called over the years the DNA adduct capital of the world and some of us believe that and there are people in our Microbiology group who are working with artificial GI tract which is a human GI tract and we feel that this is a process that can be used in helping us evaluate nonspecific way effects of dietary supplements and perhaps genetically modified food. You will

hear a response by Dan Sheehan this afternoon on the work with the Estrogen Knowledge Base and Estrogen Computational Toxicology arena. We have done work in nutrition. This is not the preliminary chain reaction it is the project on Caloric Restriction and this effort has generated a whole new great number of hypotheses. We developed and modified transgenic animals for use in detecting mutagenic and carcinogenic agents … So what is the function of the Science Advisory Board, for the new members who have read all of their materials. I thought I would bring this to the floor. Your function is to advise the NCTR Director on Science budget and other issues and today we are going to be discussing the possibility of moving this new subcommittee under the umbrella of the NCTR Science Advisory Board for the non-political science and subcommittee. Jim MacGregor, our Deputy Director for Washington Operations will present this to you in a rationale for this subcommittee being under the age of the NCTR Science Advisory Board. The members serve on a full SAB for review of science visit reports, site visit reports so that is one of the functions today you will hear. Updates of the reports that are provided by the site visits teams and hopefully the chairs of those site visits will respond in a positive way or however they feel is appropriate to how our managers responded to their critique and also the probably the hard part of your job is to serve as chair or committee members of the program or division site visit teams and generally we review our programs and divisions on a cyclable basis and it averages out to every three or three and a half years. The end of this year we will be putting together a site visit team to evaluate the Division of Chemistry so you will be hearing from me in the near future and perhaps Dan as well regarding volunteers and potential appointments to that. The members of the board serve in their specific expertise relative to the various programs or divisions that are being evaluated and we also solicit Ad Hoc members in that specific area. So what is going to happen in toxicology in the millennium? This is what is going on right now and perhaps we can discuss this. If one looks at the top of … we go from gene expression to toxicity. The way we have been evaluating the toxicity up until now is in the green arrows where we start with the organism and will end up with slides of the tissue or try and to make some statement as to what is occurring at the cellular level, then hopefully understand the biochemical mechanisms so that we can make reasonable models that we are using to extrapolate to the human. The new paradigm will be moving from genomic to proteomic and to get to the Biochemical mechanism and concert with the continued relationship of these early biomarkers to what is occurring at the cellular tissue organ. So we will be evaluating up regulation or down regulation of gene expression and what effect that up regulation or down regulation has on protein synthesis and modification of proteins and the effect that the chemical of interest then has on the functional activity … And of course you have seen this depiction. We will be utilizing and hopefully developing areas that will utilize the various homics. And what we are interested in is developing better predictive tests or prediction of what is occurring in the human and not what is occurring in our rodent surrogate systems. So there are the emphasis on DNA protein based technologies and we will be designer animals using transgenic and the biomarkers will be a greater fitness upon the surrogate and the human homologues. Of course there will be a decrease in the use of animals and we will be becoming more dependent upon in vitro systems that have relevance to the in vivo and since there will be a tremendous amount of data generated from these various omics we need to apply computational science expertise to the understanding of the data that we are developing at this time. We have a couple of current genomics projects at the NCTR and they have to do with human geno typing. They are developing a risk chip that contains a variety of DNA fragments associated with polymorphines and cytochrome 3-450, gene products and also phase II metabolism enzymes. And we are using

high through put gene expression model to try and develop and understand biomarkers, which are indicative of toxic responses. In one of these is the chemical toxicants on gene expression profiles and basically we are using in vitro primary rodent cells to predict the in vivo response and that particular organ from which those mammary cells are derived from and then utilizing primary human cells and hopefully predict in vitro response.

Tape 1 side B

Casciano: And this is the SNP chip I was just talking about. We are interested and we think it has a use in understanding the adverse drug reactions that are now showing up in a variety of drugs that have already been proved to hopefully help us understand cancer susceptibility about drug efface and subsets …unintelligible… and eventually get down to individual drug design. At the present time we are in the process of developing the Proteomic area and we are doing that initially by making a commitment to purchasing of analytical equipment to help us identify protein changes. This is primarily occurring in the Division of Chemistry to provide an infrastructure there so that we can utilize the infrastructure as a recruitment tool to enhance the biological questions that we are interested in. The problems that we have are the problems that most organizations are having in getting in to this …unintelligible… and that is one developed in house Chips and one utilized commercially prepared chips and it is a difficult process because the technology is moving so fast that by the time one is set up to make unknown chips the genes that you are interested have been produced at a much cheaper level than what one can do. Then of course recruiting the staff and retraining the staff here at the NCTR is not an easy process. Many of us are only five to six years away from retirement age and there is a probability that 20 to 25 % of our staff will be turning over in the next five years and our location is not the most ideal for recruiting the staff that are required to develop the programs that we have interest in. The location is not the east coast or the west coast and also there is the added problems of the individuals that are, everyone is looking for the same people, and the individuals that we have interest generally have a professional spouse as well and the pools for positions for professional spouses are not quite as obvious here in Central Arkansas as they may be in the Boston area or the LA area. So we are looking for creative solutions and Bern mentioned some of them today and we are attempting to utilize some of those recommendations. We are utilizing creative recruitment now and I am in the process of recruiting individuals for a new group that I am developing the cellular and molecular toxicology group and we are in the process of doing some heavy leveraging. The leveraging, the NIEHS has a toxicogenomics group and we are communicating to a high level with them and to enhance our desires to participate in this specific area and it is necessary for the FDA to be players in this area because industry is already using these technologies. In the near future they will be developing safety data generated from these technologies and the FDA needs to be ready to respond to that or else we will take the most conservative approach and we will become bottlenecks to the process and not be catalysts. I feel collaborative efforts, our colleagues, are highly creative and interactions with academia and industry and we also have the possibility of purchasing academicians through the intergovernmental personnel act where we can hire academicians for a year or two and they can spend their time here or work at their home institutions on problems that are of interest to the NCTR and/or the FDA. So I come back to this and I think some of my colleagues are high enablers of the new technologies and the application of these new technologies to the various disciplines in toxicology and some of my colleagues are disablers of the process. One of my

well-respected pathologists indicated to me that he does not believe anything he can't see and we have technophobe so it is a very difficult process. A difficult hill to climb but we are attempting to make it. Any advice that you can help us in moving in a positive relationship would be very appreciated. I will stop there.

Acosta: Okay thank you. We have a couple of minutes for questions from our SAB members old or new. Does anyone have any questions?

Unknown: Dan I have one, a couple really but how did you manage to give raises and other things during those years. Is there such a thing as merit raises?

Casciano: One of our uniqueness and it is a real asset as far as we are concerned and unfortunately we will not make that presentation but the FDA owns this Facility so every dollar that we bring in we squeeze it to a dollar and a nickel to as it goes out the door and it is because we have developed, and it's mainly through our interactions between our scientific side and the research side and the administrative side where we track everything that we do so we know what everything costs us. And it is primarily a requirement for good management of the Facility as well as our interactions with the NIEHS, they would come in and ask us how much would it cost us to do a specific cancer bioassay and we give an answer in which they did not think it was too much and it wasn't too little so we are short changing ourselves so we feel we are very good managers and part of the answer to your question comes through leveraging the dollars that we make through the NIEHS and Bill Allaben will tell you a little more about that.

Acosta: You derived revenue from fresh tag that you can use?

Casciano: Not yet but maybe Dwight might, Dwight the inventor is standing right there.

Acosta: When fresh tag becomes more prominent can revenues generated be given back to the NCTR?

Miller: The royalties come back to NCTR to support research programs. A portion of it.

Casciano: And it's sort of on the low part and we have great expectations and we are going to have a steep increase. We are going to be sending money back to the FDA.

Acosta: Okay, well thank you very much. Appreciate it. One question over here.

Gillett: It didn't seem like you were as successful as you might have hoped for your out of year request for 2002. Do you have any better prospects for the 2003 funds?

Casciano: Well what we are doing that helps us has to do with our strong ties with our sister centers and there is a higher probability that dollars will go to food safety initiatives and to CFSAN and the Center for Veterinary Medicine so what we are doing so that we can participate in those extra dollars is developing strong interactions with them so that they come to us to help them with the regulatory question. Now as far as the next year, nobody really knows what will happen next for 2003. I think there is a high probability that we will get current services again

and we will get cost of living again since there is quite a good chance that we are going to get it this year and once it gets in to the base it ends up being pretty uniformed. But you heard Bern say in his talk that for 2003 they had asked us to only for 4% increase and at the present time they being the Administration, have asked us to limit our request to 4% increase then we being the FDA are asking for more than 4% and trying to justify the need for the administration to support that is anyone's guess.

Acosta: Alright well thank you Dan, appreciate it. Next on the agenda will be Jim MacGregor, Deputy Director for Washington Operations and is Jack Reynolds going to be contacted now or how is that going to work.

MacGregor: If all goes well Jack is going to be calling in. He is in another meeting, which occurred at the last moment on Friday, and he has got to come out of that meeting to call us. We are hoping that will be happening at any moment. As Dan has said we have unfortunately had two problems with our other representatives if we are going to speak about his topic during this hour. John Doull who is chair of the nonclinical subcommittee originally was going to come and then could not because of a conflict with a National Academy meeting. Jack Reynolds who is on the committee and who is the former chair of the Pharma Drew say for the drug safety committee for the Pharma organization who has been a member is going to be joining us by telephone. He was hoping to come in person but he an emergency that arose on Friday that made us change to this format. What I am going to do to introduce the topic is to address first some of the general issues that were raised by Bern and his comments this morning and also the issues that were brought up by Dan Casciano. In terms of how is FDA going to deal with the excelleration that is occurring in science in the limitations and resources that we have and what is the mechanism by which we should be interacting with our stake holders to address some of the new scientific opportunities and in the most efficient manner possible to work with our stake holders to address these opportunities and turn science in to new regulatory methodology and new regulatory approaches that can be brought in to a regulatory process. Since I personally came to FDA about four years ago this has been one of the major focuses of my personal efforts, is to try to develop mechanisms within FDA to work with all of those people that are concerned with our product development and the impact of our products and that includes both FDA, other public and private institutions, the industry and the public and public institutions like NIH, all of whom have a common interest in doing the best possible science as it relates to a regulatory process in the development of the products that we regulate. And so first I'm just going to spend a minute or two on the general topic and then as Dan said I'm going to introduce to you a case history of a subcommittee that has been formed specifically for the purpose of addressing new scientific issues in the pharmaceutical development area and I will give you some of the history of how that committee was formed, the direction it has taken and when I do that you will see that the direction that that committee has taken has been in the direction of new methodology and biomarkers as applied to the field of toxicology which of course is one of the major mandates and focus on the NCTR. And so I will come to that and to NCTR in this specific Advisory Board's possible role in the activities of this existing committee. So the general question How can FDA best focus and leverage resources to capitalize on new scientific opportunities many of us in FDA have been dealing with this issue for a number of years and one of the approaches that we developed, Bern mentioned some other approaches that are being taken, but one of the approaches we developed is to use the existing Advisory Committee structure and to consider the

formation of specific advisory subcommittees that are charged to identifying the new scientific opportunities within a disciplinary area and then to bring together appropriate experts within the areas of opportunity. To do this in a public way that uses the public mechanisms and the public for that the advisory committees are structured around. So to have the whole process but public announced through the federal register to involve all of the stake holders that are involved and included professional societies in the disciplinary area and then ask these subcommittees to go one additional step beyond the traditional advisory committee. And that is to go beyond simply just giving advice to actually having them play an active role in steering collaborative projects that would evolve from the focus areas that are identified by the expert committees. And so then this subcommittee may go this extra step to play a steering committee role to actual collaborative projects that would arise from these expert groups and to oversee the output such as workshops and reports and recommendations that might come out of these activities. Now Bern mentioned a slightly different approach that had been taken in the Center for Drugs, the product quality research institute which was a similar idea that was done outside the Advisory Committee structure just via an Ad Hoc consortium development and that has also been done. I think JIFSAN is another example led by the Center for Food Safety and Applied Nutrition of building collaborative structures to bring FDA together and to working together with it's various stake holders and academic partners to pursue some of these objectives. I would say the first example of the subcommittee that has been charged under this model that I just described is the nonclinical study subcommittee of the Advisory Committee for Pharmaceutical Science and this is the subcommittee that I would like now like to spend a few minutes talking about to give you some of the background and of course those of you on the Advisory Committee received a background package prior to the meeting to review the concepts and some of the history and activities. So I will go over these quite briefly. But basically this committee really grew out of a concept that was initially and Ad Hoc consortium concept called the Collaboration for Drug Development and Improvement that was begun by Carl Pack who was a former director of CDER before Janet Woodcock and a number of academic collaborators and others within the government as a way of focusing on ways to use science to use drug development. Discussions on this began back around 1996, 1997 and actually they entered in to some subcommittees and structures to pursue these and for reasons I will not go in to that really never came to fronton but in late 1998 I would say when it became apparent that the CDDI was really not gelling and not going forward the committee that was involved at that time in the nonclinical studies area decided to move that activity in this advisory subcommittee structure that I just described. And essentially to try the experiment of using the advisory committee structure as a mechanism and vehicle for achieving these goals that I just set out. And so in August of 1999 there was a meeting to develop the concept and the parties involved agreed that it would be a good idea to try this concept through an advisory subcommittee. Having decided that in the next month in September the concept was brought to the Advisory committee on pharmaceutical science and presented to them. They agreed with the concept and agreed to take on this subcommittee within their advisory committee. Subsequently in December the committee met and got in to a substance of discussion and including bringing in outside experts for talk about really what were the main focus areas that should be pursued and two were selected and this was Molecular Biomarkers of Toxicity and Noninvasive Imaging and Imaging Chosen because of the concept that as the new molecular approaches that Dan just described that many people believe is going to transform the field of toxicology as these molecular markers are identified and brought in to practice you are going to have to have accessible, is that, that's probably Jack (phone call from

Jack Reynolds). His Sandy I'm here too you are on the speaker in our Advisory Committee meeting.

Yes, Dr. MacGregor, Jack Reynolds has just called me from a conference room. He is still behind closed doors in a meeting and can not break. He gives his apologies. The only thing he can do is if he can break call in.

MacGregor: Well, we are in the middle of our topic at the moment so do you know will this likely happen in the next ten minutes or so?

Well, I can tell you that this meeting was suppose to break at 2:30 prompt and he is still behind closed doors with Newblack and some of the other execs.

MacGregor: Okay, well we will play it by ear. So if he can call please have him do so.

Thank you Dr. MacGregor.

