Your in vitro systems really give you an indication of whether there will be or won't be an interaction. It seems to me that you still have a difficulty as a continuum of magnitude of response, and where does that magnitude start to interaction with the therapeutic boundaries. So, it is a difficult are to make absolute statements because each statement has to be tempered to the drug. I am just curious as to what the current role is, and are you proposing changing that?

DR. HUANG: Yes, as was discussed earlier this morning, we would like to see more information and actually more prospectively designed studies so that we can use the information to help us answer the question. A lot of times what we are doing is, when we have the problem, we go back and look at our data to see where it comes from. Oftentimes, if the drug interactions are conducted very early on we actually don't have the information. So, initially we may come to a conclusion but later on, with more information available, we might change our conclusion for that drug interaction result, depending on how comfortable you are with the boundary. For example, if the patient has never been exposed to certain levels we may not be comfortable but later on if the information is provided which actually gives us confidence on the safety -- if you have a number of patients exposed to that level without additional adverse

events, that would be really helpful.

DR. BYRN: Roger?

DR. WILLIAMS: Well, I am very interested in the committee's discussion because I think you are struggling with things we sort of struggle with all the time. I would like to make some general comments. Again tied back to what we have talked about a lot in this committee meeting, risk assessment, risk management and risk communication, I think we are talking now about risk assessment, probably in terms of the three questions or four questions -- I guess there are only three for Louis; I added another one.

Risk management and then risk communication -- let me start with risk management, I think somehow risk management involves putting something in the labeling. But I might also remind everybody that for mibefradil the way we managed that risk was to take mibefradil out of the market because we felt there was such a pervasive risk for so many drugs that we couldn't allow it as a safety and efficacy sort of situation.

You see, there are many different things that the agency does in terms of risk management. And, we have done it now for terfenadine. It also happened for astemizole. I think as a society we are sort of saying collectively these drugs can't be labeled in such a way that safe use is allowed. So, there are some very thorny issues going on with

risk management.

Let me back up to risk assessment in terms of the three questions. I think if I speak to the substrate drugs somehow the basic question is has an interaction occurred such that I need to change my dose? I am watching Louis to see what he thinks about that question. Which is sort of like the bioavailability/bioequivalence question. Do I need to change the strength of the product to bring it back up to where I thought it should be in the first place? So, I think somehow that is a more refined view of the question of a drug-drug interaction.

Now, willing to assume gets to the issue of are we willing to say that our Baysian understanding -- I am trying to use Louis' terminology -- is such that we can rely solely on a pharmacokinetic systemic exposure measure? For the most part, we are willing to do that. I guess it is based on our collective understanding that we don't see too many PD alterations in the exposure-response relationship.

Now, the third question, of course, is the one that I always struggle with because it is the regulatory standard question. It relates to that whole issue of goal posts, equivalence criteria, confidence intervals. We have agreed I think collectively now that we do not want to use a frequentist statistic approach on this. It is an equivalence question.

Then, once you get past that branch point you get to the point is it a switching question or a population question. If it is a population question -- and I sort of feel that it is a switching question; you heard me argue that case. Then you get into the question if it is switching, do you just want to do comparison of means or do you want to take into account variances.

Now, as we talk about all this and you get to the practical reality of what we really observe, the practical reality is that in 80 percent of the cases we don't see drug-drug interactions that are of any importance. Maybe even some of the ones that we say are important and somehow intrude themselves in the labeling aren't important. For example, we might say AUC increases 30 percent. Well, if you scale because of a highly variable reference, in this case the substrate without the interacting drug, you might be willing to say to the practitioner community nothing is going on here that you should need to be clear about. So our communication becomes faulty because we haven't taken into account variability of the reference drug.

The committee is expert on all these criteria and I am sure you can think about all the permutations, but I will close by saying this, you know, a lot of times we see doubling of the systemic exposure measure and a sponsor will say, "gee, that's okay. I saw that dose range in my clinical

trials -- you know, that I could go from 10 mg to 100 mg and the study population was okay." I will argue that is okay if you are using it as a prescribing approach, but I wouldn't argue that you could have somebody stabilized on 10 mg of a drug and then the next day give them 100 mg and say that it is okay. If you do say that, believe me, I am going to widen the generic substitution windows quite a lot. That is all I wanted to say.

DR. BYRN: Any other comments from the committee on that issue?

[No response]

I think this is a little bit of a continuation of what Roger was discussing but let's see if there are any comments on the committee on this general question under the first bullet.

[No response]

Do you want to ask the question a different way? It doesn't seem that anyone has a comment or maybe we are just not experts on labeling. Arthur?

DR. ROSENBERG: I would like to join those two bullets together, and I think that if a risk assessment level can be assigned, then that can be communicated to the healthcare providers by means other than the web page or by conventional means. In California there is a law that when a prescription is dispensed the pharmacist must have a patient

consult the first time he fills that prescription for that patient. So, every time a pharmacist receives a prescription from a doctor for a drug that he has been notified by the FDA has a risk assessment of A, he has to notify the doctor. So, the doctor would be notified 12 times if he goes to 12 different pharmacies but at least he will be notified, and there is a way of mechanistically forcing that through law.

DR. LESKO: Steve, I want to ask the question a different way.

DR. BYRN: Go ahead.

DR. LESKO: When we think about current labeling and drug interactions there is a number of sort of observations. One is that all of the drug interactions in the label sometimes are clumped together without distinguishing features between those that are highly probable in terms of their occurrence or in terms of their relative risk if they did occur. So, I think this question sort of gets to can we leverage, at this point in time, information that comes out of drug development in applications in a better way to communicate the risk and probability level of an interaction?

For example, we can get quite a bit of information from in vitro studies that might be done on a substrate and inhibitors of a substrate that could sort of steer one towards which clinical studies would eventually be done in a

drug development plan. The reality is the clinical studies are relatively limited in numbers so you tend to rely on those plus some extrapolation perhaps, or some extension of the in vitro information.

So, the question really comes down to scientifically, are we in a position to utilize this information to assign risk levels to potential interactions and then convey that into a label in a way that would say high probability or high risk, medium risk, low risk, and then base that risk category on in vitro data, supplemented with what we know about in vivo studies? Then, in doing that, would that help manage drug interaction risk better in terms of the prescriber and patient? That is kind of the rephrasing.

DR. BYRN: Robert?

DR. BRANCH: Just recently I had a patient come up who is currently a depressed individual who is hypolipidemic. He has thin bones. He has a large prostate, and he has an infection. He is on 12 different drugs. And, the question is, is it reasonable to take all these drugs? Do they have a potential for interaction? I would echo the difficulty of going through that list of 12 different drugs and looking at the product labels. I am doing that exercise with him right now because he is an intelligent lawyer who is looking very hard at his own treatment.

I think the idea of creating a risk profile or a risk rating within this would be a tremendous help to pharmacists and their communication to patients, and to physicians in terms of being able to create a rank order of priorities. It is just so complicated. You then put in some demographics of gender, age and a few other variables into the individual and you have a very complicated picture.

I think that within that the only way of trying to come up with an overall recommendation to an individual is to create a relative risk to each component. I think this is a great idea.

DR. BYRN: Other comments?

DR. LESKO: Going beyond the idea, would one be comfortable assigning that risk based on in vitro data that comes out of these typical microsomal studies where we might look at, say, the KI value or the unbound concentration level and use that information to assign this risk, as opposed to relying strictly on in vivo data? So, it is sort of a question as to where is the state of the knowledge and the confidence level in these parameters in terms of using them in this kind of way. Can we be misled, or to what extent would we have to be careful about that?

DR. BRANCH: It seems to me that we are in the process of trying to validate the in vitro to in vivo information right now. If you look at p450, the correlations

appear to be standing up reasonably well. If we look at p-glycoprotein we certainly haven't got to the full level of understanding to be a good predictive model.