MacGregor: Okay, so the concept being as these molecular markers are brought in to practice the genomic technologies and the gene chip technologies that many people initially were excited about obviously are going to be very useful discovery tools but in general they don't provide an accessible biomarker. You need nucleic acids to run a gene chip and you can't readily get those out of internal organs and tissues so you are either going to have to work on accessible markers or imaginable markers. And so this was the reason that imaging was selected as a co-topic. Having made that selection in March the committee again met, again brought in some more focused experts in these areas and decided to focus on two topics that were of current interest to the Center for Drugs Cardiotoxicity and Vasculitis Biomarkers. The public process was initiated in July with a call for nominations in the federal register and letters to professional societies in the area and other mechanisms and then in January the first two expert groups were constituted or selected and formerly constituted and a meeting was scheduled and then the first meeting took place the first of May, May 3rd and 4th of these two groups, the groups on Cardiotoxicity and Vasculitis. So basically without going in to the scientific detail of the topics that is a history of the focus areas and again you can see that this has come down to really a focus on essentially molecular markers of toxicity. So then back to the general concept of the committee, as I have already said the function of the subcommittee was to provide advice on improved scientific approaches in this case focused on drug development, pharmaceutical development and to foster scientific collaborations among FDA, industry, academia and the public. In terms of the committee as it was constituted this focus was in the area of nonclinical information related to drug development. The productivity of nonclinical tests for human outcomes and the linkage between nonclinical and clinical studies and again to go this extra step beyond just providing advice but to actually facilitate collaborative approaches to advancing the scientific basis of applying these technologies to pharmaceutical development and regulation. The current organizations that are involved in this particular subcommittee are three of the FDA Centers, CDER, CBER, and the NCTR, two major industry organizations Pharma, the pharmaceutical research manufacturers of America and Bio, and the Biotech industry organization. Academia and public research institutions as represented by NIH and NIEHS. The actual people that are representing these organizations are listed in this slide. As I have already said John Doull of the

University of Kansas is chair. I am the FDA coordinator. Dave Essayan is the CBER liaison and the other FDA coordinator. Jack Reynolds who we will hope will get on the phone in a moment initially came on representing Pharma. He is from Fizer. He is the vice president for nonclinical development and safety at Fizer and was at the time he came on the chair of the Pharma drug safety committee. Joy Kavanero from Bio, Jack Dean and Jay Goodman past president of the Society of Toxicology. Ray Tennett who is director of the National Center for Toxicogenomics that Dan just mentioned and Dan Casciano representing NCTR. Now the reason for bringing it before this advisory committee is because internally we have discussed within the FDA the direction that this committee has taken and as I have already said the direction that this subcommittee has taken has been down the path of Molecular Markers for Toxicological Evaluation and Safety Evaluation which essentially is the mandate of the NCTR. As you have heard from Dan there is a major focus in the program here at NCTR to focus in the same areas that have been selected to pursue by that committee. In the meantime not only have I moved over to NCTR but Len Schechtman who is your executive secretary. Along with Len in addition to being exec sec of this committee he is also the FDA Agency lead for the interagency coordinating committee for new methodologies in toxicology. And what this brings to NCTR is essentially the interagency method for bringing new safety evaluation methods in to regulatory practice. So a lot of the functions and commitment of NCTR are such that this has led to internal discussions within FDA among CDER and NCTR and the commissioner and the Office of Science all of whom have pretty much come to the internal conclusion that the commitment of NCTR to the objective set forth by this committee may be better served should this committee move over to the NCTR SAB because the path has taken it down the road that aligns it with the activities of the NCTR. The NCTR program and resources are committed to supporting the kinds of activities that are being recommended by this committee and so we are bringing this to you to ask if you agree or have thoughts about the potential moving of this specific subcommittee over to be under the auspice of this NCTR Science Advisory Board as well as any comments and insight that you would like to present to us in terms of the general concepts of using the Advisory Committee structure in this way. The structure's specific subcommittees to focus on not just advice on specific issues but to focus on identifying new areas where FDA can collaborate with it's external what we call stake holders, other people involved in our processes and serve as a steering committee to help the FDA not only identify opportunity areas but also to oversee and steer collaborative efforts that would ultimately lead in to developing new science and bringing that in to regulatory practice. So those are my comments and I was hoping that we would have Jack who could make a few comments on behalf of the existing subcommittee as well as to present some thoughts on behalf of the pharmaceutical industry because this particular subcommittee obviously was formed in the pharmaceutical science subcommittee and some of the questions that I'm sure you will have would be the breath of focus and should the focus remain pharmaceutical and be broadened to other classes of products. This is where we would like to have your input and I hope will get some comments from Jack before we have to move on.

Acosta: Jim maybe before we have questions, it is very possible that Jack may not even be able to make the meeting, so could you give us a few comments on what Jack would have said or do you have an idea of what he would have said if he were here?

MacGregor: Well, before I resort to doing that I guess I prefer to wait. Obviously I have discussed this with Jack and I believe Jack and John Doull, other members of the committee as well as people within the FDA, the reason we are presenting this to you today is that we have essentially reached the conclusion that because of the focus of NCTR the resources and the program direction that we have here at NCTR that it would make sense to make this move and to move this in to this committee. Now I'm sure the pharmaceutical companies that have been involved already and visioning putting resources in to collaborations and so on will have a certain concern that they will not want to diverge to far from the path that they have already set out so I think that, here I said I wasn't going to speak for Jack and in a sense now I am, but I would guess that he would not like to see the current objectives be diverted too much from the course that has been set out but I believe that he does concur that it makes sense to make this move because of the focus of the NCTR.

Acosta: Okay, why don't we open up for discussion at this point. Questions from the SAB members.

Gillett: Jim, how are you envisioning the mechanism of how the committees would interact? And I think there is a lot of expertise on both sides that could be gained from focusing on these questions but I'm not real sure of how structure (unintelligible).

MacGregor: When you say the committee I'm not sure I understand.

Gillett: When you are saying the subcommittee will come under the SAB is that forty mechanisms have been reviewed where they are going and make suggestions.

MacGregor: Yes, absolutely. The structure now is that the subcommittee with the membership that I presented are members, is a subcommittee of the Advisory Committee for Pharmaceutical science. So there really are three layers of organization. There is the nonclincial subcommittee itself which is charged as I laid out with identifying areas of activity and serving as an oversight steering committee and identifying appropriate experts to pursue specific objectives and to develop particular areas. So two groups of experts have been formed. One in the area because you don't have all that expertise right on that committee. So the subcommittee charges experts to research a particular area and come back for example, I have to learn the rules and I have to be careful about what I say because I'd really like recommendations from the expert groups but I have learned that expert groups are not permitted to make recommendations. What they do is fact find and they can research an area and bring that information back to the subcommittee that then reports to the full advisory committee which then interacts and makes a final recommendation. So should this move happen, what would occur would be the subcommittee would become part of this SAB, those expert groups would pull together all the necessary information upon which that subcommittee could come to this board and lay out the facts and ask for an advisory recommendation. And then the final recommendation comes from the main advisory committee. So in that circumstance the final recommendations have final approvals and blessings for activities which come from this advisory committee rather than (unintelligible). But presumably the same subcommittee members could still function and should we stay on the course that has been chosen obviously because it is related to problems in pharmaceutical development we would need a strong tie with the Center for Drugs and with that advisory

committee, John Doull is on that advisory committee so John would provide that link. He would still be a member of the ACPS for information exchange between that committee.

Casciano: Well that's one model. Another model may be to appoint several of the members to this Science Advisory Board and the rest would act as Ad Hoc of the subcommittee so that they would then report to the Science Advisory Board like the site visit subcommittee report to the Science Advisory Board. And the Science Advisory Board has the potential to act as formulating the recommendations and also accepting the response to those recommendations, or rejecting them. And we are open to any suggestions by the Science Advisory Board for mechanisms that they feel might be appropriate.

Tindall: So to follow up the organization question with respect to the pharmaceutical science advisory committee, obviously this original subcommittee was developed under them and I think he pointed out good reason why it might get to the Science Advisory Board but there may well be projects to point out that (unintelligible) pharmaceutical sciences, what is their thinking or opinion (unintelligible).

Kaplan: I'm new and sort of self confused by the organization. The Advisory Committee for pharmaceutical science is what organization.

Casciano: Center for Drugs. Which is one of the Center's for the Food and Drug Administration. Which is a sister Center.

Kaplan: So this would be moving from that organization to this organization.

Tindall: So my question is as I understand that organization, thank you for that question because I think that is a good one for all of us, they function very much like the SAB does here. So in moving this particular subcommittee to the Science Advisory Board here at NCTR, what impact does that have on pharmaceutical sciences? Would they like to convene a new subcommittee of their own? What is the impact there? Has this been discussed with them?

MacGregor: It actually has not been discussed with the full committee but there are two committee members on the subcommittee and the two committee members that are on the subcommittee are t hose that are involved in toxicology. In fact they are the only two that are involved in toxicology. The rest of the focus of the ACTS is in the area of Biopharmaceuticals, Pharmaco Kinetics, product quality, chemistry issues and there are other subcommittees and expert groups in that committee that are focused on those areas. The two members of the committee Jack Dean and Jack Reynolds having discussed all the ins and outs and maybe we will get Jack to speak for himself feels that the advantages of coming here probably outweigh the advantages of staying there. Because of the heavy focus on heavy toxicology evaluation, the resources that are here to follow up and put resources in the consortia and so on.

Rosenkrantz: It would demean the entire subcommittee on nonclinical studies to move under the auspices of the NCTR SAB in some way shape or form, not just the part that is being viewed as toxicology.

MacGregor: This of course is open for discussion. This is the point of the discussion to discuss the ins and outs but the concept for discussion that I hope I presented was the concept of moving the subcommittee including all the present subcommittee members, although you may want to talk about there is one consumer representative which you must have from each of the committees and in fact there is one on this committee too so whether it would be best to carry somebody in that committee or have a new member there could be discussed but I think the concept would be to carry the full subcommittee over in to this Advisory Committee.

Kaplan: And that's because you expect that they are out for this …(unintelligible) NCTR's mission and CDER.

MacGregor: Yes that's right. Because the collaborations that we would envision and the follow up activities turn out to be focused on nonclinical toxicology safety biomarkers which is really the activity of this Center.

Casciano: let me just interrupt for second, Jerry. Although we are separate centers we all work for the FDA so you have to think almost schizophrenic. There is the NCTR mission, there is the FDA mission, there is the Center for Drug's mission and then the missions overlap and we have specific expertise's to direct towards the mission of the FDA. So we need to think in terms, it is difficult it not easy, secondly I think we can mention this is that this is a research activity and the Center for Drugs is diminishing their research organization and we feel that this is a strong component that requires maintenance within the FDA. We are somewhat concerned that this will go away and we don't want it to go away. We being the Center Director for Center for Drugs because she has to make various priority decisions and how to utilize her pharmaceutical board. The present acting commissioner and we. So this is the dynamic. The dynamic is that this is a research subcommittee that is directed towards mission of the FDA.

Acosta: Can I bring up one point? You as the Director of NCTR and the Director for Center for Drugs have obviously discussed this and are both in favor.

Casciano: We have discussed it including the members of the subcommittee that Jim mentioned and also the acting commissioner, yes.

Acosta: One other thing. All of these individuals listed on that subcommittee are toxicologists that I am familiar with. The only one I am not sure is Dave Essayan. All the other ones and Gloria Anderson, the other ones are members of the Society of Toxicology. So these are very well none toxicologists and as you said are interested in research and other aspects as it relates to methodology.

Tape 2 Side A

Rosenkrantz: Well actually you clarified, Dan clarified. My next question was going to be to tell me about the politics of such a move if it were to occur and I think that you answered that.

Gillett: I just kind of think I was impressed with the subcommittee report. I think this was such an important area to try to get some of these technologies out of discovery and drug development, so whatever move would most make sure that settlement happened I think is the one we should support. It seems to me like it is a research question but it goes beyond that because if the research does not translate it in to some techniques being used in the drug development process by the regulatory agencies the purpose of this would have been lost. So I think it would be a very important end point to try to identify new techniques quickly that could be used on some trial drugs that would be looked at by regulatory agencies and the biggest concern for Pharma is not going to be adding anything that if we are unsure the end point will kill the drugs. So I think it is a very important question and I would want to make sure that whatever move we did we didn't lose the focus of trying to push these technologies in to development.

Casciano: Right. I was using research in the broadest sense and here at the NCTR when we say research we mean the whole continuum.

Donnelly: Is there a way**,** right now you are proposing that the group become a subcommittee of the Science Advisory Board, but I can see the pit with NCTR. I'm not sure I can see the pit with the Science Advisory Board and I'm wondering if you have thought about other ways that this group could work with NCTR.

Casciano: Well that's I think the main reason for the discussion at this point was to consider the possible mechanisms by which this group can survive. And initially in our discussions with the Acting Commissioner and the Center Director, the first thing that came to mind was utilizing the presently constituted board and developing new committees is not very easy within the organization. It is almost an act of congress required and we are limited to the numbers of committees that we have and the committees that are in existence now are pretty well established and new ones will be difficult to generate.

Acosta: So let me ask you this. Then in terms of this particular subcommittee, would they become full members of the SAB but given the charge specifically for this particular subcommittee or would they be Ad Hoc committee members?

MacGregor: My understanding, well I can tell you what already exists. There are rules for subcommittees that are well defined under FACA and there are a minimal number of full members that are required on the committee, which is two.

Rosenkrantz: I know, Federal Advisory Committee Act.

MacGregor: That's the act that sets the rules under which all advisory committees operate. So subcommittees can be, you can constitute as many subcommittees as you wish and the rules are if you constitute a subcommittee you will have to have two members of your advisory committee on that and one of whom must be a consumer representative, understanding correctly. So this existing board, John Doull, Gloria Anderson, and Jack Dean are three people who are ACPS members. The others are not ACPS members they are just subcommittee members. And experts

are pulled in as necessary and they are not members at all. They are just expert working groups that serve the subcommittee.

Acosta: You said John Doull, Gloria Anderson and who was the other one?

MacGregor: Jack Dean. And I believe actually that Jack is in process, I'm not sure if he is finalized or not but he was being finalized as a member while he served.

Rosenkrantz: What are the arguments against having this subcommittee become a subcommittee become a subcommittee convened by both the ACPS and this SAB? I mean it was originally formed under that one and since you have ACPS members on that subcommittee it seems kind of funny that we would just have to increase our membership in order to make this a subcommittee of this SAB. On the other hand seats for or something like that because it will have to have some membership from this SAB. So instead of just taking on new members of this SAB and I'm always in favor of small numbers of committee members left at large, it is much harder to make a decision with a lot of (unintelligible), why not just put essentially put one member of this SAB on this subcommittee and agree with CDER that we would have a joint subcommittee.

Tindall: We have formal recordings to both.

Casciano: Well we never really considered that option and we have considered the single options because of the control factor. But that is a viable option to consider, to think about. Do you have any priority negative reactions to that?

MacGregor: Well it just means you would have formal meetings, you would be reporting twice which could be done and to some degree would be done in any event under the model that we were thinking about. In other words, if the model we were thinking about were to happen you would still have John Doull on the other committee. So it could be done.

Acosta: Dan mentioned that in talking with the director, Janet Whitcock I guess at CDER that there was this reduced emphasis in CDER on research and I didn't quite understand that and therefore it made more sense for this subcommittee to come to NCTR SAB. Did I get that correct? If that is the case does that mean there is less money now for this subcommittee at CDER?

Casciano: No, it really, correct me if I'm wrong. My view is that without a champion there it will not exist to a high level. And the champion is here. So that is our view.

MacGregor: So in resources

Rosenkrantz: The champion within the Food and Drug Administration agrees not the respected Science Advisory Board.

Casciano: Correct.

MacGregor: Well beyond that as you envision, if this idea really works and you begin to form multiple expert groups and develop consortia then you begin to need to think very seriously about resources because somebody needs to pay for travel for all of these people. Somebody needs to organize the meeting, somebody needs to arrange the sites, arrange the meetings, arrange the travel, do all these things and this is the reason that the internal FDA discussions have led to the conclusion that maybe it should come here because this is the major focus of this major center and CDER is now looking at all these expert groups and travel and all this plus the people that we are leading are now moving over here.

Rosenkrantz: So let me ask the other question. Does this organization have the resources to take this on?

Casciano: The answer to the question is depending on how it evolves, yes. And you see it becomes part of our budgeting process for requesting dollars from the FDA. We need to indicate the value of this activity to the FDA and if it has value to the FDA dollars will come from the FDA to support it.

Gillett: Isn't it also, I'm guessing, I need some validation on this and that would be some options of this that would help to provide guidelines or focus for some of the research that will be done here whose efforts might need be a need for (unintelligible) for biomarkers since that is really a legitimate (unintelligible) bioassay and that would make a lot of sense that this could be where that research is done and so it would be to an advantage to have the same board with both the research activities here as well as with (unintelligible) to make sure there is some cohesiveness.

Casciano: Right.

Acosta: Let me just say if we go that route would we just appoint two members of the subcommittee so there is now John Doull and Jack Dean, have them be permanent members here and those two will represent SAB on the subcommittee or do we have to have two SAB members from here be on that subcommittee and have all the other ones just be Ad Hoc members. Which would be the best way of doing that?

MacGregor: I believe the rule is that there needs to be two full advisory committee members on the subcommittee. So that would mean that this SAB would need to identify two members to serve on that subcommittee.

Acosta: Yeah, my question is if they are present members could we then be, or could we add two more from that subcommittee.

MacGregor: One of who preferably should be a consumer representative.

Rosenkrantz: You have nine members that are with the charter. If you want to increase it you have to go in and have the charter amended.

MacGregor: Okay that explains it.

Acosta: So the idea would be then that two members from SAB would be put on this subcommittee along with these individuals that are listed.

Rosenkrantz: Wait a minute. What is the charter of the subcommittee? This subcommittee, this one on nonclinical studies. Does this one have a charter that limits the number of people.

Hansen: Let me ask Barbara a question actually because we just went through this process in CFSAN of restructuring our Advisory committee to include subcommittees and we had to go through a fairly lengthy process to in fact charter those subcommittees and amend the charter of the parent committee now. So that is a factor.

Jewell: That's why we like to call them site visit teams and working group.

Hansen: Just speaking from experience it was not a quick process.

Rosenkrantz: Okay so then my question remains. When this subcommittee of CDER was born was there a limit stated on the number of participants in that subcommittee? And if there were, what did we have to increase, wouldn't we have the same problem as if we were increasing this committee?

Jewell: Jim is there a chart?

MacGregor: I don't have an answer. I'm sure there are rules.

Casciano: Well you can because if you recall the site visit team that evaluated Genetic and Reproductive Tox did not have a member from this body. So the idea is that it is possible that the next opening on the Science Advisory Board we can choose one of these individuals as a member and we can maintain our number nine and that individual is not so narrow in his/her thinking processes that they will only think in terms of the subcommittee. They are toxicologists. They can have impact on all of the programs here at the NCTR and as Nancy indicated that then there can be a greater probability of cohesion in the direction. So there are multiple ways to skin this cat and what we are looking for is some encouragement to look at the multiple ways to skin this cat so that we can indicate to our supervisors that there is enlightenment on our Science Advisory Board and they see the value of this and it should be maintained with the Food and Drug Administration. Then we will find mechanisms to do it.

Kaplan: So the board question is can this board in some manner cleverly and administratively constructed have some sort of over sight control over in this second group regardless of how whether it is called the subcommittee or a working group or site visit. So I think that you are really asking the first issue is the going question.

Acosta: And maybe this might be a good time to ask the SAB if they agree in principal to what you just said and if we do we can allow the regulators and other rules experts to come up with ways of how we can do it. Is that fair? Is that a consensus from this group that we can

move forward and get more information on how we could make this a formal part of SAB regardless of how you want to call that subcommittee?

Rosenkrantz: When is our next opening on this SAB? June 30th of this year they may be (unintelligible).

Hansen: I would like to as a general question. Dan, do you when you look at the SAB and it's interactions with the NCTR and the role and valuable input it has played on the program, do you foresee a need for or have a vision any utility of other subcommittees of the board and I guess I'd ask the same question of the board? Then there is that very general question apart from the subcommittee.

Casciano: Well what we are trying to do through this mechanism is extend the value of the NCTR's fundamental research mission to the Agency. And that is the motivation for doing this and so the answer would be yes and any way that we can make our input in to the Agency of higher value because my motivation is to increase the dollars coming in this direction that are appropriated to the NCTR from the FDA. This is one mechanism for doing it.

MacGregor: And I guess that I might, although I did not say explicitly but I hope that it is understood that a large part of the concept of having a fully public and open Advisory process focused on fostering collaborations will be to come to a public consensus on what is important thereby providing all the organizations that might be involved with the necessary leverage to find resources from their management to collaborate. So that this mechanism being open, public and then developing a common consensus on important goals hopefully will catalyze a generation of resources to support the efforts.

Hansen: I think you may have realized part of where my question was coming from.

Acosta: The next opening is in 2002. June 30th. Well let me just ask one other question in terms of just working in this. I was looking at the expert working groups who are working via the subcommittee. In other words the subcommittee selected those individuals and I guess,

MacGregor: That is not exactly accurate.

Acosta: Well tell me how that will work then.

MacGregor: Well expert groups and advisory committees in fact are selected by FDA. They are FDA organizations so the expert groups were selected by an intercenter committee put together from three different centers of FDA based on nominations that came through a docket through

Acosta: But they report to the subcommittee.

MacGregor: They report to the subcommittee, correct.

Acosta: Then the subcommittee reports to the ACPS. And that being the case I only see one person from the subcommittee on this expert working group on biomarkers and that was David Essayan. Is that is? I saw the minutes of the expert working group for biomarkers of cardiac toxicity and listed all the members and then I only see one person from the subcommittee that is on that expert working group. Is that the liaison? Is that how that works?

MacGregor: Well there are the expert groups are expert groups and if there is not an expert on the subcommittee or the committee they are not members. They are liaisons. So the way the expert groups are structured the core members are experts in the field selected and then there are various kinds of liaisons. So in that cardiotox I in fact am the NCSS liaison so there is a liaison there. Each of the Centers that are involved is also asked to appoint liaisons so Dave is the CBER liaison. I'm doubling as the NCTR and regulatory divisions that might be impacted are also allowed to have liaisons there so that there can be an interaction with whoever might write a guidance in this area in the end that they can be involved in the process. So that is Liz Housener from CDER and on vasculitis Tom Popoen from CDER because those are the pharmaceutical regulatory groups that would perhaps use advice that would come out of these. So that is kind of the full concept is that there are liaisons from the regulatory.

Acosta: All of the liaisons were from the FDA. Non from the subcommittee non-FDA people. For example, John Doull, Jack Reynolds, Joy, Jack Dean, Jay Goodman. They were not there but they were all FDA people who served as liaisons. So that is alright I know but I was just curious why there wasn't a member from the expert group.

MacGregor: Well the expert group is a group of people that the subcommittee asked to identify information and summarize in a report to them. So the full subcommittee, or the expert groups are going to come to that subcommittee and report all their findings to them. That is why they were constituted.

Acosta: So theoretically we could have for SAB an expert working group or a site visit team. Could we have an expert working group for SAB?

Jewell: Now do we? No.

Acosta: Can we?

Jewell: Yes.

Acosta: So if we could have an expert working group for SAB could we designate this current subcommittee as an expert working group.

Rosenkrantz: Or would we have to readvocate it?

Tindall: Where does that end with the value of that committee in terms of recruiting dollars to NCTR.

MacGregor: I think the answer is you could designate them to be an expert group then why was it set up to be a subcommittee. The reason that it was set up to be a subcommittee is because subcommittees operate under the full public process of an Advisory Committee. So if you want to at the end of the day be able to say everybody in the world had opportunity for input because everything that was done is in the public record. Every nomination that was taken was announced in the federal register. You do that through a subcommittee and that automatically has to be true where as an expert group can meet on it's on and so we did feel that it was important to have this public process so that the end product would carry that weight.

Acosta: But Barbara just said we don't have in our bylaws the opportunity to have a subcommittee of SAB.

Jewell: We can have one but you have to go through the whole process.

Acosta: That whole process, how long would that take.

Kaplan: For the processing of this group does the public process incorporate for them to make recommendations which they go to a public advisory committee and then get to discuss the vote.

MacGregor: Are you asking me? I think it just depends on who those people are. In the case of the ACPS there were only two toxicologist on the whole committee and it went down that road and so it is felt there needed to be a subcommittee of knowledgeable people that was put together. If this Advisory Committee, for example, were to feel that the full committee has the time and expertise to serve that same role then there would really be no need for the subcommittee. You could just go directly to the expert group.

Kaplan: That working group could be a working group (unintelligible) official designated subcommittee. And all their findings which are now (unintelligible) are presented to the SAB which is public and that might be the way to view it.

Acosta: It's three o'clock. I think we agreed in principal that we want to have some type of working arrangement. However we are going to need your advice, Barbara, you Dan, in terms of how we can work this out.

Casciano: So you could charge us with that action. So we will do that.

Tindall: (unintelligible) short term

Casciano: Our expert working group is called Site Visit Teams come and go. Yes.

Kennedy: (unintelligible) working group it would not have the long term collaborative (unintelligible) discussing what you might think you have for the development and collaboration in the case. Is that right? You've got an expert working group here on cardiac toxicity and did their report and I assume they are now no longer (unintelligible). And what I'm saying is if we appoint this group that you are talking about bringing on board as an Advisory Subcommittee to

us if we appoint them as a working group and not a subcommittee they are (unintelligible). And they don't fulfill your goals of providing continued influence and guidance in to your projects. (Unintelligible) Is that a logical way to even think about this?

Casciano: Well this is still an experiment Rich. Yeah I know it is still an experiment and we need to develop another hypothesis. The question is whether or not the first hypothesis has merited developing the second one and it might just go away. It might just go away. We wear rose colored glasses and we have grand ideas on whether future can go but there is a lot of ifs in this and my biggest difficulty is that since this is no longer associate with Center for Drugs will the pharmaceutical industry have any interest at all and so we have to make it interesting to them.

Kennedy: And so my point is I would like to see it (unintelligible) I would rather see it as a subcommittee than as a working group.

Tindall: I would like to follow that and support that thought. What I wrote down here as you were talking Jim is that this committee will take an active role in steering collaborative projects and that is a very exciting way to think about how to bring together these merging technologies. I think that that is very important. Whether it is a working group or whether just exactly what the structure is we can decide, we need to depend upon you to tell us how to do that. It sounds like we might be able to just change the (unintelligible) from nine to eleven and I don't know how hard that is to do.

Rosenkrantz: And quickly that can be done. That was my question. What is the imperative here? I mean how quickly will CDER give this thing up?

Casciano: Well they like to give it up as soon as possible I think and we would

Rosenkrantz: …(unintelligible) convinced to hold on to it until we (unintelligible)

Casciano: I think we could find ways to do that.

Acosta: Did you have one more point Nancy?

Gillett: I just wanted to make one comment. I think the way to keep (unintelligible) industry interested in to still see that commission at CDER or CBER and have it translated in to something (unintelligible). So if it becomes bogged down (unintelligible)…

Casciano: I think we have just found a chair for our fist subcommittee.

Gillett: This is something I feel strongly about.

Acosta: Why don't we break for about 11 minutes. We have got to get back by 3:15 so we can keep on schedule.

Acosta: Okay, why don't we begin. The next item on the agenda is the Endogen Disrupter and Knowledge Base Program. It is the response to the SAB Site Visit report. Dr. Sheehan. Len has to make an announcement.

Schechtman: Excuse me Dan, just an announcement or two that I have to make here. On the issue regarding dinner, we need your money. It's pretty basic. Barbara Jewell will be collecting everyone's monetary obligations for dinner based upon what you have ordered. I think you all know the dollar figure that you will need to donate to the cause if you will so if you would sometime during this period of the session we will have to collect your money so sort of just meander by Barbara's table and see what you can do to help her out. Otherwise it's on her.

Casciano: Actually it's on Len.

Acosta: Okay thank you. Dr. Sheehan.

Sheehan: Well thank you. I'm sure some of you know but probably not everyone this is going to be my last appearance before the SAB. I'm scheduled to retire on August 3rd so let me just thank the SAB for everything that they have done through the years with the various programs that I have been involved in. I think these are very important purpose that the SAB serves. I put out a handout for everybody. One is our research accomplishments, a single page written at the end of fiscal year 2000. You can sort of compare our plans for 2001 with the information I am going to be giving you. The next handout is a list of the, there should be 19 publications in that publication list. I will try to see what happened to that last page. I should point out that virtually all of those with the exception of perhaps three or four were written and published after about the first two or two and a half years of the EDKB when we were using literature data instead of our to develop models. Third is the response to the SAB report. This is the same response that we had provided earlier. It has not changed and so I think that this like the SAB report can go in to the file as a completed document and then I have gotten copies of the slides that I am going to present today. As I said what I would like to do today is give you an update on where we stand on the development of the EDKB and for those of you who are new to the board I apologize this is something that we can't present in detail in about a 15 or 20 minute presentation. I know you got a look at some of the activity this morning over in the ROW area so if there is anything that is left hanging just give me a holler and I will fill you in as best as I can. The first thing we want to do is to define what a toxicological knowledge base is. It is a computero or now in silico aggregated set of the most literature citations and biological activity data sets together with computational models which correlate those activities with chemical structure and ultimately can be used as models for risk assessment. So in this case it shows a dose response curve of what we are going to be talking about are receptor binding data and a correlation with the chemical structures. We originally conceived this as a circular process to provide training sets that are designed to produce robust living predictive models. These models are based on software that comes from the drug industry and particularly the area of lead drug discovery. The predictive models that are used to determine which chemicals in large libraries might be the most active chemicals for development of subsequent drugs. In our case we started off with data in scientific papers and after a significant amount of work corralling all of the data on the estrogen receptor binding affinity for a wide variety of chemical structures it became clear that this was an inadequate approach. There was too much difference between one lab and

another and the types of techniques that were used and therefore within a particular technique there was still a lot of variability, people design their assays differently and there was too much variability in the data sets. So this was no longer feasible for the purpose of developing predictive models. Now we were able to get some stuff together but not for the purpose of predictive models. This lead us to have to do our design assays and run them in our own laboratory to provide sufficient number of chemicals with a wide enough range of structural diversity and a wide enough range of relative binding affinities to be able to develop adequate models. These started with data validation and selection and the diversity analysis and training design now applies here to the data that we have developed in our own lab and of course these also lead us to new data needs and research hypotheses. In particular, in our hand, the E-8KB team functions as a unit with respect to the computation chemists and the laboratory folks so that now selection of chemicals is decided upon in terms of strategies in meetings between the two groups together to determine what types of chemicals are going to be available and provide good models. So our objectives, and this is a rewrite of what we had earlier to become a little more specific about what I'm talking about today to develop and validate predictive computational models for estrogen receptor and deandrogen receptor by first developing appropriate data sets to train the models. Second to examine a wide variety of models for performance and ease of use. There have been several dozen models looked at all together for potential incorporation in to the battery. Validating models by three types of validation. The first is an internal validation process that gets a little complicated but basically it is a procedure where you drop one chemical out of the model, recalculate the predictive value or the model and then predict the chemical that has been dropped out and you do that for the end chemicals that are in the data set. The second type of validation is external validation. We have completed this by using published data sets that in some cases uses other techniques and we have examined the correlation between the assay technique used for a number of large data sets and have shown that they are generally in good agreement and so we can convert data sets from other types of assays such as reporter gene assays in to the equivalent for relative binding affinity assays. The last part is what we are involved in right now, is external validation from a randomly selected group of chemicals from the 58,000 chemicals, the priority of setting data base of EPA that has the 58,000 chemicals of concern. And then we also want to develop the training set by design as we indicated earlier for structurally diverse chemical structures in a wide range of binding values. The structural diversity has to incorporate the structural diversity that is known for existing chemicals that bind to the estrogen receptor and a wide range of binding infinities in our hands we were able to develop assays that could measure RBA's over a tenth of the sixth range of activity so we cover the range of from very low activity to very highly potent binders or high affinity binders. For the ER models we assayed 238 chemicals. These were duplicate tubes in each assay and then two replicates. Techniques were developed for identification of potential binders by EDKB teams in particularly we could develop based on early data provisional predictive model and use that predictive model to go in to chemical data sets and determine which of those might be binders and which are nonbinders and then buy those chemicals and assay them. The filters, the phase I, and the 11 categorical SAR models faced too are finished and I apologize for not having time to go in to this but the models are set up in different phases that run from the simplest and the ones most quickly run to those that are the more complicated and require more investigator time such as three dimensional COMFA models. And the models have been validated against literature data sets. The status of the models they are biased toward fall positives in order to minimize false negatives. If you want to predict activities of chemicals that may be endocrine disrupters

you want to make certain that you don't leave any out because when it comes time to try to select among the 58,000 chemicals as to which should go first. An implied no biological activity entry under the estrogen receptor will drop it's priority for entry in to screening. The RBA's predictions and these are categorical predictions through phase II have now been made for all 58,000 chemicals that are in play. We have a hand out of the publications. For about the first two or two and a half years while we were developing assay techniques and the computational chemists were putting together the types of software and hardware necessary to develop the models we used literature RVAs and then subsequently used the NCTR data set. So that is why most of the publications are more recent rather than early. For the androgen receptor competitive binding assay, which we have just about finished now, we looked at two assays. One was the use of the ventral prostate from castrated adults. It is the richest site for androgen receptors and we could not obtain reproducible results. We could not reproduce what was in the literature. We were getting statured plots that had too shallow a slope and we spent a lot of time on that and could not get it straightened it. We then turned to a product put out by PanVera corporation which is a purified androgen binding domain. It is 80% pure of which about 20% of that protein is active in binding. And there is a lot of advantages to this in addition to the assay issues. We got very good saturation and competitive binding results. We spent a lot of time validating it by diluting the protein and then getting the radio labeled lygan right from a chemical perspective. We then were able to validate the assay for use by comparison against other literature data sets. It is in our hand somewhere around 70% is expensive as using the Ventra Prostate Assay and for those that have to procure animals wit their own money it is going to be even less expensive to the relative to he Ventral Prostate Assay. I think a very important issue currently. This assay uses no animals because it is a recombinant protein. I just want to give you look at some of what the competitive binding assay results look like. This is for a set of androgens and you can see here is the radio labeled standard which is our competed with cold R1881 and a variety of other steriodal androgens going down to about five orders of magnitude below the RBA of the standard. You will notice that there is a couple of curves that come back up again at very high concentrations. We have seen this in both the estrogen receptor and some of the serum binding protein assays. It is likely due to some kind of problem with insolubility or something of that sort. We cannot see it as a problem but others have noticed the same sort of thing. It really occurs at very high concentrations of competitor.