So, I think as the science leads you, you can have a level of confidence in prediction. But I think the difficulty is the accurate prediction of what happens in vivo from the in vitro data.

DR. DOULL: I would agree with that. You know, if your laboratory data indicates that you have the potential for a risk from some kind of an interaction, that is only half the information. You need to know the magnitude of that potential.

There are books on drug interactions, you know, millions I suppose of those kinds of interactions. But we don't teach our students about all those interactions. You have a relatively small list and you say to them, "these are the ones you really need to be concerned about." So, if you do p450 tests and come out with 10,000 potential reactions, for example, you don't really do us all a great service by telling us about that unless you also say, "these ones you really have to worry about because they're going to happen and you're going to see those, and you ought to be alert to it."

So risk communication has somehow got to -- you know, we have to be able to not only talk about the

potential risk but we also have to figure out how we are going to communicate that information.

Let me give you an example. We have a schoolhouse, out in western Kansas, where recently the exterminator went bananas and got too much chlordane into it -- it wasn't chlordane because that is bad; whatever he was using. So, the school board called and said, "you know, we have to do something about cleaning up this place." We said, "well, yeah, you have to do all these things. That will clean it up and get it down to this level." Then I went out to talk to the physicians out in that community and all the townspeople came whose kids were going to that school. They said, "how-come you're saying it's okay for our kids to be exposed to 2-3 ppm? This stuff's a carcinogen. We want a zero level out there." And I spent three hours trying to communicate to that group that, in fact, 1-2 ppm was, in fact, a safe level.

It is hard to communicate the argument that, you know, there is something less than zero exposure which will not have any risk. I don't know how we do that but I think one way is comparative risk. If you can say, yes, the risk for this interaction from these two drugs is like the risk of getting struck by lightning or an airplane going down, sometimes that helps. Not always, but sometimes that helps.

DR. LESKO: I totally agree. I think we have the

same problem with the drug risk, and that is a good point, communicating that relative risk.

DR. GOLDBERG: But I also think that forewarned is forearmed, and if this is a way of potentially having a database picked up by physicians in their clinical practice, by being alerted to the potential risk, I think it has value. That would come into the question of risk level -- known to be clinically relevant; or unknown whether it is clinically relevant but is laboratory relevant. It would be some kind of information that could be imparted and the physician would know to look for problems.

DR. BYRN: Go ahead, Shiew-Mei.

DR. HUANG: I was going to extend the question, the first one. Dr. Lesko talked about the in vitro use of I over KI but once we identify this compound as an inhibitor, for example, mibefradil and ketoconazole, in vitro they show they are inhibitors. But how do we differentiate these two from others and, therefore, the initial recommendation that they will receive through comments is that, once we identify this compound as an inhibitor based on in vitro data, then we select certain substrates, which is also clinically relevant and can show pharmacodynamic effects, and based on one standard substrate and see how this AUC is changed of the pharmacodynamics are changed for us to assign a risk level. I want to ask are we there yet? Do we have a standard

substrate? In particular 53A4, are we comfortable with one substrate? And, if we compare all agents and their effect on that agent, that will give us a comfort level of how potent this one is? I mean, mibefradil in some cases is actually more potent than ketaconazole since it has some mechanism-based inhibition. So, are we comfortable at this stage to assign that level?

I think our working group has said we will continue to take up that suggestion and work on this, but I would like to hear your comments.

DR. BYRN: I am comfortable with a working group coming up with some of these answers. I don't know about other people. Yes, Robert?

DR. BRANCH: As a point of clarification, the amount of change that mibefradil did I thought was about the same as ketaconazole. Ketaconazole hasn't been taken off the market as a dangerous drug yet. I thought that mibefradil was taken off the market because it really wasn't thought to have much of an advantage in efficacy over alternative drugs and the company voluntarily withdrew it. Was it really taken off the market or was it voluntarily withdrawn from the market?

DR. HUANG: It is voluntary withdrawal, but there was a lot of discussion between the FDA and the sponsor, especially after the congestive heart failure, showing there

is no advantage. Therefore, the risk-benefit assessment indicated that really the risk outweighs the benefit.

DR. BRANCH: But would you then say that ketaconazole should have strong warnings? Or, maybe it already does have. I haven't actually looked to see in the boxes for it.

DR. HUANG: Ketaconazole is almost standard in the labeling of any 3A4 substrate.

DR. BYRN: I have just a general question. What is the status of computer programs that healthcare professionals have access to with the respect to the level of risk, and especially the question Robert asked? Do they assess risk or do they just put out 100 interactions?

DR. HUANG: We recently looked at the first data bank and also Micromedics system, and these are two, I believe, that are used in large hospitals, and they did assign risk levels. That depends on the outcome of interaction, how serious the adverse events are. They say it is high, moderate or mild. But it doesn't give you the extent of interaction. So you wouldn't be able to get the information like mibefradil, how that would affect others.

DR. BYRN: Are those widely available or just available in the hospitals?

DR. HUANG: My understanding is that it is the most often used. It is 80, 90 percent that is being used.

DR. LESKO: Steve, both hospital and community practice has access to these databases and software programs, and they are apparently widely used. We are very interested in this because I think we are trying to link to these databases in some way -- there may be a way to update them quicker through the review of drug interaction information, and then somehow transmit that information to these databases in a more efficient way so that they are up to date so that the healthcare provider and patient can benefit from the knowledge quicker than waiting for some events to occur perhaps, or something like that.

DR. BYRN: I was even imagining where the FDA would have a computer program that they would make available. That is probably going too far.

DR. LESKO: It is a great idea. It sounds like a budget issue.

DR. BYRN: Yes, I am sure and maybe a liability issue too.

DR. DOULL: Micromedics you have to buy. If it were on the internet and anybody could get a hold of it, then it would certainly have a lot wider application. But I am sure that is a pretty expensive undertaking, to replicate the Micromedics database.

DR. BYRN: Are there any other questions?

[No response]

Thank you very much, and we will take our lunch break and reassemble at one o'clock.

[Whereupon, the proceedings were recessed, to be resumed at 1:00 p.m.]

AFTERNOON PROCEEDINGS

DR. BYRN: We are going to have a report from the nonclinical studies subcommittee, and it is going to begin with Jim MacGregor and then continue with Jack Reynolds. So, Jim, the floor is yours.

Nonclinical Studies Subcommittee Report on Research Topics

Overview

DR. MACGREGOR: Thanks, Steve.

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What I would like to do is introduce a new subcommittee. This committee has just come into existence within the past month. For those of you who heard me before the committee, at least two times I have update the committee on the activities on the Collaboration for Drug Development Improvement or CDDI, and the concept behind that initiative in trying to develop a forum for collaboration among the FDA, industry, university academia and public institutions to address issues of common interest science related to the drug development process.

The last time I did that, which was a little less than a year ago, the CDDI had actually come to a stage where the nonclinical committee, of which I was the chair at that time, had selected a number of individual projects that it thought it might move forward with which had been approved by the CDDI Structure Committee, which consisted of a

steering committee and also a management team that was overseeing that initiative.

So, at that point when I last talked to you, we were ready to move ahead and actually begin to formulate some of these collaborative activities but, unfortunately, the CDDI itself had not yet formalized itself into a working structure, and so far still has not formalized itself into a working structure. So, the question arose what is the best way forward for the nonclinical technical committee to be sure that they remained on target as far as FDA interactions with these various groups in fostering collaborative science and, at the same time, being able to move forward in some formal vehicle that provided appropriate input from the public and all of the various stakeholder groups that are involved.

It seemed logical that perhaps doing that under the auspices of this advisory committee would be the best forward. As a result of that, it was decided to form this committee and to define a structure under which this advisory committee and specifically the new subcommittee of the advisory committee could serve as a steering committee to oversee and facilitate the kind of activities that had been discussed and endorsed under the CDDI initiative.