Tape 2 Side B

Here are four steroidal estrogens and you can see that just like before the curves are parallel. We can get good estimates of the dose given half-maximal competition for each of these chemicals and the estrogens are not so good of binders but some of them are pretty good binders to the estrogen receptor. Antiestrogens, this is a group category of chemicals that really don't bind very effectively at all and that is all these kinds of data sets I guess you can imagine what all the rest of them look like. There is probably about 15 data sets of this sort that we have developed. Here is the status of the AR assay. The data that are shown here are up to May 9, 2001 which included 134 chemicals. We are now up to 196 chemicals and just about complete unless something shows up in the model development that strongly suggests we should do some other type of chemical. And this is the distribution of the number of chemicals versus a very general structural category of steroids, DDT like chemicals, phytoestrogens, chemicals with a DES skeleton, fallates, PCBs, various pesticides, this is a mixture of chemical structures. Flutomide

related chemicals which is an antiandrogen. Other antiandrogens and then a number of other chemicals which do not have enough numbers to be put into specific structural classes. So we've got a good distribution of all of the known chemical classes that bind to the androgen receptor. What we did find differently from the estrogen receptor is we did not have very many chemicals that were in the high activity category and we had a bunch of chemicals that were in the low activity category. This was different from what we found with the estrogen receptor in terms of the distribution of the relative binding affinities and we have pretty well covered representative chemicals in the data sets that we selected so we really don't think that this distribution would change significantly if we were to add more chemicals. Here is the comparison of the PanVera Assay with the EPA assay, which is the ventral prostate. You can see here there is a good correlation, if we leave out progesterone, the R^2 increases to about .9. Progesterone is almost certainly and outliner because in the ventral prostate assay medroxy progesterone acetate has to be added to produce glucocordicord receptor binding and this is going to induce an artifact with respect to progesterone binding because of the structural resemblance's. This is a pharmacophore model that is a model where you will ask the computer to go through a large data base of chemicals and find chemicals that have these kinds of 3-D pharmacophores. There are eleven such models enfaced to that some of pharmacophore 2-D, some are 3-D and there are other kinds and models so we have a diversity of models in that second phase. Here is a CoMFA 3-D quasar model. First of all here is the actual log RBA as measured in the laboratory. Here is the calculated log RBA on this axis. That is the predicted log RBA. As you can see there is a very good correlation on R2 at .96 and a Q2 of about .65. Now there is about 35 chemicals on this data that set to Q2 may go up as we incorporate other chemicals but this is the first model of AR that we have developed and it is for the steroidal estrogens. Over here it is a little hard to see but this is an androgen lodged in the binding pocket of the androgen receptor and these various colors indicate we are adding or subtracting hydrophobiscity or adding charge or subtracting charge will have an effect on the binding based on the analysis of the data set. So it is very important to do an external validation of both the assays and the models and it is important to do these de novo and not from constructed data sets. So the EPA has funded an $850,000 contract with Batelle Northwest for conduct this validation and compare the performance of the NCTR and EPA assays and models. Those assays are the ventral prostate assays; the PanVera assays both for the androgen receptor. The estrogen receptor assays that are used at EPA are virtually identical to the ones that we use so we are just running one set of assays for those and here they are listed. And that is in process. We have data back on the first 25 chemicals. There are some significant glitches and we still have to resolve this but we are working as a group with EPA headquarters with two laboratories Duluth and RTP and our laboratory to analyze the data and to advise EPA with respect to the contract. So in addition to the $850,000 that EPA has used to fund the external validation effort which is very important to us we have also gotten significant external funding over the course of the slightly less than five years that we have been since this project has started. The Food and Drug Administrations Office of Women's Health we got $185,000. The numeral one here means that these were experimental collaboration with the University of Missouri. We are not necessarily for model development. For the FDA's OWH also contributed two separate awards for development of models. We have two separate awards for the CMA CRADA that went to support of postdoctoral fellows. We have an EPA grant again that was for an experimental collaboration. The EPA interagency agreement is for two million dollars. Five hundred thousand of that is for Fiscal year 2001 and one and a half million for the subsequent four years. So about $375,000 a year thereafter. So the total here adds up to

$3,355,000 in external funding and in a lot of ways the external validation for another $850,000 could legitimately be incorporated in to this because it is something that we had been asking for the last two years. Okay I want to end this presentation with just a little comment here. I asked the question, what did the Buddhist say to the hot dog vendor? And what the Buddhist was make me one with everything. And so I think at this point with respect to the estrogen receptor model we have one with everything. The computational chemistry group has looked very hard at a great variety of computational chemistry models and has come up with the eleven enfaced two that performed the best. Several 3-D quasar models evaluated, the CoFMA model performs the best for phase III plus the phase I which involves some simple filters to reject chemicals based on certain structural characteristics. So we don't know of any other group that is publishing in this area that has done the kind of job with respect to rigorous validation of binding assays and collection of the appropriate kinds of data to analyze the very diverse data sets that are in the EPA priority setting database nor any other group that has done the kind of work the computational toxicology group has done in evaluating such a wide variety of models and picking those that are best and putting them together in a sequence that provides the best performance. So with that I will stop.

Acosta: Okay, well thank you very much. Marcy can you lead the discussion from the report please.

Rosenkrantz: Okay, Dan there were lots of things that we said in the site visit report. And one of them is that I don't see (unintelligible) look at your response. One of the things that the site visit team suggested was mainstreaming the knowledge based work in to the rest of the activities of the Center. And I was just wondering I did not see that in just a quick look at your response to the SBT and I was just wondering what the status of that was.

Sheehan: Well I think your visit this morning over to ROW should have given you some idea of the general flavor of the sorts of things that are

Rosenkrantz: Well we saw two things. I was just wondering, the site visit team was I think concerned about how the further studies were being funded through the Center and competed with other projects and I'm wondering how that has gone. Maybe Dan could answer that question or somebody but I would like to see some discussion abut that.

Casciano: You want to respond then I will respond.

Sheehan: Well I don't know that I have ever seen any kind of tally on the total expenditures from NCTR but I should say that $3,300,000 plus the $850,000 for the external validation has defrayed substantial chunk if not the majority of the expenses associated with developing these models. And as you can see from the number of sources that we have gotten support from we have been quite vigorous and looking outside to provide those resources for us to move forward, Dan.

Casciano: Yes the reason that Dan proposed up there, the androgen receptor and the EPA work is all totally funded by EPA. So the NCTR's budgetary input is relatively small compared to the dollars that are directed by EPA so that is where we are evaluating the model. So we

responded to the site visit's recommendation and secondly I don't know if in your demonstration if the fellows talked about their input in to the development of databases for the DNA micro array and the proteomics so they are directing the database knowledge that they developed to other activities here at NCTR and what has occurred is an expansion of the team development in addition to the team that Dan mentioned, that was relative to the estrogen knowledge base. The team is making it put in to the genomics and proteomics in combination with chemistry, the biological investigators and biometry. So I think that the critique was taken very positively and we responded to it.

Rosenkrantz: Any other comments? Since I was the only one on the site visit team it makes it a little bit difficult I'm sure for the rest of you. Let me tell you I am hesitating to ask for a vote on this since people haven't had a chance to read it. So I would suggest that we put it off until a vote on accepting the response. Do we have to vote on it and accept it at this time?

Casciano: Well you do for the record. You could do that by e-mail I think. Where is Barbara. I think you can do that or you can look at it tonight and

Rosenkrantz: I would like to give people the chance to read the response before I just ask for a vote. Reading the response may generate some other questions and I would like to give the committee

Casciano: So are you suggesting reading it tonight and

Rosenkrantz: Yes, if people still don't have any more questions then we can vote on it tomorrow.

Casciano: Dan can you make yourself available tomorrow morning the first thing so that if there are any questions regarding it you could respond to it.

Sheehan: Okay I will. I've got a short timer attitude.

Casciano: I still haven't signed your retirement papers.

Sheehan: I understand that. That's why I'm here.

Acosta: Okay why don't we hold off until tomorrow morning for a formal approval and if you are available that would be great. I think we want to thank you for your report and I'm sure that you will do very well in your retirement.

Sheehan: Thank you.

Acosta: Okay, the next item on the agenda is the Division of Microbiology. The response to the SAB site visit report. Dr. Khan.

Khan: Thank you very much and as you know Dr. Cerniglia is not here. He is in Rome attending a meeting on Food Safety. So I will be presenting you with the responses to the SAB

review committee. And also presenting you with the update on the Division of Microbiology research that we are doing. Well the SAB at the time consisted

Casciano: Saeed can you hold on just for a moment before you continue we are going to bring in another member. This is Dr. Marilyn Lightfoot, she is a liaison member from Center for Devices. Good afternoon this is Dan Casciano.

Lightfoot: Hi this is Marilyn Lightfoot.

Casciano: Welcome we are just beginning the Division of Microbiology response to the SAB site visit and the update.

Lightfoot: Okay fine. Thank you.

Khan: Well the subcommittee at the time consisted of the following members here listed in the slide. Dr. Catherine Donnelly who is here and the consultants to Advisory Board members Dr. Raul Cano, Dr. Thomas Federle, Dr. Mike Johnson, Dr. Susan Kotarski, Dr. Robert E. Anderson, FDA liaison members, Dr. Peter H. Cooney from CBER, Dr. Roger A Jones from CVM, Dr. Arthur Miller from CFSSAN, Dr. David G. White from CVM. The committee had two kinds of comments on the general comments and recommendations and the comments on the research focal areas. I will be addressing the comments to those responses individually. The comments about strategic planning well the committee asked us to develop more collaborative research projects with other Centers of FDA and ORA. So I would like to mention at this point that we have about 20 different research projects. Almost ten of them are with Center for (unintelligible) medicine. Three with CFSAN, Six with ORA and one with CDRH. So we have worked hard and followed the committee's recommendations to establish these collaborations. At the same time the committee also recommended that we should hire some food microbiologist. So we, I think Dr. Cerniglia has already talked to Dr. Casciano and we advertised the position some time in February already so I don't know about what happened. Somebody was offered the job and because of some problem I think the person could not come. But that position was already advertised. In terms of the new philosophical paradigm, the committee recommended that we carry out most of the studies that are based on mechanistic approach. In terms of the work related to antibody resistance. And how does that fit in terms of risk assessment and how does it address the (unintelligible) use of the FDA. So I would like to say probably we felt at the time that when we do these kinds of studies we take in to consideration the views of all of the members involved with whom we have the collaboration and if we carry out the mechanistic approaches then only we can find out whether or not the risk associated with the transfer of antibody resistance can be really justified or not. If we do (unintelligible) confused at that point that we are not doing the applied research work. It can not be applied for regulatory work but I would like to say that the basic mechanistic approach can give you the answer whether or not the antibody resistance can be transferred to the other organisms. We have clearly shown in our publications that the poultry isolates can transfer the resistance from poultry isolates to human isolates and that be submitted to CVM and then CVM now understands that what is the role that CVM can play in controlling the use of such antibiotics in poultry industry. About the leadership role there was a suggestion rather question of what happens if Dr. Cerniglia decides to leave. Is there anybody who can take up the

leadership role or are there individuals who are being groomed up for leadership role? I would like to say that Dr. Cerniglia always gives opportunity to other senior members of the staff and then those (unintelligible) for attending training and building up leadership qualities is posted on the bulletin board and the Division Directorship was rotated among the senior staff of the division when he goes on vacation or attends any meeting. So that is my response to that question. About the building facility I think we appreciate the committees recommendations for the Division of Microbiology needs more building space and then we are moving in the right direction. Dr. Cerniglia has already discussed with Dr. Dan Casciano and the maintenance engineering staff here at the division we will probably be moving in the chemistry division after some modifications are made there. In terms of the public relations and communications the subcommittee recommended that we develop a website so we did that and then we posted the skills of the PI's in the Division of Microbiology, their research interests goals and accomplishments. So on that aspect that is the response from the Division of Microbiology. Now there are some comments on the research focal areas. These are about the food borne pathogens, food safety and methods development. We do a more major research in this area of food borne pathogens, food safety and methods development. The major area of focus in this area of research is CVM and CFSAN. So we have about ten projects with CVM and out of ten we have seven or eight are on the food safety. The committee also pointed out that we try to quickly publish the results in this area of research. Whenever we try to publish the research, no doubt we published quickly but at the same time I want to say that we don't compromise on the quality of research. And at the same time before publishing this data we send the reprints to all the people involved in this collaborative process to their supervisors so if they have any comments we take those comments in to account before writing those publications. The committee also said that we need to put more standards and controls. So whenever and wherever necessary we always try to put the controls in the standardized methods before we publish them. About the determination of the role of intestinal microflora in activation or detoxification of xenobiotics the subcommittee also complimented this research area and in fact asked us to strength this area. So we take their word in trying to strengthen this area in the division. We have developed the chemostat models that mimic the human large intestine and what we are trying to do there is study the effect of low level of antibiotics that are used in veterinary medicine and to see the effect on human microflora. At the same time we are also trying to find out what happens if we use the lower amount of antibiotics whether it compromises the human intestinal microflora or if there is a chance that the antibiotic resistance bacteria will (unintelligible) the human intestine. So what is the threshold level that will come from this kind of a study that we are getting out in the division right now. What the environmental biotechnology this area was also recommended by the subcommittee and this recognizes one of the strengths of the Division of Microbiology. We are continuing to work in this area. There are a lot of other individuals who are working to find out what is the rule of the fungi that we have isolated and some other bacteria, how they can biodegrade the PHS or other pollutants in the environment. Use of Microorganisms as models to predict the metabolic pathway by which drugs are metabolized in animals. We are using a number of microorganisms to study the metabolic pathway by which these drugs are metabolized. In fact we have established a research collaboration with the USDA labs here in Arkansas and we are also trying to isolate the bacteria from the fish ponds as to how the antibiotics that are used in the fish industry like poultry industry, how are they degraded the environment and whether or not as a result of the presence in the environment some antibiotic resistant bacteria accumulated in the environment. And it that

happens whether or not they are transferring the resistance to other bacteria in the environment. So those kinds of a study are underway. In terms of the Microbiology surveillance and diagnostic support of research (unintelligible) comments about this program in the Division of Microbiology. So we continue to offer these surveillance and diagnostic services to the NCTR and the FDA Center. Now I will move on to the update and the Division of Microbiology.

Acosta: Could you hold on for a second. Maybe we could have questions at this time before you go through the update. Cathy can you take over as moderating the session?

Donnelly: Yes, Rich Kennedy was part of the review team as well as myself. Rich did you have any comments?

Kennedy: Not particularly. He seems to have covered this letter pretty well and (unintelligible) and I have nothing (unintelligible).

Casciano: I would like to add something before you move on Saeed. The NCTR took to heart your comments about public relations and communications so we've just completed development of a manuscript which will go on to our public website which is a science journal that the NCTR is putting out for the FDA and it would be assessed internationally as well and the first paper that was written was written by the Division of Microbiology and so we will have a copy of that for you to give you some idea about the content of that publication and what we are trying to do and we have asked a various members of the other FDA Centers and other regulatory bodies to act as editorial board members so that they can make contributions to this since this is a regulatory research interest journal that hopefully will be useful in communications between the centers and not gossip newsletter but a scientific newsletter. And it is a venue for the regulatory scientist to get a thought across or communicated or develop an idea that they would like others to understand them.

Donnelly: Could I just ask one quick question about the status that that food microbiologist position because I think of all of the recommendations in the report that was the most critical the site visit committee strongly recommended. Not only just hiring a food microbiologist but one of fairly senior standing who could come in here and really h it the ground running and direct a lot of the research with applied outcomes to take advantage of all of the resource that appears to be coming to the Agency to deal with food safety. Is there any update there?

Caciano: Carl has the slot and he has gone out and sought an individual and he had someone identified and that person did not accept it after lots of communication so he is looking at the second and third people on the list. So we have taken that to heart as well. Thank you. And also, excuse me Saeed, I would like to comment on the leadership. This was a pretty unanimous comment by all of the members of the site visit team and Carl is making an active effort to expose his senior scientists to the administrative roles as well as having them represent him in critical meetings.

Acosta: Hold on one second. Since we have this material beforehand do you want to make a recommendation Cathy on acceptance?

Donnelly: Yeah, I would move that we go ahead and accept the report that was circulated by Barbara in the packets that came to us. I hope everybody had a chance to review it.

Acosta: Is there a second?

Second

Acosta: Okay, any discussion. All in favor. I. All opposed. None. So note this please. Okay you can continue.

Khan: Okay thanks, Now the update on the Division of Microbiology. Here is the organization chart about the (unintelligible) FDA and NCTR. Division of Microbiology is one of the nine divisions here at NCTR and we have a mission that reads like the Division of Microbiology at the NCTR serves a multipurpose function with specialized expertise to perform fundamental and applied research in microbiology in areas of DA's responsibility in toxicology. The Division of Microbiology also responds to microbial surveillance and diagnostic needs for research projects within the NCTR and FDA. We have two major programs in the Division of Microbiology. One is the surveillance and diagnostic program and the other one is the research program. In surveillance and diagnostic program we have three groups that offer services in the area of bacteriology, parasitology, mycology, virology and serology, media prep. And this virology and serology group offer services for surveillance and offer support for research scientists. The surveillance division branch maintains a breeding colony, quarantine facility, primate colony, NTP animal studies, Non-NTP animal studies, and they have the animal husbandry contractor services, diet prep contractor, environmental health and program assurance. In terms of the research support they offer research support to the Microbiology Division plus the other divisions at the NCTR including Biochemical Toxicology, Chemistry Division, genetic & Reproductive Toxicology, Molecular Epidemiology, and Neurotoxicology. We have several areas where we have the research programs. We work in the environmental biotechnology, food safety issues, microbial models in toxicology and intestinal microflora projects. There are about eight PI's. It is very difficult to read I think because of the color combinations. I apologize for that. There are eight PI's the research division. These include Dr. Bruce Erickson, Dr. Ashraf Kahn, myself, Dr. Mohamed Nawaz, Dr. Jairaj Pothuluri who just retired last month, Dr. Fatemeh Rafii, Dr. John Sutherland, Dr. Rong-Fu Wang. There are four post doc students. We have two intern students and we have got only tow technical assistants. The surveillance and diagnostic program the leadership is provided by Mr. Warren Campbell. They also have a support staff of about eight people with one Ph.D who is also sometimes involved with the research projects and serves as PI in one of those projects. We have a multitude of technical abilities and skills available in the Division of Microbiology. These include the anaerobic bacteria culture and detection, bacteria isolation and identification, cellular fatty acids analysis (MIDI), the list is quite big I can go on reading but you probably have the handouts so you can read from that but we have a whole multitude of skills and technical abilities available in the Division of Microbiology that we can apply and use any time in collaboration with other Centers if the need arises so we are not short in terms of the technical expertise available in the Division of Microbiology. As I mentioned earlier we have about 20 different collaborative research projects. In fact we have one at the FDA interscience collaborative research for 2000 for the detection of BSE in animal feed. Out of these 20 projects we have 10 with Center for Veterinary

Medicine, six with ORA, three with CFSAN and one with CDRH. So as you can see as per the committee's recommendations when they say you need to establish more collaboration with other centers of the FDA so that you can participate more in the development and offer the regulatory help to the FDA and support this mission. So we have taken that seriously and we are working very hard to establish those collaborations. But at the same time we also noticed that and we heard this afternoon about the formation of a subcommittee who can help establish the collaboration and identify the major research areas for collaboration with other centers so I appreciate the efforts of the FDA and their thinking in this direction. But we are working (unintelligible) at the same time I want to mention that even if we are interested sometimes we have problems with the other end so that I think when the committees form that will (unintelligible) these kinds of collaborations and interactions. The subcommittee said that we probably need to have more protocols in the area of food safety because of the expertise available in the division to redirect our focus on certain food safety areas so we have a couple of projects that are associated with food safety and I have listed a few of them that we have with CVM. These include the in vitro model and molecular analysis of competitive exclusion products. I don't want to explain what the objectives for each of these projects are but I wold like to say that this is the new concept about using the pathogens in the poultry industry. What they are doing is using the bacterial mixture to spray on the chicken so when the chickens ingest those bacteria the pathogens are not (unintelligible) chicken. So we have a project that we are working on. Then we have molecular screening methods for the determination of vancomycin resistance in selective competitive exclusion products. As most of you know that vancomycin up until now was regarded as the drug of last choice for treating the infection (unintelligible). Now the only competitive product that is approved here in the USA contains some vancomycin resistance bacteria. So what I am doing in this project is trying to label those bacteria and then characterize what kind of gene markers are present in those competitive exclusion products. And whether or not those markers are transferable. So in other words whether the use of this competitive exclusion is safe for using in poultry industry or not. So (unintelligible) would probably help the use of such products so you can see the produce in question now or the forthcoming competitive exclusion products. All of this has set forth a mechanism of a way to detect (unintelligible) antibiotic resistance markers and to see whether or not they are able to be transferred to the other organisms. So we have a very good workup going on in this area and we have the studies on the fluoroquinolone resistance in *camphylobacer sp.* isolated from poultry. So as a part of surveillance we are monitoring the presence of fluoroquinolone resistance bacteria in poulty farms here in Arkansas. And we also monitoring the presence of fluoroquinolone resistant *salmonella spp*. isolated from poultry. We go in the field, collect these samples and analyze them for the presence of fluoroquinolone resistant bacteria in poultry liter or turkey liter for that matter. Then we are screening the animal feeds using molecular techniques for proteins derived form mammalian tissue to detect possible bovine spongiform enchephalophaty. So we have developed and validated an assay for detection of BSE for which we won the FDA interscience collaboration for 2000. We have also developed molecular methods to identify and quantitate human foodborne pathogens in the animal production environment. And we have also developed the presence of these pathogens in a variety of food sources for vegetables, poultry, fish, and salads. The other project that we have is on biodegradation of Veterinary Drug Residues. We have established collaboration with USDA lab as was suggested by the previous subcommittee that we need establish some type of collaboration with USDA because they are also cutting out research in the antibiotic resistance area. Also to make sure that I want to first

not duplicated and if any other government organization is also putting out these similar kind of a study that we are doing in the Division of Microbiology. So it looks like that most of the USDA people are working on characterizing these strains by (unintelligible) analysis. What we are interested is to isolate these bacteria, identify them and carry out the mechanistic studies to find out whether or not some of the resistant markers are transferable to other organisms and in other words we are probably trying to help the Agency to regulate the use of certain antibiotics if we find some of those markers that are transferable to the pathogenic organisms. Then I would like to give you an account of the accomplishments that we have done that we have made in the Division of Microbiology. We have developed molecular techniques for detecting human intestinal microflora and we have developed the methods to detect 13 different strains of food-borne pathogens, animal pathogens and environmental isolates. We have also the guidance document entitled "Assessing the effects of antimicrobial residues in food on the human intestinal microflora and this guidance document is used by FDA for assessing the risk of a low level of antimicrobial residues and microflora. Then we have also developed the alternative microbial methods for studying the metabolism of drugs. We have developed the bioluminescent assay to determine the tuberculocidal activity of disinfectants and developed multiplex PCR methods for the determination of vancoymycin resistance genes. A cell based model of colonization resistance again Salmonella invasion by using the (unintelligible) products and developed a multiplex PCR method for the detection of *Salmonella typhimurium* DT 104. We have also characterize the microbial cytochrome P-450s and glutathione transferase, the aerolysin toxins genes, and erythromycin resistance genes (erm) in *Staphylococcus* sp. isolated from chickens, azoreductase and nitroreductase enzymes in bacteria isolated from human intestinal tract, fluoroquinolone resistant *Campylobacter* spp. from poultry samples. We have characterized competitive exclusion products. When we got this competitive exclusion products the company said it consisted of 29 different well-defined bacteria.

Tape 3 side A

Khan: Now when we started investigating this problem then we found more than 29 bacteria's listed by the company so the test that they used probably are not as good as the ones we are using. Sometimes there are bacteria that are cutting the antibiotic resistant markers that we don't desire so what we have developed a method to isolate and characterize those bacteria and then we are cutting it out a step further in the area (unintelligible) antibiotic resistance transfer. Now then we have as I mentioned earlier also completed and validated a trial method for the detection of BSE. Then we determine the survival of *Shigella* on foods, discovered an agent in oyster homogenates that is lethal to *V. cholerae* and *V. vulnificus*, discovered new strains of bacteria and fungi that degrade environmental pollutants and elucidated novel biodegradation pathways for xenobiotics. We have some future plans for the fiscal year 2000. All these plans are listed. Every PI in the division has different projects and what their future plans are for the year 2000 they are listed here in these slides. We have to initiate a new chemostat experiment for testing veterinary fluoroquinolones. The PI on this one is Dr. Bruce Erickson. There is another PI, Dr. Ashraf Khan. He has the plans in 2001 for isolation and molecular characterization of fluoroquinolone resistant *Salmonella* spp. and *E. coli* from chicken and turkey litters. Myself I am planning on doing the study for the plasmid profile of vancomycin resistant bacteria isolated from competitive exclusion projects and genetic fingerprinting and strain typing of vancomycin resistant organisms isolated for the CE product and this will be carried out by

pulse field gel electrophoresis and molecular probing. Dr. Nawaz is working on the fluoroquinolone resistance to camphylobaters. He wants to correlate the data that he has obtained from the poultry litter with the environmental data available for human subjects. Also characterize all fluoroquinolone resistance camphylobacters at the molecular level using the PCR-RFLP, PFGE. Dr. Jairaj Pothuluri has just retired last month so myself and Dr. Nawaz will be taking over this project and working on the biodegradation rates and metabolic fate of the antibiotics used in aquaculture. This protocol is in collaboration with USDA. (Unintelligible) Arkansas, in Stuttgart, Arkansas. Dr. Fatemeh Rafii is working on these diadzein and genistein the food additive food supplements and she is trying to detect the specific bacteria from the human intestinal tract that convert these phytoestrogens to estrogenic and non estrogenic end products. Also wants to evaluate the effect of fluoroquinolones on resistance development in anaerobic bacteria from the human intestinal tract, mechanism of resistance development, impact on metabolic activities and the dissemination of resistance to bacterial pathogens. Dr. John Sutherland, he is involved with the identification of the metabolites produced from norloxacin and sarafloxacin by fungi grown on poultry litter. Isolation of new strains of fungi from litter in poultry houses and screening them for the biotransformation of veterinary fluoroquinolones. Dr. Robert Wagner is working with the competitive exclusion products and he wants to complete an in vitro assay of competitive exclusion products. Well at the end what is our future vision in the Division of Microbiology. We want to strive for scientific excellence and strengthen the relevance of the research in the Division of Microbiology with the mission of the Food and Drug Administration. Maintain a world-class research program to solve current issues that face the FDA in the next millennium, so the Agency can make sound science based regulatory decisions on microbiology. At this time I will stop and take any questions that you may have.

Acosta: Okay before we begin Dr. Lightfoot I just want to be certain that if you had any comments to make either from this report or the previous report.

Lightfoot: No I don't.

Acosta: Okay we will continue the discussion then for the SAB members any comments or questions for Dr. Khan.

Tindall: I have one question. You had quite an impressive list of recent accomplishments and I congratulate you on your winning of the PSE detection technique award for that. My question is, are any of these, and I appreciate also that these are all research projects in various stages of development, have you patented anything or are you thinking patenting anything.

Khan: Well that is a nice suggestion and a good idea but as when we feel comfortable well this is what patenting something and discuss with other collaborators involved with these projects we will definitely go in that direction.

Tindall: So there are no patents.

Khan: Not yet.

Tindall: Dan what is the practice for technology transfer here?

Casciano: Well we have a technology transfer office here that integrates with the FDA's technology transfer and we encourage our investigators to use that office when they feel that something that they have is a discovery that is useful. So we don't discourage. We do encourage and there is a various level throughout, you will hear different values put on that process from the various individuals in the various divisions.

Acosta: Cathy.

Donnelly: Have you thought about extending your work on salmonella typhimurium DT 104 to salmonella newport because salmonella newport has now acquired that same gene cassette and it would seem to be a logical extension of the work you are doing.

Khan: Dr. Ashraf Khan, he is the PI who is working on salmonella DT 104 and he has several restraints of salmonella including

Acosta: Could you speak up a little bit? Dr. Lightfoot cannot hear you.

Khan: Dr. Ashraf Khan in the Division of Microbiology, he has a project on salmonella. He has isolated several of the strains from poultry litter and he has also developed a method for detecting the salmonella DT 104 and he is course, I'm not sure but I think he is using salmonella newport also in his studies so I think the work is going on in that direction too.

Acosta: Could you give us an idea of how much external grants or other resources you get in addition to her interim resources to do this many projects?

Khan: Well most of the projects that we have at CVM, we got some money from CVM from the other Centers. That is the money from within the FDA. But other than that I don't think that we have any money from the Division of Microbiology.

Casciano: Well I can help. As many of you know there is a directed funds from congress and there is the food safety initiative dollars certain percentage that goes to the FDA and through the Center for Food Safety and Nutrition and CVM where the dollars collide we collaborate and leverage dollars within the Agency.

Acosta: Is that ten, fifteen, twenty percent or do you have an idea.

Casciano: In this division it's probably ten percent. You will hear from Fred Beland tomorrow and he leverages probably 85% and so it varies.