So, what we are doing today is we are asking you, the full committee, to consider the concepts and the ideas

that we have formulated on how this could work through a subcommittee, to comment on that and, hopefully, to endorse the general idea that using an advisory subcommittee is, in fact, a good structure to try to identify priority areas of common interest science, and to actually perform something of an activist role in overseeing and facilitating the execution of that science.

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This summarizes the two main functions that we are envisioning for this subcommittee. That is, to provide advice on improved scientific approaches to nonclinical drug development drug regulation, which is a function that this committee has been serving over the past number years. But now we are introducing the second bullet, and thinking about how the committee could oversee a subcommittee that actually provided a means to foster these collaborations and to facilitate the execution of these collaborations.

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So, this subcommittee came together for the first time just barely three weeks ago, on August 31. The composition of the committee is the old CDDI nonclinical technical committee -- in just a moment I will show you the members -- with the addition of two ACPS committee members, which is a requirement of a subcommittee, who are Jack Dean and Gloria Anderson. We had an organizational meeting, not

yet an open public meeting, just to discuss the details of how this might work; what might be the specific objectives that might be undertaken by a subcommittee such as this.

These are the objectives that we formulated: To recommendation approaches and mechanisms; to improve nonclinical information for effective drug development; improve predictability of nonclinical tests for human outcomes; to improve the linkage between nonclinical and clinical studies; and then, secondly, to facilitate cooperative approaches to advancing the science and regulation of drug development.

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Now, the envisioned collaborators is something that I think will be an ongoing topic of discussion, and this is something we need to think of up front.

To go back to the history of the CDDI, the collaboration there was initially developed among two of the FDA centers, CDER and CBER; two industry organizations, PhRMA and Bio, the Pharmaceutical Research Manufacturers Association of America and the Biotech Industry organization; and academia.

At our first meeting we had a lot of discussion centered around the need to bring in the public sector and, in particular discussing the concept that perhaps NIH is an obvious collaborator that ought to be brought in that had

not been part of the original CDDI. So, the idea here is to bring together representatives from the FDA, industry, academia, and the public and public institutions to identify areas of common interest science where the FDA should be collaborating and taking collaborative approaches.

Then, we are raising this kind of novel idea, which I think is a role that advisory committees have not traditionally undertaken, to actually serve as a steering committee for activities that might arise from these recommendations.

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At this first meeting that we had on the 31st, we discussed the major focus areas that had previously been extensively discussed under the CDDI, and there was consensus among the members present that the five general focus areas that had been identified under the CDDI were, in fact, appropriate areas to consider pursuing.

So, these were basically optimizing regulatory scientific approaches; the general area of biomarkers and surrogate markers; non-invasive technologies; models for metabolic profiling and interaction; and knowledge management and communication.

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So, I have given you a little bit of the history of the CDDI and how this particular technical committee --

if you recall, there are actually five technical committees under CDDI -- the other committees, in fact, are not as far along as this committee in terms of choosing specific projects that they might want to initiate. At the meeting that we had on the 31st, as I have already said, we identified a need to define exactly what would be the objectives and the operating principles of carrying out these functions through a subcommittee. I think we have defined objectives and we are setting them out for you for your comment.

Operating principles -- I will tell you a little bit about our thinking. They are not yet fully defined, and I think Jack Reynolds may address this in a little more detail as well. Obviously, focus areas need to be defined, and then specific initial projects and mechanisms for implementing collaborative activities need to be undertaken.

So, we are envisioning that this would work by the nonclinical subcommittee, serving as a steering committee for expert groups so that the steering committee would identify areas where common interest science should be undertaken, and then setting up appropriate expert groups to actually carry out the science.

Another issue that we will come to in the future will be that of resources, and that is something else that you might want to discuss as a committee. In our initial

discussions our thought is that we initially ought to focus on common interest areas of collaboration where there would be value added by bringing together groups that are already working in an area, such that it would not be necessary to bring in outside funds. But at some stage, and certainly under the CDDI discussions, the whole concept is that it would be nice to have a way to bring in external funding to foster collaborations. Certainly, if any of these collaborations require the exchange of funds, then some appropriate mechanism would need to be set up for that. For example, CRADA or memoranda of understanding, or at the extreme, as the product quality research initiative that you are already familiar with, to set up a separate entity such as a non-profit foundation that could serve that role. That can work. It has worked, and it has come into being under the product quality research initially initiative and now formal institute which, obviously, a number of you are involved with and familiar with.

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Here are the current members: myself; Dave Essayan from CBER; Jack Reynolds from PhRMA; Joy Cavagnaro, the Bio representative; Jay Goodman from Michigan State, who is the current president of the Society of Toxicology; and then from the full committee, Jack Dean who, we were hoping would, in fact, be present as a full member of the committee

but there have been some technical delays in that. Jack did participate in the subcommittee meeting and we are hoping he will become a full member of the committee and remain the committee representative because he has been very active in this area. Gloria Anderson, who is present and also is the consumer representative and gives us an avenue to consumer representation on the committee.

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Now, in terms of the working structure, an advisory subcommittee is set up to bring external advice to FDA, and it needs to have two things: It needs to have an FDA coordinator and it needs to have a chair to organize and run the committee. I have been serving the function of chair and, from FDA's perspective, it is envisioned that I would continue as the FDA coordinator for the subcommittee, and the consensus of the nonclinical committee, when we did meet three weeks ago, was that Jack Reynolds should assume the chairmanship of the subcommittee. We also had more detailed discussions, that I think we do not want to divert into today, about how long should a chair hold the chair and should there be a vice-chair and transition, and so on. So, we need to think about operating principles and how this would all work.

But basically we did agree that this committee should serve a steering committee role and work through

expert working groups to manage and execute projects; that we should try to encompass the identified collaborators that had already expressed an interest in collaboration. The initial members have been chosen through the mechanism of allowing the organizations each to name their representatives.

So, the way we got these individual people was PhRMA recommended Jack, whom I will introduce in a moment -- I will just introduce him right now, I guess, since he will be coming up in a second. Jack is the vice president of global safety evaluation for Pfizer and he is chair of the PhRMA drug safety committee, called the DruSafe Committee. PhRMA has operated under the principle so far that the chair of their DruSafe Committee would be their representative to the collaboration.

Bio has identified Joy Cavagnaro. Jay Goodman was invited because we thought that we ought to have a channel to the professional society, the SOT that would be involved. Then the two CDER centers identified their representatives. So, that is how these individuals came to be on the committee. Then, Jack Dean is coming on the committee because he has been very active in a number of the areas of science that we are considering.

So, basically that is as far as we have gotten in terms of the general operating structure, how we would like

to function, and so on. Jack will come up now and he will talk in a little bit more detail about his personal perspective and industry perspective on the collaboration, and he will tell you just a little bit more in detail about some of the specific focus areas because we did discuss potential specific project areas. We didn't come to conclusions yet, but Jack will summarize those discussions for you.

DR. BYRN: James, would it be more politically correct to industry when you invite PhRMA to participate to also include people like GPIA?

DR. MACGREGOR: There is a question we are presenting to you for discussion because what we are doing to get started is we are bringing the preexisting technical committee from the CDDI into this committee structure. Kimberly will have to tell you what this meeting was. This was an organizational, definitional meeting. To move ahead, we ought to have the endorsement of this committee that this is a good idea, and then we will need to set down some operating principles, like who should participate; how do you go about selecting that, and so on. Those are issues that will need to be decided if everyone agrees that it is a good idea. If we don't all agree that it is a good idea, then there won't be much point in going into those details.

DR. REYNOLDS: Jim, thank you very much and,

Steve, as the chair, thank you for allowing me the opportunity to come and speak to you about this new subcommittee.