Acosta: Any further questions? If not Dr. Lightfoot we want to thank you.

Lightfoot: Thank you.

Acosta: Good bye. Thank you Dr. Khan. The next item on the agenda is an update on the Division of Neurotoxicology. Dr. Slikker is passing out his slides.

Kaplan: Does the NCTR get grants from

Casciano: We can't directly apply for grants but we can serve as coinvestigators and we can serve as co-PI's. Well we can get some funds through either equipment or post docs. We are part of the public health services so we can't, NIH, it's not because there is a law it is a NIH policy. However if we have an expertise that is not located in academia or for some reason there needs to be a fast track, there are mechanisms of obtaining dollars from other public health services through an interagency agreement.

Kaplan: I was just very curious because NIH plays (unintelligible) which to me is a solicitation (unintelligible). If you fit that solicitation (unintelligible)

Casciano: For all the reasons you can think.

Acosta: Okay Bill can you give your talk on the update.

Slikker: Yes, can you all hear me first of all.

Acosta: Yes.

Slikker: Well thanks Dan for the opportunity to do this. Now I just wanted to mention to the group some of which are new that we have been reviewed as a division approximately two years ago and so I will not be giving a response to a report because that has been done in previous groups. But I will give you an opportunity to see sort of an update version of how the division is doing. So let me start by talking about a mission statement. We all have one. Ours of course is focused on the nervous system and it is again to develop and validate quantitative biomarkers of neurotoxicity and utilizes them to elucidate toxic mechanisms and increase the certainty of assumptions underlying risk assessment for neurotoxicants. So with that it is sort of a broad brush. I will begin and also by giving you a definition of neurotoxicity as we move through this process. Now it can be defined as any adverse effect on structure or function of the central and/or peripheral nervous system and as you can image within the FDA it can be a biological agent, a chemical agent or a physical agent. To define adverse effects it can include unwanted effects and any alterations from base line that diminishes the ability of an organism to survive, reproduce or adapt to its environment. So a broad definition of adverse. And of course it can be permanent or reversible and have can have long term effects especially on neurodegenerative type effects. Now what about the impact of other agents and other kinds of situations that effect brain function? Well first of all we realized that one out of four Americans will suffer from some sort of brain related disorder during their lifetime. This includes neuroses, alcohol/drug abuse, variety of different psychotic situations as well as various kinds of poisonings of the nervous system. One out of ten school-aged children have some sort of functional deficit. Anything from ADHD, hyperactivity syndrome, various kinds of neuroses or it can include of course deafness and a variety of other kinds of disease type situations. This has a tremendous economic impact in that in the US brain related disorders account for more hospitalizations than any other major diseased group and this includes cardiovascular and cancer primarily often times because brain related disorders require long term hospitalizations. The

estimated cost of this treatment, rehabilitation, related consequences if $400 billion each year. So people put this as high as $600 billion so therefore a brain related toxicity can result in long lasting human health and economic impact. Now of course we don't say that all the agents regulated by the FDA and other regulatory agencies fall in to this range but what we are saying even for a small percentage of those agents that we regulate can produce some of the effects it is certainly a worthwhile class of agents to be studying. Now the approach that we have to use is multidisciplinary in nature. And this is because we look at many of the relevant effects can be measured by neurochemical, neurophysiological, neuropathological or behavioral techniques. That it is not just one single technique. We usually function in terms of assessing the nervous system. And also it is necessary because the neurotoxicity is often times complex and it is diverse as the nervous system itself. Now we use this approach which we call our discipline-continuum approach and basically what we are trying to do here is link together the various kinds of approaches that we use. Everything from the psychological testing that can be done in human and animal models through behavioral assessments, physiological assessments such as EEG, and various kinds of motor function tests. Morphological assessments are very critical. You can image the nervous system loss of brain cells is thought to be certainly not a good thing. Neurochemical alterations very important to many drug effects and then of course a linkage to the molecular. And this kind of linkage can be done using genomics, proteomics, of which we are doing quite a bit of work in that area currently and have been doing for several years and also computational modeling. We heard a little about this earlier. We feel that this is very important as well for the neurotoxicology arena and we have been using this in conjunction with a variety of different other agencies as well as different centers within the FDA. Now to get a little more specific we talked about these various kinds of end points and within those you have a whole range of kinds of assessments that we can do in the neurobiology block for example, neurochemistry is very important for the nervous system obviously. Microbiological approaches, microdialysis allows you to collect information from the nervous system in a waking animal. Protein biochemistry very critical now with photonomics and of course cell culture approaches were necessary. So each one of these blocks contribute to the overall neurotoxicity profile for an agent. And often times it is very critical to have more than one set of endpoints support your particular claim for either safety or toxicity. Now how do you get a group of individuals together that can look at all these different disciplines? You have to be very careful when you hire individuals and you have to hire the very best. These are certainly among those. We have Syed Ali who is a Neurochemical specialist; Dr. Binienda who is has both a CVM and Ph.D. degree. He heads our neurophysiology laboratory. John Bowyer has been spear heading our work in the omecs area and particular genomics. Sherry Ferguson is a developmental neurobehavioral toxicologist. Her work has been very fundamental both for the National Toxicology Program and Endocrine Disrupters and other areas as well. Merle Paule heads the Behavioral Neurotoxicology laboratory and also has great expertise in pharmacokinetics and other areas of pharmacology and toxicology. Andy Scallet is our experimental Neurohistologist. He has done a lot of great work in bringing qualitative information in to a quantitative form that can be used in Risk Assessment. And Larry Schmued is our Neuroanatomical Histochemistry expert that has developed many techniques some which have been award wining in the FDA and with the United States. So these individuals are able to handle the various kinds of disciplines that we need to integrate together to solve problems within the area of neurotoxicology. Now I want to give you some specific examples just in passing starting with our behavioral assessment tools. This is an operant test panel. As you can see this child is operating this panel. This

particular panel is also available and we use it in monkeys and rodents other species for the rodent model we reinforce the behaviors of correct responses with banana flavored pellets and for the children we provide nickels. But they both work the same way it is to reinforce behaviors that we want to test. We have been doing this for a while. We have testing laboratories both at Arkansas Children's Hospital satellite lab and also one at University of Arkansas at Little Rock. This individual right now is about my height and is a senior in high school so you can see we have been collecting data for a while and we have all that data stored away and have made may publications from it. One of the things that you can do.

Rosenkrantz: Do nickels still work with him.

Slikker: Right now it seems like there are other things that may be more reinforcing for this particular fellow but in the age range we are looking at we sometimes have to go up to quarters or more. Yeah. This is an idea of the incredible utilities of these approaches. Many of you know about full scale I.Q. We can relate that very nicely to one of the test results that we generate from this intelligence panel (unintelligible) repeated acquisition which is a description of a new learning task and you will see the size correlation very highly significant correlation that was uncovered over the last ten or so years. This gives great little confidence that our operant test battery can be instructive and understanding more traditional type of approaches that are often times very subjective in nature. Ours are very quantitative in nature. And to make this linkage though, of course you can can't test every chemical in children and so we have the opportunity at NCTR to have a primate center and it has the general capability of providing animals for general toxicology and pharmacokinetics studies. We have a breeding colony portion of that which can be used to breed time related pregnancy. Certainly the neurotoxicology aspect has been talked about to some extent in behavioral assessment. We have the ability to behaviorally evaluate up to 90 primates a day in our system which is unmatched anywhere else in the world as far as we are aware. Extramural funding for this has been good. You can see over a half million dollars for the last 13 years and productivity has also been excellent. It is a unique FDA facility and also unique in many ways to EPA and NIEHS. So it does have it's utility in that regard. Now you can use the particular animal models where you can do studies that you can not do in the human situation but you still want to learn much about the human situation under various kinds of treatment. For example, here we were treating these particular groups of young monkeys with various kinds of anticonvulsant. Obviously children do have epilepsy and unfortunately they need to be treated for that particular disease state. There is a linkage between interaction of many of these chemicals with the NMDA receptor complex and learning and sure enough in this particular situations at a high dose this particular anticonvulsant shown here in the red dots, you can see that their ability to learn over the dosing period which started here begins to drop off as compared to the control groups and the low dose groups of the same agent. And from this arrow forward we had a significant difference between this population here that was dosed at 50 mg per kilogram versus the control or the other dose levels of (unintelligible) or an agent that is somewhat similar MK801. So you can use these particular animal models and these particular test systems to identify learning disabilities and certainly this is one example of that. Now the thing is that does the information you collect in monkeys allow you to extrapolate the human? Well here are some examples that we have collected over the years. What we have here are acute effects of various drugs. These range everything from THC to Chlorpromazine a major tranquilizer, Diazepam minor tranquilizer, Morphine and Atropine a

(unintelligible) agent and if you look at the primary effects here they are the same in the monkey model that we generated this data here on campus versus various human studies that were done either before or after the monkey work was collected. So what this allows you to do is make a nice comparison with these agents here and show that the same affect can be seen in the monkey model and in the human situation. The same thing for chronic effects. Here is an example of marijuana smoke and you get the same effects in the monkey and the human. So this gives you a great deal of security that the kind of data that you are generating in the monkey can be valuable to extrapolate to the human situation. Now another way to use various models, especially primate models where you have a large brain size and that is you can do various kinds of three-dimensional reconstruction using MRI approaches. We heard about this earlier that imaging was becoming more and more important. You think about the number of images that have been made since the early 80's it has increase dramatically in the clinical setting and I think we are going to a dramatic increase in the use of imaging for safety and toxicological studies in the future. The reason being is you can reconstruct certain brain areas or the entire brain is done here by Andy Scallet working in conjunction with our colleagues at CFSAN and CDER and here you are able to look at areas that are affected by the anticonvulsant treatment. This kind of approach has great promise because not only does it allow you to look at anatomical regions as this does but in the future we will be able to use the same approaches looked for neurochemical changes and even molecular biology changes. So we think that this is something that we need to be involved in on the ground floor and move with as the rest of the scientific background of this nation moves forward with this approach. Here is an example of something more classical type testing. This work is done in conjunction with CFSAN, Andy Scallet, here at the NCTR, also Larry Schmued and others. What we are able to do here is show that under control conditions that you get very little silver staining even in this Hipp(unintelligible) area of the brain but with treatment with domoic acid you get a lot of silver staining which is this dark color and these are cells that are either dead for dying. This approach under high power here you can see has a dramatic effect especially in the hippocampus. And this particular approach was used to generate quantitative data so you could actually take this information and do a risk assessment with it. We found that hippocampus is the most sensitive area and showed sensitivity in the primate also later this was confirmed in the rodent species and the humans that had accidental exposure to domoic acid showed problems in the same general area. Larry Schmued developed a nice technique called Flora Jade which is this bright yellow cells here that allows you to do the same kind of assessment as seen in the previous slide. I will say though that the previous slide to generate that data takes about three days. To generate this data with Larry's technique takes three for four hours and in doing so Larry was able to publish this in many different forms and able to also win the award from FDA as one of the analytical techniques in 1999 that got an FDA wide award. So with this particular approach we are able to quantitative type work and just to give you an example of this we compared three different kinds of risk assessment procedures with traditional loael approach, the newer bench mark approach and a newer method to deal with continuous data that Dave Gaylor who just retired from the NCTR/FDA and I worked out and published our first paper in 1990 and ten years later it looks like the EPA is going to pick those up as one of those benchmark dose approaches for working with continuous data. But this just gives you an idea of how you can this what use to be considered generally qualitative data, make it quantitative by using the techniques that Andy Scallet has developed put it to the various models that Dave Gaylor and I have worked out and come up with a nice approach to look at safety of seafood pertaining to domoic acid and you can see the results are very similar for the

three techniques, 12, 6.4, around 10 parts per million is considered to be a safe level. It matches nicely what is currently being used as the trigger level for food safety and seafood food safety across this nation. So this approach can be used and what we found out here is that quantitative biomarkers and intertoxicity can be determined both from behavioral end points and from neurohistological end points that continuous or non (unintelligible) data can be used in a quantitative risk assessment. This was really a step forward because this allows you then to use a lot of data that will be generated in the future. A lot of our new techniques that use proteomics and genomics and that sort of thing are going to generate continuous data and this approach allows you to use that and we found out that you can then compare these risk assessment approaches and they seem to be very comparable. We have no published about ten papers in this area and it seems to be being picked up broadly right now. Let me move on to another area. I want to focus mainly on genomics at this point and time. This is work by John Bowyer in our group who over three years ago had a protocol that was focused on the use of clone tech arrays and uses this particular approach to look at changes. And the generally hypothesis is here. That low doses of substituted amphetamines and this includes agents such as methamphetamines, definflouritamine which many of you heard about Fen Fen, one of the components of that. You have probably heard of ephedrine. Many compounds fall in this class. What his hypothesis is is that substituted amphetamines that do not produce overt signs of neurotoxicity may produce long term ultra structural interochemical changes and this could be monitor by looking at the DNA expressions. And so this is just an example from RNA collected from Substantia Nigra in one particular area in the brain fourteen days after a multiple dose of amphetamine here and control here and there are some subtle differences between those. He is now chasing this down to identify which genes are being altered and what the proteins are. So this approach is firmly entrenched and has been going on for some time within the division. Now let me just give sort of a quick overview and close. I would like to say that we have been very fortunate to have covers of some of the more prominent journals in the scientific arena. This is a brain research. This is Larry Schmued's work here, some of that award winning work that Larry has produced with Flora Jade here and black gold which is another agent that the developed here. We generally have both peer review publications and book chapters amounting to about 40 per year for this division. We have been able to do that over the last six years. The other thing that we do a great deal of is provide leadership on various kinds of committees. Here you see Redbook II with CFSAN. We are on the Reproductive and Developmental Toxicity group. We help them there. Of course UAEPA different agencies within the United States and some in Europe or Internationally such as WHO working group on Pharmaceutical agents. Just in the last year we have been on four other committees dealing with child risk assessment. And this is a big area now. The prenatal period post natal period in particular and so these are LC committees, most of you are probably familiar with LC and some of that groups work as well EPA. So we feel that this is very important. We are also involved heavily now with CDER on one of their committees that looks at various pharmaceutical agents in particular, some of the anticonvulsants. Again a couple more covers this one on the Toxicological Sciences that we are very proud of that Andy Scallet was author on and one of his graduate students and also this one in brain research. Now let me close by saying that we believe in a diverse portfolio of leveraging opportunities and we follow that with CRADAs. This one has been funded by NITA to the University of Arkansas at Little Rock, one of our previous post docs has that award and through a credit mechanism which is nearing it's final hoops at FDA headquarters it will bring in $250,000 a year for five years to do this study. This is a primate study done here on campus. This is another one here with the

NTP/IAG arrangement on Endocrine Disrupters here. Sherry Ferguson and Andy Scallet have been playing a major role in this particular program and the money comes via the National Toxicology Program, which Bill Allaben will talk about next, but it supports some very fine work. As a matter of fact Sherry has published more papers on endocrine disrupters than any other group out here and also published first so we are every proud of that and both of them have been working hard to get their work completed. We do have an interagency agreement with EPA that brings in a couple hundred thousand a year. This one is on quantitative risk assessment procedures and does a lot of work that you saw earlier with some of the quantitative methods of comparing structure and activity. WE are doing this with food bone pesticides such (unintelligible). And then also we have another large agreement, which is another CRADA with AstraZeneca. Here is your opportunity to interact with industry on very broad questions of how anticonvulsants affect learning and memory. You can see that it is well funded and Merle Paul is the one that is the particular PI in this project. So this helps supplements our NCTR/FDA funding in our particular division. Now let me just show you a couple of projects that have either been approved or just begun in the last year and you are probably not aware of our system but we now have a concept paper that has to be approved first by the direction then after that you go through the protocol review process and then finally the protocol is approved and you can start the work. Here is one that has been ongoing and has been approved for about six or eight months now by John Bowyer using multiple cDNA arrays to look at these temporally changes after various kinds of exposure especially substituted amphetamines. This is with a variety of collaborators. Some from NIOSH, Syed Ali from our division here. Also Angela Harris from the Division of Genetic Reproductive Tox here and also some folks from Wakeforrest University. Another one that has been approved and ongoing is the one with AstraZeneca to look at this long-term anticonvulsant treatment. Another one that the protocol is under review so it has made the first hoop is now in the second bin for scientific review, animal care and use review by Syed Ali and also Bill Girley from UAMS who is an expert at looking at the various dietary supplements, especially ephedrine type compounds and this is also in conjunction with some individuals that are at Right Patterson Air Force Base and some of the rest of the folks in the division here. But this is a very important one to look in ephedrine containing dietary supplements. These concept papers have been approved. We have one on development effects on nicotine and this is mainly considering the nicotine patch situation that you have FDA approval for and looking at developmental effects of that with some of our colleagues from Duke University Ted Slotkin and Fred Seidler. Also another concept paper approved is the one on Mitochondria energy metabolism. It is a very important aspect that a lot of dietary supplements at least say that they modulate and they say that this is good for you when mitochondria energy metabolism is modulated and we are looking at this in quite a bit of detail. And again this one has a chance of being a CRADA in that we have collaborators form one of our regulatory industry folks involved in this. Now future directions let me just make two comments here and then I will close. Thimerosal, a big issue within CBER and also within CDER. But CBER is pushing this one through as an NTP compound. Bill will talk about this in a moment. This is a very big issue because as you probably are aware Thimerosal is a preservative in many of the vaccines that our children get on a routine basis and even though some of this is being eliminated by going to single dose vials it still will be in some vaccines. It has been in a lot of a vaccines especially for the last ten years as a vaccination schedule has been enhanced for our children and will continue to be in vaccines and especially in vaccines not only here but also in other countries. And we think this is a very important issue and so does CBER being able to evaluate

Thimerosal exposure and developing monkeys and in particular comparing that to what might happen in the human situation. Nutritional Supplements. We have already talked about ephedra and related compounds. Infant formula is another one that we are discussing with CFSAN and hope to do more of that while their representative is here today. And also therapeutic agents, we mentioned anticonvulsants, various kinds of neuroprotectants and also now (unintelligible). We have some active dialogue going on with CDER looking at the influence of catamine especially with its pediatric use and how to evaluate that in terms of safety. Now getting down to very end, the future directions and resource development. As I mentioned we think imaging is very very critical and we are doing imaging development with other centers and we need to actually reach out to NIHS and other places to obtain collaboration and funding for this. Animal model development is key. Transgenic, as mentioned earlier by Dan Casciano. Of course we have showed the importance of using it on primates with certain kids of studies and this kind of work has been in conjunction with other centers as well. And then genomics and proteomics are very important areas to us and one in which we are building on quite rapidly right now. I just would like to close by saying that it would not be possible to sort of keep up with what FDA needs and what we think you may need in the future without having various kinds of working groups. This is our FDA Intercenter neurotoxicity working group. IT was begun in 1994 so it has been around for seven years. This group has represented us from each center and our role is to assist FDA to address regulatory concerns, especially those that deal with neurotoxicity. We do have an active site on the first which is part of the FDA intranet and it allows us then to communicate and we have also meetings scheduled throughout the year. So this particular approach by interacting with others interested in safety assessment, especially neurotoxicity safety assessment within FDA all the centers get together and talk about these issues and try to come up with solutions that will be helpful and address the FDA concerns and needs for future. So with that I will close and be happy to answer any questions you may have.

Acosta: Okay well thank you Bill. Any questions or comments from the group?

Rosenkrantz: Bill I have actually two related questions. In the future directions you talk about imaging and in your discipline continual approach is like seven, we talked about competition modeling and you discussed work with other centers. I was wondering how much internal NCTR work you were getting from the computational science group.

Slikker: What we were doing there is that we were able to obtain funding from EPA at the Research Triangle Park Group to do collaboration with them to solve a problem about how to develop a biologically based model for (unintelligible) and related (unintelligible) agents pesticides that are food borne. This seemed like a very important project. We were able to hire a post doc and buy a certain piece of equipment that was necessary in doing the modeling. We now have a manuscript that is submitted to the Toxicological Sciences and we are hoping for a good return on that here very shortly. So that is the approach that we used was to not only collaborate with ROW staff but also have a post doc on site that could carry that work out in our own neighborhood. And that has been very important to us to be able to do that.

Rosenkrantz: So the ROW staff is (unintelligible)

Slikker: Yes, they are.

Rosenkrantz: In the imaging as well.

Slikker: In the imaging, now the imaging is more complicated. Imaging we are doing in conjunction with GIFSAN which is part of CFSAN in the Maryland campus that you are probably aware of. We are also doing this in conjunction with folks at CDER which they have relationships with folks at Duke and various universities. And so we do not have the imaging on this site. Now what we are trying to do is develop relationships with a variety of different other outside institutions as well as our own campus that is close by here. WE do have imaging capability at UAMS and so we are trying to build those relationships that we can have access to equipment. Right now we are going it through GIFSAN and through the CDER relationship with Duke and other locations. That is definitely done in a collaborative way. We have the samples but don't have the instrument here. How great it would be in the future to have that instrument here because it is not only useful for neurotoxicological problems it is important for the cancer and tumor development and a whole host of other kinds of ailments. So we are hoping to have that in the future.

Casciano: Well maybe I can help too Marcy, the proteomic and genomic effort which all of the disciplines are utilizing are interfacing with the biophomatics group and they are developing software to image for protein spots and to identify intensity of spots plus lend creditability to the development of data sets and this is a team oriented effort where these developmental projects are applicable across various platforms.

Gillett: (unintelligible) beautiful pictures. The work (unintelligible) reference to some of the discussion earlier about the subcommittee if you look at the drug development process with all of the (unintelligible) pipeline that there needs to be evaluation (unintelligible) with this interagency group are you having the impact with expertise's in your group in terms of telling some of the people (unintelligible) should be evaluated (unintelligible).

Slikker: Well that's a good point. Yeah. To this intercenter group that I talked about, the FDA Intercenter NeurotoxicityWorking Group and just our interaction by knowing other individuals in other centers especially reviewers were able to communicate on a variety of issues. Some times they would call and say well what about this particular approach. Can you suggest an alternate approach. What about this interpretation. And so that has been very enlightening for us and also very fruitful for them to get his dialogue going to try to understand perhaps new or different techniques could be done. I have been very excited recently also to see that the pharmaceutical firms are using imaging now to look at neuroprotective agents to uncover not only the damages produced by the particular challenge that they give but also the protection of the agent that they are wanting to support as a neuroprotective agent. I think this is going to be a trend that you see much more of that allows you to get real time information about the damage before you start the therapy and that is going to be done not only for developing drug but of course to use them in the effectiveness and to show the beneficial effects. So I think these techniques are coming along and we try in every way that we can to interact with the reviewers at the various centers not only to help them develop guidelines but also to provide information about newer techniques and that sort of thing.

Acosta: Perhaps one last question I have is in order to recruit top scientists here you mentioned the fact that you do have the ability to work with graduate students. Is this something that could be used and how many graduate students do you have in this collaboration with UAMS I assume?

Slikker: Right. But we don't have to hold just to UAMS. We do have students from other universities as well as well as traveling fellows from various foreign countries that come on funding basis as well. So that really is very helpful to us. As already mentioned was the postdoctoral program which is key. My mention with the seven senior staff we also have eight or nine post doctoral fellows, many of them supported with outside money that are very critical to us. But right now we have the opportunity to have as many as eight or more graduate students here. We do not have that number. We have a couple of graduate students here if we are fortunate enough to do that and that is ones that come from UAMS and our collaboration there. We would like to see more but then I think everybody would. I think graduate students are at a premium right now

Tape 3 Side B

Both on UAMS campus and here to recruit more and better quality graduate students to compete in our discipline.

Acosta: Okay well thank you for that excellent update Bill. We will go the last item on the agenda. The NTP update. Dr. Allaben.

Casciano: While Bill is getting ready to pass around this manuscript I mentioned earlier about that is going to be place don our web site and the name of our virtual journal is Regulatory Research Perspectives Impact on Public Health and this is a NCTR generated issue.

Allaben: Well thank you very much. I know that I am last on the agenda and everybody and anxious to get to dinner. This is going to be a two-prong approach. I am going to give you about a 15-minute overview and then Dr. Howard is going to talk to you about the FDA/NIEHS phototoxicology research and testing laboratory. This is an interagency agreement with the National Institute on Environmental Health Sciences which also has the responsibility for directing the National Toxicology Program and I don't know how many of you are familiar with the National Toxicology Program. I hope most of you are but just to give you a brief background on that the NCTR/FDA has a prominent role in making

TAPE 4 SIDE A

Up the National Toxicology Program. Even though it is directed and resources go through the NIEHS the charter members are the FDA's National Center for Toxicological Research and CDC's NIOSH National Institute of Environmental Health Sciences. And it really comprises the three major agencies that comprise the NTP under the direction of the National Toxicology Program that director Ken Olden reports directly to the secretary, not to the director of NIH. But it actually has secretarial responsibility and is directed through the Department of Health and Human Services. There are several oversight groups. The main oversight group for NTP is the

Board of Scientific counselors. Much the same responsibility that you have for NCTR and then there is an executive committee which is comprised of the heads of public health service organizations and also the EPA and OSHA comprise the management or executive committee of the NTP. FDA's mission. We all know that to promote and protect human health. Under the Food and Drug administration modernization act, FDA has actually directed to share interest to find resources to help us accomplish our mission and by doing so we hope that identifying intellect time, money, resources in a manner that maximizes our opportunities to provide the FDA regulators with the kind of information that they need to make appropriate scientific decisions. And with regard to leveraging it was stated by Commissioner Henney last year that an example of ongoing successful partnership is one that the FDA enjoys with the NTP NIEHS with regard to funding research and bioassays on FDA regulated products. This in 1992, this interagency agreement was singed when Commissioner Henney was then the Deputy Commissioner for Operations for the Food and Drug Administration under the Commissioner at that time was David Kessler. This interagency agreement was signed and I kind of like to think that it provided her with the ideas that allowed her to go forward with her leveraging ideas and resources that she has supported so strongly during her tenure as commissioner. IAG concepts. Innovative applied toxicology studies. The ability to design studies to give the regulators the kind of information they really need. Very important. The FDA scientist at the table during the design phase. These are the regulatory scientists who are the end users of this product. And so if they are at the table they can help us formulate a research plan that incorporates their needs from a regulatory perspective. It also provides resources for doing mode of action and mechanistic studies. It's not just a lump and bump product. It has additional information with the package to help appropriate risk assessment decisions to be made. We like to hope that we can do this in a very timely manner and importantly it utilizes NCTR's expert scientific staff and our unique facilities. We are unique. We do have a unique facility here at the NCTR that is hard to be matched anywhere. It supports high quality science based safety assessments, reduces the uncertainty in risk assessments or risk benefit analysis, and it's measurable. That is, the product that this interagency provides to the regulators in measured in real time. It's not something that may have utility five or ten years out. IAG history, I showed you in December 1992 the IAG was signed. That's our fiscal year 1993. In 1995 proof of concept was such that the director of the NTP open ended the product. Otherwise originally it was a five-year concept but it was proven to be so effective that he went ahead and had an open ended agreement signed. That means there is no projected end to this interagency agreement. As long as both sides are committed, then resources will be provided. In 1996 the NCTR/FDA in an agreement with NTP agreed to do endocrine disruptor studies. We looked at five putative endocrine disrupters. These are very complex, time consuming, four multigenerational studies, terribly terribly complex and in fact it was the NCTR was really the only facility that could perform these types of studies. In 1998 resources for developing a phototoxicity research and testing laboratory were provided. This was a center that Dr. Howard is going to talk about very shortly. It is a state of the art facility that exists no where else in the federal government. In 1992 we set aside resources and were hoping to get appropriate resources from the NIEHS but that renovation and expansion of the phototoxicology research laboratory and providing additional animal rooms to support these studies, that agreement is still pending. We are still in negotiations with them. In the year 2000 additional high priority FDA compounds including some of the dietary supplements were brought in under the interagency agreement and most recently we are entering in to a most complex series of studies that Dr. Beland will talk about tomorrow. The Aids therapeutic

mixtures study. Some of the compounds that we have tested under the interagency agreement chloral hydrate which were the Center for Drugs nomination. Fumonisin B1 which is a microtoxic contaminant in corn crops it was a CFSAN nomination. Malachite green is a substance that is used as a fungicide in high-density aquatic farming with fish farming. Urethane/Ethanol. We all know urethane is a carcinogen but the concept was what does ethanol do to modify the carcinogenic effect of urethane and the reason for that is because a lot of our liquors, brandies, wines, you have a produce of fermentation urethane is produced. And so it's there in various quantities and the number of the alcoholic beverages consumed in this country. Riddelline is a contaminate that is found in some of the herbal products and also some of the herbal teas. It was a FDA/Center for Food Safety nomination. Glycolic and Salicylic Acids are phototoxicology studies that really were the driving force in back of developing the phototoxicology research laboratory here at NCTR. Paul will talk about that a little more. I told you about the endocrine disruptor chemicals. The phototoxicology nominations, there have been several that have come in recently. Dietary supplements and again very highly visible issue for FDA even though we don't have regulatory responsibility for the dietary supplements we certainly have a need for comprehensive toxicology database on them. And the NTP gives us the opportunity to get that kind of information. Aids therapeutic studies. Again this was a cooperative research agreement between NTP, CDER and NCTR and Bill Slikker told you about thimerosal and other important chemicals that is coming in under the umbrella of interagency agreement. I told you about the endocrine disrupters and this shows you the ones we are looking at. Methoxychlor, genistein, and of course that is high on everybody's priority list right now with regards to it's toxic consequences or beneficial effects, depending on who you talk to. Nonylphenol, vinclozolin, and ethinyl estradiol, these are all the chemicals that are going through this complex series of multi generation studies. And then aloe vera as the first dietary supplement we are looking at. These are phototox studies as well as systematically administered studies and the Aids therapeutics. Some of the nominations that the NTP has forwarded to the NTP that do no go through the umbrella of the interagency agreement includes radio frequency. This is cell phone frequency admission radiation. This was a CDER produce nomination. DNA based safety assessment of selected vaccines/therapeutics, which was the Center for Biologics nominations. Two of these antibiotics they had the agency had need for the genotoxic information on these and the NTP provided an opportunity to obtain that information. P53 studies with Senna are the replacement for Phenylthalene. Phenylthalene was found recently to be a four cell positive carcinogen and by four cell I mean male and female rats and mice and was taken voluntarily withdrawn from the marketplace but we are seeing a lot of over the counter products with Senna in addition to in prescription drugs. And then there was a nomination for doing p53 & TG-AC studies with pilocarpine. Last year's nominations. These are all nominations that will be coming to NCTR for testing under the umbrella of the interagency agreement. Most of them are photoxicology study nominations. Thimerosal Bill has talked to you about the importance of that. Studies with regards to starts for this particular year. We have a protocol approved and in place for phototox studies with aloe vera. Dr. Mary Boudreau is the principal investigator on that study. Trans-retinyl palmitate, Dr. Sandy Culp the principal investigator for phototoxicology studies and the Aids mixtures which Fred will talk about tomorrow. Scientific oversight. We do have a scientific oversight with regard to this particular interagency agreement. All the science we look at comes through what we call our toxicology study selection and review committee. This is a scientific oversight body that comments on the utility and the quality of the science not only from a pure scientific perspective but also from an

Agency perspective because as I have told you we have scientists from all the FDA agency product centers at the table during the design phase. And then of course we go through a series of protocol reviews both at NCTR at the product center and at the NTP NIEHS. The responsibility of that oversight group is review research concepts and plans; the PI protocols are discussed and commented on. IT recommends that any protocol modifications with regard to dose level selection design changes and so on and importantly we meet twice a year not only to review new science projects but also the monitoring of the projects that are ongoing within our interagency agreement. This is just an example of putting some names to some compounds Fred Beland, Paul Howard, Sandy Culp, Paul Howard again, he shows up all the time. Barry Delclos, Andy Scallet, Sherry Ferguson, Dan Doerge, Suzanne Morris are all involved in the comprehensive endocrine disruptor studies. Riddelline Dr's Peter Fu and Ming Chou of whom have done an outstanding job with regard to identification of biomarkers for this particular substance. Aloe vera, Dr. Mary Boudreau. Retinyl palmitate Sandy Culp and again Aids Fred and Thimerosal Bill Slikker. What are the benefits, these are my thoughts, enhances regulatory decision process, supports quantitative risk assessments, new/innovative research approaches, speeds the research and testing process, provides data to the regulators, they are at the table during the design, they are at the table during the monitoring the progress of those studies, they are the first to see the results of these efforts. It utilizes NCTR scientific and contract staff. It provides FTEs and post doc support. Facilities renovation and Paul will talk about the phototox lab. Equipment purchase and provides resources for travel to scientific meetings. This is my last slide and Dr. Howard will pop up here and go through his. But what I want to show you is the yellow is the salary and benefits package for NCTR employees over the years. The purple is the NCTR operating funds. This is the funds that NCTR gets from FDA. Dan talked about that this morning. The green represents the interagency agreement with the NIEHS/NTP for resources coming in to the Center and as you can see there has been a substantial increase in resources. It is a package, a benefit package that is good for NTP and certainly good for NCTR. It is definitely an example in my opinion of leveraging to the best possible way. I think that is it. Dr. Howard.