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I would like to start off with my commendation to Roger Williams and to Carl Peck and others who saw the wisdom of the CDDI activity, and I am happy that it has evolved into the advisory committee structure because I think that is a very effective way for us to conduct our business. But I would also like to acknowledge all of the work that Jim MacGregor has done for the subcommittee, and I think his homework and his diligence in preparing a lot of our initial topics for discussion. It is really going to allow us to get off to a very rapid start, and I think that is very good.

Just as a personal comment, as my role as chair, I think it is important to understand what really motivates me to do that. During my career in pharmaceutical development, which spans almost twenty years, I participated very actively in two projects where I was a benefactor of FDA and industry and academic collaborations. I was very active at Bristol Meyers at one time working with anti-AIDS drugs but then, also, with Taxol, and both of those projects were projects that could not have proceeded at the pace at which they did if there was not a very active collaboration,

especially with FDA and industry, and I think we all know today those have been very successful drugs and they have saved hundreds of thousands, if not more, lives. So, that is the kind of thing that gets me involved in this, and I see some of the activities that we are going to discuss to be of a similar kind of nature, that we can really impact both the development and regulatory components of that and harness new technologies, and I am looking forward to that challenge.

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As jim briefly stated and I will discuss just a little bit more, and part of my comments will be intended to give you some of our thought processes, some of the thinking that is going to drive our activities, one, so you can understand what we are thinking about but, two, so you can comment on that and redirect our activities or thinking if the advisory committee thinks that they need to do that.

But what we think is our major objective, as Jim highlighted, is to improve the design, the application and the utility of nonclinical studies, and we think that most of that activity would focus around enhancing candidate selection, especially within the pharmaceutical industry. I think from a toxicology and a drug safety evaluation perspective, we see this technology and our activity having a lot of benefit in the area of developing risk assessment

metrics. And, I think the most important outcome of all this activity will be to facilitate clinical development.

One of the topics that many of us see these days, and some of us more than others are aware of, are aspects around risk management. I happen to think a lot of the activities that the committee will be focusing on, in fact, will make significant contributions to our ability to manage risks better. I think our ability to quickly and very effectively define mechanistic assessments of what toxicities or adverse events are will be very beneficial, and I think we will be able, with the new technologies, to very early on, even in the discovery phase of pharmaceuticals, begin to develop surrogates of both response to disease, characterization of disease, but also develop much better ways to monitor and predict adverse events.

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So, what we intend to do as an overriding objective is to really position the science around these new technologies, the evolving technologies, as a basis for regulatory guidance. We think this will facilitate drug development. It surely should reduce drug development time and make it more effective and I think, importantly, we should be in a position that we will help to retain and build confidence that the regulators and industry can bring

safe drugs to the market that are effective, all the while reducing time and cost of drug development.

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So, one of the major ways we see our activities functioning is, in many ways, like a technical steering committee for the FDA. Jim alluded to the notion that we are trying to identify areas of collaboration, and we really do want this to be an open and broad participatory kind of activity. Obviously, we are collaborating with FDA and industry. We have academic representatives, and we will have many more. We will probably have collaborations with government or other non-profit organization and I think, importantly, we want to make sure that the public, special interest groups or others, has an opportunity to engage in our ongoing activities as well.

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Some of the ways we see that we will accomplish our activities -- one is in the meetings of the subcommittee and reports back to this committee, but I think one of the main things we will do is form working groups around the topics to be selected, but we will spend time selecting experts and opinion leaders in these areas, bringing them together to discuss the science, come to some conclusion there, all of which we hope to facilitate and focus the evolving science on these new technologies.

I think we have a broad array of potential collaborators that we want to draw from. I think we might be able to initiate collaboration directly with some of these persons but I think, importantly, we also may be able to establish CRADAs or other ways in which we can initiate this activity.

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One of the things that I am personally not clear on, and I think Jim and I have talked about this and we will need advice from this committee and from the FDA, is really how do we derive mechanisms of resource exchange between FDA and collaborators? We want to make sure that there is equity among all participants. We want to avoid any even appearances of conflict of interest and we, obviously, want to have the input of special interest or broad interest public groups as well.

What we see as the outcome of our activity or the output of our activities, obviously the report back to this committee will be very important but we can see some of our activities resulting in conferences around special topics. We can see perhaps literature publications resulting from this, and perhaps recommendations in the form of guidance documents or other public notices. We think those will be some important outcomes from this activity.

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So, I will talk now about some of the topics that we have looked at. We have kind of narrowed down the topics to three fairly broad areas. One is the screening IND. Another is an area of biomarkers, and we are just using the term biomarkers to encompass molecular biology and other broader aspects. I think we want to focus as well perhaps on novel and non-invasive technologies that could be used both preclinically but also perhaps used clinically as well.

We do need to have further discussions. It is Jim's and my hope that by the end of this year we will have narrowed our choices down and actually have selected at least three topics for discussion. But we want to have more and broader discussions to ensure that we engage in activities where we can have the broadest impact. We do want to have topics that do have broad industry and regulatory interest, and we are going to work very hard to try to do that before the end of the year.

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So, just briefly to describe the context in which I see a lot of our activities occurring, many of you know, some better than I, that the whole drug discovery and development paradigm is just really evolving, if not undergoing a revolution right before our very eyes.

A lot of what is going on in the pharmaceutical industry is being propelled by a field we all know of, the

genomics, high put-through screening and combinatorial chemistry. Through those activities, which are all technology driven, there has been a remarkable increase in the number of potentially acceptable new clinical entities that we could select for development.

I think, in addition, a lot of the diseases that especially the pharmaceutical industry is focusing on really are complicated diseases. They are really multifactorial diseases with many potential areas for intervention. All of this has caused extended development times. It has caused us to have to conduct larger clinical trials because of our inability to define precise or robust markers of some of these complicated and chronic diseases. In fact, in some cases for some of the diseases this activity has really caused us to even be pretty competitive for some of the patient populations that we need to work on to show our drugs work.

I think that we are focusing on more complex disease states. In the pharmaceutical industry the consolidation within the pharmaceutical industry I think is having maybe not such an obvious impact, but what it is really causing is that there are fewer companies who are more intensely focused on specific disease targets, and I think that really intensifies the amount of knowledge that can be generated around these disease targets, and I think a

lot of our activity will find ways to better manage and to make decisions around that burgeoning amount of information.

Also, because of this intense focus on chronic diseases that take long periods of time to study, especially since the pharmaceutical industry obviously has to make money or they are not in business, it really is almost impossible for us to tolerate iterations in drug development cycles. So, we really do feel compelled to get it right the first time, both from a cost perspective but I think, moreover, in the public's interest it really does behoove us to get good drugs to the marketplace as quickly as we possibly can irrespective or what companies have to do to make money.

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So again, I think to kind of put the perspective from industry. as I see it at least, with these burgeoning numbers of precisely targeted potential therapies, we as an industry cannot build our buildings fast enough. We can't train and hire specialists fast enough. We can't even synthesize the bulk material fast enough and expand clinical trials broadly enough to really keep up with this rapid pace of discovery, and accommodate and thoroughly investigate all the numbers of potential drug candidates that are being presented to us.

On the other hand, I think we really do need to

position ourself to take full advantage of these new technologies and how they may facilitate and improve our decision-making processes and utilize these enhancing technologies.

All of that, to me, says we just absolutely have to evolve new drug discovery and development paradigms. I think the activity of this subcommittee perhaps will help us focus on some of that.

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So, I think some of the aspects we see that may come from some of these new paradigms that we would discuss or advocate -- I think it will allow, especially us in the pharmaceutical industry, to achieve proof of concept sooner. Proof of concept to most of you probably has a different definition but, at least to us at Pfizer, the proof of concept for us is any point in which we make a business decision to rapidly accelerate our expenditure on a particular drug candidate. So, in many respects, when we talk about proof of concept it really doesn't have a medical or biological point to it; it is where we decide to rapidly increase our investment there. Anything we can do to facilitate our getting to that decision point, like applying new technologies, I think will serve all of the pharmaceutical industry very well.