Howard: I know we are suppose to be totally professional here and everything but I think the thing that is most important about this interagency agreement and the concept in which we are doing this is that all the screaming and yelling gets done at the beginning of the study. I remember on some of the earlier fumonisin studies the fist pounding and cursing that went on in this very room about purity issues. But yet we got it all out of the way up front rather than doing a study and saying gee we need to do it again with a little bit different purity levels. So it is very beneficial I think to the agency in that whatever gets done is as best as possibly can be done. Did we lose it. This is going to be a very quick talk then. I will be very quick because I know everyone is a little fatigue and looking forward to a dinner. Where are you guys going?

Casciano: 1620.

Howard: Okay. Big checkbook. Well there's Bubba's catfish kitchen just down the corner.

Casciano: We don't let Paul out too often. We save him for the end of the day.

Howard: Yeah, why is it I'm always at the end of the day. I can't figure this out. Is that mine by the way. Well it depends on which who I'm talking to. Today since this is a FDA committee this is the FDA NIEHS phototoxicity research and testing laboratory. When I'm at the NTP it is the NTP Center for Phototoxicology. It just depends on who I'm talking to what I emphasize. But basically there are four centers for research excellence within the National Toxicology Program. First one is NTP Center for evaluation of Risk to Human Reproduction in which they take a particular topic. They research it. Everything is known about it. Pulled together a panel of experts and come up with expert opinions on risk of certain chemicals to human reproduction. The second is the Interagency Center for the evaluation of alternative toxicological methods, which works in collaboration with ICVAM to do alternative methodology. The next one and it is really not under the NTP it is more under the NIH itself, which is the National Center for Toxico Genomics. Ray Tennett heads up that facility in NIEHS. And the fourth center, third really within NTP is the NTP center for Phototoxicology, which is built here at the NCTR. The purpose of this facility is to provide the expertise and facility that will allow the conduct of toxicological studies, which require the exposure of animals in light admitting sources. A good example of this is a patemate o, which is one of the sunscreen agents. It's dimethoeminol ester of paba. It has been under the NTP study for about two and half years. None of the studies conducted to date have added light to the toxicological testing. That is the primary mechanism of why it is on your skin is to block light. So what started the whole process. We are told that no matter how old we are or what we do with ourselves we are supposed to have skin that looks like this. This is a bill of goods that has been sold by the cosmetic industry and others that we are always suppose to be beautiful like this. But yet we are also suppose to be very tanned which causes photo aging but you know we tend to want to have everything. The way this whole nomination process occurs to be rather blunt about it they say alpha hydroxy acids. What are you going to do about it? So we convened a committee within the FDA which have already been working with the cosmetic ingredient review panel to determine what does CFSAN really need to make a regulatory decision concerning these products. Well it became very obvious very quickly we needed to mimic the human model which is we apply these agents to the skin that is also sun exposed. The primary use of this product is to correct photo aging on the skin. I'm not looking at anyone in particular but as we get a little older we get these wrinkles around our mouths and around the eyes and if we can correct those wrinkles and look like the lady in the picture everything is fine and wonderful. And these products work. I have the best looking mice in Arkansas. These mice are gorgeous when I treat them with these creams. But what source of light, so we can get creams made that mimic what is in over the counter products but what source of light do we use to mimic the human situation. Well we are exposed to the sun and I proposed to move the laboratory to Hawaii but Dan said we didn't have the budget but the other thing is the sun is a moving target. If you consider today or yesterday, June 10, the amount of ultraviolet radiation that we were getting in Arkansas was quite suppressed because of there was a lot of moisture in the atmosphere and you can see this green around the gulf coast is that big storm moving through. It really blocked a lot of ultraviolet radiation. But if you happen to have been in Colorado yesterday you were extremely high levels of erethemiol UV light. It is a moving target across our country. Not only based on weather patterns and what season of the year it is but for instance right now in the Indian subcontinent extreme levels of UV light. It also changes with year. You don't get a sunburn in the winter because there is not very much UV hitting the United States. This happens to be December 21st of last year. So how do we mimic a moving

target? Not only that ozone is considerably involved in the amount of ultraviolet radiation that reaches the planet. If you look at ozone levels this is on January 6th of last year, look at ozone levels, across the United States are quite variable. Not only that September of last year we had the largest ozone hole ever detected on this planet which encompassed part of South America. How do we mimic this? Well the best thing to do is to just pick one and say this is what we are going to do. This is sunlight that was taken the day Dr. Henney last visited as the last FDA commissioner to visit, I need to take one today since Bern was here today, but July 6th of 1999 we looked at the sunlight in Arkansas which is about the 34th parallel and the sunlight we are able to generate in our Facility we are using a sunlight that looks somewhat like this. From all photophysics and from a physics standpoint this level of light is the ratio of the different wavelengths of light that we are using is very reminiscent of sunlight. Very representative of sunlight. If the sunlight, the amount of ultraviolet light we are giving our animals is somewhat equivalent to what you would get in the mid Caribbean. Fred said we had to do that since he is in the Caribbean about half the year. How do we generate the sunlight? The sunlight is generated with a Zenon ark lamp. It is basically a continuous lightning bolt in a Zenon gas tube and if we have glass panels around the light. If it were not for these glass panels the light would resemble extra-terrestrial sunlight. But by using specially made quartz glass panels we can trim that spectrum to match anywhere on the planet. You want what will happen if there is an ozone hole over Washington, D.C. we can imitate it in this laboratory. The animals are exposed and housed in specially designed racks which is a proprietary rack designed of Lindenking Corp but it meets all the guidelines as far as animal health and welfare. But the nice thing is that they are exposed horizontally to the light. To expose mice vertically or from a vertical exposure light is somewhat inhuman because they can't get their eyes out of the light. They get a lot of cataract and eye damage. This way they all do like this one. They all go, they put their little nose in the back corner and go to sleep because they are nocturnal animals. As a result we get sort of the most of the tumors are on the rear end of the animal. We have quantitative equipment so we know exactly how much light we are giving to the animals. The target animal is the SK-hairless mouse. No comments about knock out genes because I think I have one. It is an albino animal and it has juvenile sort of fuzzy hair but it does not develop the adult hair. It is a fully immuno-competent animal as opposed to the nude mouse. It was developed at Temple University in the last 1970s the old fashioned way. They were breeding animals and developed the straight and it has been the primary target animal for photocarcinogencity study since then. Again they are housed in their little individual cages exposed horizontally. This is just a right now the current study in the Facility is the alpha and beta hydroxy acid studies, which started July 17th of last year. They are now off dose. It is 40 weeks of exposure to the cream and the light then they go off the cream and the light and are held for 12 weeks and then sacrificed. So as opposed to the traditional NTP study which is a two year lifetime study, these are one year studies and they get, the matrix is they get no light, low level of light, medium level of light and a high level of light and then no additional treatment control cream. Four percent or ten percent glycolic acid which is what is out on the over the counter market. Ten percent glycolic acid ph 3.5 is very typical of what is used or two percent or four percent saliscyclic acid which again if you get Avon anew with beta hydroxy complex that is what you are getting is two percent saliscyclic acid pH 4. So these are very reminiscent of what is over the counter. With this type of matrix and I don't like this talk already, but what we looked for is we know that these two doses of light are photocarcinogenic in animals? One hundred percent of the animals in this group have basil (unintelligible) by week 25. A hundred percent of these animals have it by about week 35 or 40

and almost all of these animals in the control group with get either basil (unintelligible) carcinomas. We know light is carcinogenic. What we look for is the ability or the effect of the cream on shifting to tumors quicker, more tumors, different type of tumors that is the evaluation we use. So our positive control is the light itself. We are looking at the effect of the test agent on a positive carcinogenic situation. A little different than the normal test. Okay, what is the capacity of this Facility? Well it really depends on the type of studies if we use the number of dose groups we have essentially five dose groups in the alpha and beta hydroxy acid study. If we are going got use both males and females vehicles the number studies somewhere around three or four studies we can handle at any given time in the Facility. We have the capacity right now to house about 6000 mice and depending on the study design we can expose around 4000 mice in an afternoon to the light. The low, medium and high doses of light are half hour, one hour and one and a half-hours. Which is equivalent to about 8%, 16%, or 24% of the light given to give them a sunburn. These are sub urethemal doses of light, which are carcinogenic. Alpha and beta hydroxy acids just very quickly, this was nominated through the interagency agreement by CFSAN to make a regulatory decision about the safety of these cosmetic ingredients in the market. IT will be done this next fiscal year. Actually the animals will come on the study in July and August and it is really addressed this over the counter cosmetic use of these things which they basically dissolve the stratum cornium and upper stratum grandulosium causing an enhanced proliferation of the basil epidermal basil cells. The stuff works. It does. But at what risk. That's what we don't know. Especially in women who use these products because of photo aging from excessive sunlight exposure. The very people who are at risk for skin cancer you are now facilitating a change in the basil proliferation rate in the epidermis. Is that going to be a carcinogenic incident, we don't know? What are we doing mechanistic studies to understand the effects of the cream and the acid containing creams on basil cell proliferation and epidermal proliferation? We have lots of mechanistic work, which I just don't have time to go over and the one-year carcinogenic study. The next compound which will be studied in this Facility is aloe vera, Mary Boudreau, in the Division of Biochemical Toxicology is conducting these studies. It was really nominated by the National Cancer Institute to the National Toxicology Program. It was not really a FDA nomination. Aloe vera is everywhere. I put some stuff in our fish tank, we added new water to our fish tank and it has aloe in it and I'm like why do my fish want aloe. But you really, even the shampoo I used this morning had aloe vera in it. It is absolutely everywhere. The question is what are the phototoxicological properties of this compound. The next compound in the study and all three of these are actually aloe vera and retinol palmanate will start this fiscal year. Retinol palmanate you ca get it of the internet up to I believe 20% by weight in a cream. Twenty percent retinol palmatate. Well you have a lot of (unintelligible) in your skin. That is going to convert that to retinol. What is the effect on the skin of very high concentrations of retinol? Photocarcinogenic studies have not been conducted with retinol, retinol palmatate. It is something that really needs to be looked at. Dr. Sandy Culp in our division will be looking at it. I think Fred is going to talk a little bit more about that tomorrow. Current studies – there is right now currently not an acceptable rodent model for melanoma development. Woody Tulleson in the division is using, this is people who are using our studies that we use at this Facility is like a core Facility. IN collaboration with Linda Chen at Harvard University. They have a T-P rats (unintelligible) based on this promoter and it is (unintelligible) for the P1684A tumor suppressor gene. We already know that these animals if they are in double knock out they will develop melanoma so we are looking at the effects of light on this development. Several other different studies that are ongoing, CRADA with the (unintelligible) laboratories to understand dose

response and historical database on photocarginosis. What is coming in the future? Well patamate o is a nomination that has come to the National Toxicology Program from a private physician. It is one of the most widely used sunscreen agents. The senamates and benzophononme have replaced it as the most popular sunscreen components but certainly it is still widely used as a sunscreen agent and has been nominated to be studied in the phototoxicology center. (Unintelligible) all these related structurally to methoxisorline or present in lemon lime oil. What phototoxicological properties do they have? DNDI is 27 and 28 which are in lipstick and lot of red based facial applications. They should be very photocarcinogenic if they get out of the inorganic matrix that they in lipstick. That is the first thing that is being done, that the NTP asked the question do these compounds get out of the red based lipstick and red based facial applications in to the skin. If they do we will be studying these compounds. But only if pharmacologically they are valid to do. Biomarkers we are doing work with NIHS to look at potential biomarkers of puva induced skin cancer. Very few things we know and do skin cancer. One of the is sorlan plus UVA. They only do basil and (unintelligible) that therapy but also induces melanoma and we looking at developing biomarkers for skin changes. So that is the phototoxicology in a real quick nutshell. We are trying to meet the basic science research and testing needs of the National Toxicology Program, NIHS, and Food and Drug Administration. I will stop at that.

Acosta: Well thank you both. Dr. Howard, Dr. Allaben. Do we have any questions or comments?

Kaplan: I don't want to hold up this other important meeting we are going to have, but basically one question is are we going to hear from these folks in the morning as well?

Casciano: These same individuals? You are going to hear a little bit more about what is going on in NTP from Fred Beland.

Kaplan: There are two questions. One of your readout systems is cancelled.

Howard: True.

Kaplan: Do you look at other, do you ever see any cancer in the absence of inflammation from sunlight and the next question is do you have any intermediate steps in the way?

Howard: The answer to that is yes and no. It's a long answer but I will give it real quick. The last, I hope you guys understand this TSSRC committee that meets twice a year is like having a NIH study section review twice a year of your work. We are looked at extremely thoroughly. And one of the questions that came out was where is this Facility going. This is all nice applied toxicology but what other things are we doing and one of the issues that came up is we need to really understand the role of inflammation of the whole immune system in skin cancer development in this model. And we are working on addressing that need. It is something that has not been very thoroughly described. We know that one thing immuno suppression does lead to enhanced skin cancer. One thing that we need to do is address what is happening in our model and how can we also adjust our model to best mimic the human so something we are really thinking about is inflammation and immuno suppression/enhancement. What would

happen if we immuno enhanced an animal with the same light regiment. Will we not get the skin cancers, etc?

Kaplan: And the other question is there are some interesting mouse models (unintelligible) which is expected to show excellerated reactions to phototox (unintelligible) could hear it and that would be easy to put in to the system.

Howard: True. We have discussed this several times and we were going to have a meeting this year.

Casciano: Can I help you there? Part of where we are starting this phototox facility up and part of doing that is justifying our existence so we are focusing on applied technology using systems that had been acceptable for 20 or 30 years. Of course we have questions about those systems as we learn more about them and Paul is in addition to developing the justification for the system is also expanding by looking at other possible sources to answer the questions that you are asking.

Howard: It's in the queue. It's just not here at the moment.

Acosta: Well great. Thank you very much, very interesting. I appreciate it. I guess we will reconvene tomorrow.

Schechtman: A little more housekeeping. For those of you who have not paid for dinner you are not eating tonight. Will you please give your money to Barbara at this point and time?