Again, I mentioned that I think it is imperative

that both from the regulatory side but also from the development side we keep up with this rapidly increasing pace of drug discovery.

For many things that we need to do to help clarify both disease states for the chronic and complicated diseases that we want to study, but also because of the precise targeting of many of the drug candidates that we select, we really do need to find better ways to get this drugs into the clinics earlier so we can make better decisions around those drug candidates.

At Pfizer, and I don't know how broadly that applies but certainly this group would know, we have used the term "clinical discovery." I think for us it has a particular relevance.

But to repeat myself somewhat, I really think this activity can result in getting beneficial therapies to patients sooner and I think, more importantly -- and I think it is good that we think about that, this kind of activity can really demonstrate regulatory leadership in helping to implement commercial innovations.

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So, one of the topics that we thought we would probably focus is a screening IND. I have been involved in aspects of a screening IND for several years. Three years ago PhRMA and FDA had a workshop on essentially what was at

the time considered the screening IND. So I think that if this committee were to engage in that activity we could, in fact, capitalize on the homework and the previous work that has been done around the screening IND.

But some of our thinking there is that we really haven't been able to clarify what are the appropriate preclinical toxicity studies that would underpin the screening IND, which is intended to be a low-dose, single-dose human study. I think there need to be agreements on what, in fact, is the nature of the drug substance that would be used in these early and very limited clinical trials. It is virtually impossible for us to fully characterize and to fully work up early materials at this stage for screening INDs as we would even do for a regular IND or we would do for more extensive clinical trials.

So, I think there are a lot of things that we can do to expedite and to reduce the burden upon characterization of this early drug substance. The term I like to use is that we need to think about minimally characterized drug substance that would or could be used in these early studies.

I think also from a clinical perspective there is a need to clarify and articulate the potential values of these early clinical trials or screening INDS. I think that new technologies will really facilitate some of this early

work, and I think that it will really allow us to make better assessments of an increased number of early drug candidates.

I think in particular around the screening IND that this advisory committee, but also this subcommittee, is well positioned to make decisions around and to advise the FDA on activities to the screening IND.

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So, the steps forward for the screening IND, what we would propose to do, if this is one of the topics that we would choose, is to really define and understand what are the regulatory hurdles. I understand there are some regulatory hurdles to a screening IND. We would certainly look to the FDA to handle most of that.

We need to come to some consensus on what are the preclinical studies that would be needed to underpin a screening IND. As I said, FDA and PhRMA have had some activities around this, but we would collaborate and seek the advice of other organizations, one of which would be the Society of Toxicity. I think we also need to come to an agreement on what could be minimally characterized drug substance. I think, again, the FDA, of course, and PhRMA have had some activity on this but we would seek out scientific groups like the American Association of Pharmaceutical Science to help us with those concepts as

well.

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So, for further steps I think we really do need to have this activity culminate in the definition of what is a screening IND, to articulate clearly what are the potential values that it could bring to the facilitation of drug discovery and drug development. Again, I think this subcommittee and the full advisory committee here would do most of that.

But I think what may not be immediately obvious but what I would like to present is that a lot of the activity around a screening IND can really be propelled by and really link very closely with a lot of the biomarker activity that we would like to become involved in.

I think a very important part of what we would do as a subcommittee is to be certain that we are able to communicate the success of new drug development paradigms, and I think by being able to communicate what those successes are, that can serve as prototypes and models for others to plan and strategize around drug development and get the full benefit of the activities that we would undertake.

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Around the area of biomarkers, most of us know that throughout history there have been waves of innovation.

I think that we are right on the crest of a significant wave of innovation that entails genomics, proteomics, certainly computer hardware and instrumentation, as well as computers and information technology. I think that when one looks at that as a whole, there are tremendous opportunities for us in the pharmaceutical industry to capitalize on these new waves of innovation.

But some of the areas where we think this committee can especially capture some of those opportunities is to minimize the impact of inter-individual and interspecies differences. I think that has been a major problem for us over the years. I think that we will be able to more precisely define our disease targets as well as define our adverse effects that result from drug administration, and I think one thing that has happened in some circumstances is that by focusing on biomarkers and understanding them we can even find additional or unexpected indications as we work through the clinical trial process.

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So, I think that it is pretty intuitive that there are broad and very potentially useful applications of these new technologies in pharmaceuticals and medicine. But I think you probably know this is an incredibly expensive area of focus, both in terms of the equipment and the reagents that are required to utilize this technology, but most of

these new technologies require a pretty substantial supporting infrastructure.

Because of the expense here and because of the potential commercial applications, most of the activity with these new technologies, that I see at least, is being driven by industry. But even though it is being driven by industry and we are trained to commercialize this, there are just innumerable regulatory interfaces of this technology.

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Because there are numerous interfaces, I certainly acknowledge and I think our committee wants to keep at the forefront of our thoughts that there is going to be the need for regulatory standards and guidance around this technology. But I think because it is being driven predominantly by industry the rush to regulate this activity, in my view and many of my colleagues' view, really can have a stifling effect on our ability to explore these technologies. So, I think there is really a need to allow maximum flexibility to explore these technologies, and I think that this committee activity will put the FDA and industry in a position of partnering around this activity while this exploration goes on.

As I mentioned before, and as all of you can read in newspapers and is a focus of many public activities, we really do need to find ways to enhance risk management

around the drug discovery and development process, and i think that our ability to explore and look at better ways to enhance risk management will be a very outcome from this activity.

It will, of course, improve our cost efficiency and cost effectiveness of drug development but I think, as we all want to do, it will bring effective drugs and safer drugs to more patients and to a broader patient population than we could do without this new technology.

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I think that our committee will have an impact on our ability to explore these applications and to identify the opportunities for the application of this. I think an important role that this subcommittee could serve -- again because this technology is being drive in large part by industry there really isn't the academic check and balance that we see with a lot of technologies. I think by the time a lot of academics would write grants or get funding to conduct a lot of this, either the technology would have changed or the issues or questions would have changed. So, I think this subcommittee, in fact, could serve as a very good sounding board, if not a gatekeeper in some ways, for the application of some of these technologies.

I think it also will serve the FDA's needs well to prepare to formulate guidance documents, to derive the

appropriate and timely documents. I think most of that activity would be focused around establishing surrogates of efficacy. Certainly, I think we can help the FDA come up with new paradigms in terms of clinical trial designs and more effectively monitor adverse effects, all of which I think will lead to important improvements in our ability to manage risk of pharmaceuticals.

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So, the area of biomarkers is a very broad and rapidly moving area. For the subcommittee activities, we feel we want to focus on areas that we, predominantly as nonclinical persons, can impact. So, we will focus on biomarkers that might be used in early clinical trials. A lot of those biomarkers and activities are around proteomics and, a term we are becoming more familiar with, toxicogenomics. Most of that is involved in looking at gene expression for repair genes and other genes of damage or drug injury to cells. I think aside from proteomics and toxicogenomics, this activity will allow us to develop molecular toxicity endpoints that can be used both in preclinical studies but that can also be carried over to clinical studies.

Because these technologies are really information intense and there are a horrendous amount of data generated from these technologies, I think it is important for us to

be mindful that we need to find ways that we can integrate these data across different platforms and across different divisions and different specialties.

But I think one of the important outcomes of a lot of the biomarker activity, in fact, will be our ability to define rapid markers for toxicity and to gain rapid insights into the mechanisms of adverse effects of drugs.

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The last point I would say is that we do want to explore and to try to facilitate ways of using non-invasive new technologies. One outcome is that we want to evaluate the potential outcomes of new technology, tools for application in nonclinical and early clinical trials.

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One area that we are initially thinking about focusing on is in magnetic resonance microscopy. I think that there have been recent advances in MRI that will allow expanded applications of this technology. There have been numerous applications of this in the preclinical studies, many of which could bear on our ability to define more efficacious drugs but I think, importantly, we might be able to find safer drugs by helping to define pathologic states and measure intrinsic toxicities even with cells. An important area I think where this has some opportunities is in the area of neurotoxicity.

So, I think that is all that I have to say.

DR. BYRN: Are there questions for Jack, questions of clarification?

[No response]

Thanks very much, Jack. As far as I know, there have been no submissions of names for an open public hearing. So, we will simply ask, does any of the audience want to comment on either or both of the presentations?

[No response]

Committee Discussion

Then let's move ahead into the committee discussion. Jim, do you have a set of questions you want us to address, or would you like us just to discuss different issues? I know you listed a set of questions. Do you want to put that slide back up, or do you just want to maybe remind us what they are and then we can discuss them?

DR. MACGREGOR: Let me first make one comment that I forgot to make, which is that you should have all received in your information packet a copy of the minutes of that meeting. So, hopefully, you do all have that.

I think it is really up to you how you would like to proceed. We certainly did raise some specific questions but I am thinking that perhaps some free-ranging discussion on the general concept might be valuable. I think perhaps the principal question we are asking here is just for

comment back on this general idea that the nonclinical subcommittee can extend its advisory role which it has been serving for some time, but to extend it to actually serve as an advisory body to oversee some of these collaborative research initiatives and provide a better vehicle for providing scientific advice to the FDA on how to undertake these collaborations.

I guess the one thing that I might add is that in many of these areas that we have identified for potential collaboration there are activities going on already within the FDA and the NIH and various individual companies, particular in the areas of molecular toxicology and genomics. Just the concept of harnessing that into a collaborative undertaking could really have tremendous benefit to all parties. So, I think that would, you know, be the principal question.

Then once we get past that, we have posed some specific issues that we will need to grapple with. You know, we would welcome getting comments right now so that when we meet again we will have to grapple with the specifics of how do we select who should be involved and other issues, you know, doing that through an advisory committee. It would be useful to us to hear from you now before we meet again and begin grappling.

DR. BYRN: Okay. First, are there any general

comments that anybody wanted to make? I have some questions for Jack but I think it might be better to hold those until we have some general discussions. Any other general comments?

DR. BRANCH: I think this is a great idea but I have a comment to start with. I was thinking at the beginning part of the discussion that this was based around preclinical but, in fact, it is translational, biotech, informatics. It is a much broader base and I would urge you to get a more exciting title than "nonclinical." I think you can get something that really does reflect what this can contribute and I don't really like the title right now.

My fundamental question comes back to seeking clarification of what is the role of this committee? You said you would like the subcommittee to report to this present body. My understanding of what your historical perspective was is that the CDDI was the original concept to be able to bring the FDA, PhRMA, Biotech, academia, NIH all to the same table. That is not working fast enough. You are creating an active working group and the question is how do you make that working group effective and how does it report?

My question is how would reporting to this group actually help you in these endeavors, and by reporting to this group, does that actually limit your sphere of activity

because this group is a constituted group for the FDA? It is one of those particular stakeholders. It seems to me that, if anything, you are compromising your potential for the broader range of interactions. So, is this an appropriate reporting mechanism?

DR. MACGREGOR: I might actually add some thoughts to your comment by way of answer, and that is, I think there are a number of things that advisory committees do that we actually didn't talk about in our presentation that could serve as a very significant benefit. For example, there are place through the advisory committee structured ways of announcing meetings, holding meetings, rooms available for meetings, travel funds to bring the principal technical travelers, which helps a lot for the university representatives who need travel assistance, and also systems such as public dockets that if you want to go out with, say, a Federal Register solicitation for participants and expert groups, or whatever, there is an existing mechanism there where you can open a docket and nominations can come in, and that can all be collated. So, there are a lot of mechanistic advantages to doing it through an established advisory committee in the advisory committee system.

I think the question that you are really asking is does the full committee have the correct expertise to be the oversight body. I think that is really more, if I understand

your question, correctly. I think the idea really that we are putting forward is that the nonclinical subcommittee could try to assure, with oversight and recommendation from the full committee, that appropriate range of expertise exists there to appropriately steer the working groups.

I think that is really what we are asking, rather than having the whole thing steered out of here because it is a very heterogeneous membership, and even in our case where you would pull together people who are very focused in the nonclinical development and, as you pointed out or Jack pointed out, the really critical nonclinical, early clinical overlap phase which is an area I think where we could really have very major impact. So, it is a question of what is the most efficient structure. So, we are putting up one for discussion. We would like to hear your comments. I guess my personal feeling is that there are enough advantages there that this seems like a reasonable way to proceed. That is what we are trying to do at this meeting, get the pros and cons and recommendations.

DR. REYNOLDS: One comment I would make is that one advantage in working with this committee is that this full committee really operates in the sphere of early clinical studies, clinical pharmacology, as well as chemistry. If we look at the screening IND, and I have really been active in that or have been trying to be active

in that area over the last several years, it is really difficult to bring the nonclinical people, if you will, both discovery as well as drug safety evaluation and toxicology people to the table with the chemistry people and with the clinical pharmacology people who do the early clinical trials to try to focus on what are the cross-discipline, if you will, issues to move forward. Because once you resolve toxicology issues, for example, within drug safety evaluation you want to go forward with a rapid screening paradigm or screening IND, the next thing you come up against are the people within our company, at least in the chemistry area, who say, "well, you know, you can't do this unless you have full GMP material." And, so we spend an awful lot of resources trying to characterize this material, which is probably excessive. The same thing is true on the clinical side. A lot of clinical people don't think about the value that these kinds of things may bring to the table.

So at least from my perspective, I think this full committee and our reporting to the full committee, representing nonclinical ideas, can really bring forward a lot of these cross-discipline, if you will, areas that we run up against and bring all stakeholders in these areas to the table and come to some decisions around what we should do and what we shouldn't do in these areas.

So, I am not that familiar with the reporting

relationship of advisory committees but, certainly from my functioning with this committee, I think this is an important, if not the appropriate, reporting relationship for us because it really can facilitate bringing these activities together.

DR. BYRN: I just want to go on from what Jack was saying because I think we have some of the skills needed to advise this committee because, it seems to me, we have these three issues, this preclinical toxicology issue, the drug substance and the bio, whatever type of bio studies would be done, and we have chemists, we have toxicology people and we have clinical people on this group. So, we could but I wouldn't say we have all the experts. I mean, I like your idea of bringing additional experts.

Maybe people can tell but I am really interested in this topic. I think this issue is probably one of the most important issues we have talked about. If we can figure out a way to get drugs on the market faster, this is going to be a tremendous public health thing. The advantage of getting drugs on the market faster is there is a huge financial incentive in the pharmaceutical business. So, we have a chance -- everybody will win. The public will win and the industry will win. So, if we can figure out how to this, it would be very exciting to be part of it.

But I think we have quite a few -- back to the

original question, I think we have quite a few of the skills needed. Did you want to say something, John?

DR. DOULL: yes, I agree. It is potentially win-win. You know, there is no question that we are seeing an explosion in genomics and molecular biology and that it will have profound influences on how we do tox. and how we develop new drugs, and so on.

The idea that somehow that is going to move things along -- there will be a whole grab-bad of goodies out there, and how we can facilitate getting those things in the hands of the clinician early on is great, tremendous. Like Steve says, a tremendous idea.

However, there are some problems. I think one thing we need to do is look ahead to see how we are going to deal with those problems. One of the problems -- if you look at what is happening to genomic or genetically altered drugs and foods, for example, in Europe, and you look at the hassle that they are having getting approval of that sort of thing, I don't see why we wouldn't have the same sort of problems and we need to figure out ahead of time, you know, how we are going to avoid the trap that we are kind of in now with genetically altered things.

We need to see that obstacle and figure out a good way to get around it. It is like Food and Drug using radiation to kill E. coli. I mean, you know, it is such a

sensible idea and, yet, we seem to have a terrible time actually getting that done.

I think it is more important that we pay some attention to those problems and get an early start on finding solutions because I don't think there is going to be any shortage of new genomic advances that are going to enhance what we are doing, and we will open up a whole array of new potential drugs. But I think some of those problems are major problems and I am not sure we have a good -- the old ways we have handled them have not been good and we need a way to begin to do that.

DR. BYRN: So, maybe we should go back on this general question of is it reasonable for this committee to report -- the nonclinical studies committee to report to our committee, to the advisory committee on pharmaceutical sciences. Are there any other thoughts on that that anybody would like to raise?

DR. DOULL: Steve, I think this morning Roger was talking about, you know, risk management, risk assessment and risk communications. So, clearly, that is an area that this committee is, or should be, or will be concerned about. The problems of risk communication are not unique genomics. Those are general sort of problems, and an area that we don't have a lot of expertise on. There is nothing inherent in science that helps you a lot with risk communication.

That is kind of a new area where we need to figure out effective ways to do that.

You know, I don't know what expertise you need for that. The Academy has had some committees over there that have looked at risk communication, and they have assembled all sorts of panels to get into that. You know, you read those documents and they are saying all the right words but they have no pat answers that get you around the corners. So, that is a major problem, and I think it is a problem for all of us, for the full committee and for the subcommittee.

DR. REYNOLDS: Just to comment to John on risk communication, I certainly agree with you. I think it is a challenge for both regulators as well the industry to communicate risk to the public and others. I think that one of the real things that may come forward from this technology, and one of the best things we do when we communicate is to have something to communicate about. And, when we can generate data that is relevant data that we understand around issues of risk, I think that is one of the most powerful tools that we can develop around risk communication, having some real things to talk about, and I think this technology can help us do that.

DR. BYRN: Can I ask a question? I don't know whether this is appropriate but I can't wait any longer to ask it. Are you advising or proposing a scenario something

like this, that a minimally -- let's not argue about this just now but a minimally characterized drug substance would be tested at a very low dose under an SIND in humans, maybe with a very minimal -- let's just go on with this scenario, let's say you did an Ames test and a couple of other tox. tests, and it passed those, and then you put it in a very low level in human and measure biomarkers for both toxicology and clinical efficacy. Is that what the proposal is in a nutshell?

DR. REYNOLDS: Yes, you have capsulized it very well, with the caveat that as we discussed three years ago with this PhRMA-FDA workshop, the screening IND -- it is not our intention that a screening IND would be used to derive any issues of safety in a classic sense. That is to say we would not dose humans at a level at which we would expect any toxicity to occur but biomarkers could help us derive safety parameters from these studies.

But more importantly, and I think most of the discussion that I have participated in around the screening IND, it enhances the selection of early drug candidates, or helps you make decisions around proof of concept, or whether you are going to be able to target the right disease target that you want to in people. So, safety was not a mainstay of the screening IND.

DR. BYRN: But it could become part of it if you

did look at safety biomarkers and clinical biomarkers.

DR. REYNOLDS: That is correct.

DR. BYRN: Then, at that point, just to go on with the scenario, let's say that the drug does the same things in humans at the low dose that it did in tests, whatever -- the genomic or the high put-through tests, and it didn't show any alarming markers for toxicology, at that point it would be resynthesized, or larger quantity, well characterized, and I guess there might be innovations in this area too, but then regular toxicology, if I can use that term, and regular clinical trials would be done. Is that the whole scenario?

DR. REYNOLDS: That is almost exactly right. As I understand it, one of the regulatory impediments to the screening IND is the notion that once a sponsor opens an IND there is no mechanism for closing a screening IND and reopening a full or a real IND.

But it was the consensus of the workshop that a screening IND was not a way to jump-start real clinical development, if you will. It was to facilitate decision-making around new drug candidates, in the Pfizer context at least, to allow us to come to proof of concept or come to decision-making around particular drug candidates and to invest in them.

I would just make one comment. I think that when

we had the workshop with FDA a couple of years ago what was not obvious at the time is that most drug companies, international drug companies, do the screening IND kind of activity overseas. I think that was one of the drivers, at least in my opinion, that caused the FDA to want to try to understand this early clinical development paradigm. For example, at Pfizer we do the preponderance of early work in Europe. Then, once we establish some of these early indicators that there are drugs that we want to develop, then we do bring them to the U.S. of course.

I think many of you in the clinical pharmacology arena know that we don't have as many clinical pharmacology centers in the U.S. as we used to because, simply, we haven't found ways to facilitate early clinical development. So, there is that somewhat self-serving need I guess but I think, more importantly, it really does allow us to make better decisions about our drugs earlier if we could get something like that to work.

DR. BYRN: Roger?

DR. WILLIAMS: I probably have various comments but I guess, first of all, I want to thank Jim and Jack for very lucid presentations.

I think one of the values of this is just to help understand what we are all talking about. I have heard many different kinds of ideas about just what a screening IND is.

Some people talk about cassette dosing. Some people talk about, you know, you can tie a non-commercial IND onto a commercial IND. So, I just think clarifying what we are talking about and what we need will be very valuable.

DR. BYRN: Just one more question, Jack. So, can low dose be done overseas right now?

DR. REYNOLDS: Yes, it can.

DR. BYRN: And it is?

DR. REYNOLDS: It is done, yes.

DR. BYRN: Would there be an advantage to bring it back to the U.S.?

DR. REYNOLDS: Well, I think in some respects a lot of this activity depends on a lot of the academic work that goes on. I think there is competition for patients in some of these situations, and to just have the flexibility to operate in major regulated countries of the world -- Europe and U.S. -- on an equal basis is helpful.

DR. BYRN: Are you representing PhRMA?

DR. REYNOLDS: Yes.

DR. BYRN: So, PhRMA's position would be that it would be advantageous to be able to do this kind of study in the U.S.?

DR. REYNOLDS: Yes, very much so. Yes. Again, this, in my mind -- and I think I probably speak for the consensus of PhRMA people, this is not necessarily

commercially driven. I mean, there just are a lot of clinical centers in the U.S. There is a very large number of patients in the U.S. and there is a need for this. So, it is not necessarily commercially driven for us. It just makes a lot of sense, and we ought to be able to maximize our flexibility to do this kind of work.

DR. BYRN: Judy?

DR. BOEHLERT: I would just add for the international companies it probably doesn't matter very much whether they do it in the U.S. or Europe, but for the domestic companies it would probably make it a whole lot easier if they didn't have to place those studies overseas, if they could place them in the U.S. market. You know, it is a real issue for industry. You know, I worked in drug development for many years and screening INDs have been talked about for a long time without clear direction on how to go and what to do. So, I support the concept very much and I find it also a very exciting idea to pursue.

DR. BYRN: Just one more question about is this the right committee. So, the way this would work is the nonclinical study subcommittee would do some studies and determine that a screening IND is a worthwhile idea. You would bring that back to this committee as a concept for discussion, just like the site specific stability committee could have brought something here? What is the scenario, the

logistics scenario?

DR. MACGREGOR: I think in our early discussions with Kimberly, and Kimberly might want to jump in with the technicalities here -- it is our understanding that a subcommittee can actually function to move ahead with these projects and periodically come back with the broad story to the full committee to make sure we are on the right track. So, I think our current vision is that the subcommittee could, in fact, function to bring together appropriate experts to move these ahead, and we would be the close trackers and then periodically the plan, where we are going and the choices would come before this committee for oversight.

DR. BYRN: We would be like the board of directors or the overseers. Then, the agency of this move forward working group would be formed on a SINB that would be just agency people because that is the requirement of a working group. Then, in parallel with this external group, they would work on the same issues. Ultimately a guidance would come out on a SINB?

DR. REYNOLDS: That is exactly how I would see the outcome to be. This activity, either in parallel with FDA, and I understand there might be some statutory reason why we can't work in parallel but at least, whether sequentially or in parallel, it would result in a guidance document to

industry on a screening IND that would define what it is; its potential utility and what the outcome of a screening IND would be.

DR. BYRN: Robert?

DR. BRANCH: Is there any way that this committee can help in terms of endorsement so that, say, the genomics idea is enhanced with NIH, in terms of looking for extramural support for this work? You have lots of ideas and you don't have any money to put behind it. So, the CDDI, as I initially heard, was a way to try and formulate a resource pool, and that hasn't come through. But is there any way that if this committee is involved we can endorse a platform which says it would be good for ideas that are formulated by your group to get some sort of recognition from NIH, from PhRMA, from Bio to be able to support the activities?

DR. REYNOLDS: I think probably the best source of support is just having a forum in which we can bring some of these things to the floor and get buy-in from opinion leaders and senior people in that, and then help us, if you will, bring experts together and formulate opinions and consensus documents around what some of these activities are. So, I think that is probably the most important thing that this committee could do for us. I am sure there are others, and Jim has thought a lot more about it than I have.

DR. MACGREGOR: I would certainly endorse that

idea. I think we already heard this morning from Greg Downing that there are a lot of things going on in this biomarker area, and it is true that various industry groups and the NIH, FDA, ourselves, we are all working in the area. To take that example initially, very much could be achieved just by providing the forum that enables these various groups to coordinate what they are doing, and to be sure that FDA in particular, from our point of view, is adequately plugged into that so that we are an integral part of the development of these new technologies.

DR. BYRN: So, it seems like there seems to be general consensus. I am not sure, but is there general consensus that we would support the idea that this committee report to our committee?

[Several participants nod in agreement]

So, I would say, on my part, that there is enthusiastic -- it is a pretty exciting idea. You had some other questions, Jim, that you wanted us to address? Why don't we just try and go through those?

DR. MACGREGOR: Certainly we are going to need to go back and think through some basic operating principles, and address the kinds of issues that Dr. Goldberg brought up as far as participants and what kind of mechanism do we use to be sure that everyone has access to what we are doing, and can provide ideas, and be brought in, in an appropriate

manner.

Certainly a large part of the idea of choosing the advisory committee format is that I think that choice in itself goes a long way to assure that there is open public access, that the public is involved and that we don't leave any major party out because that is the function of the advisory committee process, to make sure that all those things happen.

Having said that, I guess one of our next jobs as a subcommittee is going to be to go away and think about and define how we are actually going to proceed. You have already seen some of our ideas by who has presently been invited to the organizational meeting and is participating.

So, I guess the next question would be are there issues that this committee sees that we need to take into account in defining these operating principles?

Maybe we can start with general issues and then maybe Jim could tell us how he envisions our work and we could go back in a little more detail. So, are there general operating principles that we want to discuss? The only one I would have is that it might be wise to have this on our advisory committee agenda for the next few times with an open hearing section. It may not even need to be long, but it would then give an opportunity for anybody that we had not included for one reason or another, they would have this

fail-safe mechanism to come and, if you will, complain to us or make their point to us. That way, I think we can avoid any appearance of disenfranchising people.

DR. REYNOLDS: That sounds like a good idea to me. Kimberly, you might want to say something about the process because I haven't been through this yet with the subcommittee. So, this is new to me but my understanding is that our subcommittee meetings also need to have public announcements. So, they will all be announced publicly and there will be the opportunity for public to attend those subcommittee meetings as well.

DR. BYRN: Are there any other general comments?

[No response]

DR. MACGREGOR: Kimberly, why don't you tell us how a subcommittee works, and then Jim can tell us how he plans to do it?

MS. TOPPER: Basically, a subcommittee functions exactly like this regular advisory committee, except that they have the responsibility of reporting back to their parent advisory committee. They are required to report back at least once a year, but they function exactly like an advisory committee.

DR. BYRN: So, they could call their own meetings, select their own members?

MS. TOPPER: Yes, they can. At the time that a

subcommittee meets, we do notify all of our parent committees that the meeting is taking place, but at no time are you all required to be there unless you are one of the two members that are required, and basically they only get to choose one member. One member is automatically assigned, and that is our consumer rep. because our subcommittees do have consumer representation on them.

DR. BYRN: And, does the notice go up on the net and so on?

MS. TOPPER: It is announced just like this. It goes up on the net. It is up on the 800 line. Actually, everything is listed under the parent committee. So it will be Advisory Committee for Pharmaceutical Science, Nonclinical Subcommittee, or whatever the new name happens to be.

DR. BYRN: Jim, how would you proceed then based on that?

DR. MACGREGOR: I think the plan that we are proposing is that we would hold the first official public meeting as soon as we can get it scheduled and announced, and that we would have a full-day meeting in which we would try to work through and lay down our operating principles. We would also bring in some experts in the focus areas that we have identified to try to define specific activities that we would want to move forward with.

Then our vision I think is that the outcome of that is, once we have selected specific activities, we would bring together expert working groups that would actually carry those out. That would be achieved by operating principles that we would lay down, but would probably include public announcement in the Federal Register for nominations, and probably would include specific solicitation by the subcommittee of recommendations from appropriate professional societies. For example, in nonclinical safety biomarkers we would go to the Society of Toxicology and ask them to recommendation appropriate technical experts involved in the field.

Then depending on how we would set up the representation by continuing principle collaborators who would be the members of the committee, for example, PhRMA and Bio, we would ask those organizations also to submit nominations. Then, it is my understanding that the subcommittee is then empowered to select from among these nominations the actual members.

DR. BYRN: So, is there any committee input into that?

DR. MACGREGOR: If I just compare it to PQRI, PQRI has the main committee and then technical committees -- well, it really has a steering committee, the technical committees and then the working groups. You are going to

have a flatter organization than that. You are going to have the main committee and working groups. Okay?

DR. BYRN: Another question, will you need to have a way to get funds to do certain projects? You know, PQRI has dealt with this by setting up a non-profit organization.

DR. MACGREGOR: As I alluded to that in my introduction, it is something we need to come to grips with when we identify projects that need funds. This is all to be decided so I am giving you my personal, off the top of my head feeling. But I would think that we might first try to identify a few things that we think we could accomplish by identifying interested parties that could come to the table and truly collaborate so we wouldn't really need to raise funds. So, we could identify collaborators that have resources.

Then as we move along we would discuss what would be the most appropriate mechanism. Would it be a foundation? And, it may depend. In some cases CRADAs might be the right vehicle. If a lot of enthusiasm for this general approach were to arise, there might be a general foundation of some sort. There has even been discussion in the FDA science board of the idea of having an FDA science foundation where funds could come into the FDA for various activities. So, it could take various forms, but my guess would be that we would begin with things we could do right away with groups

that have resources. We would try to build it and when it got big enough and we had to exchange, we would look for the appropriate vehicles, and at that point think about whether a foundation would be appropriate or whether CRADAs would suffice, or some other mechanism.

DR. BYRN: Any input on the committee on any of these organizational matters? Any more input?

[No response]

Do you have any additional questions? Your next question?

DR. MACGREGOR: I guess the other obvious question is comment on the focus areas that we have identified. So, we have basically identified three that we thought we would focus on initially.

Let me just back up. We identified five general areas that the subcommittee had already endorsed, and we thought that from among those five, three specific areas to pursue first might be -- and this has not yet been fully agreed to by the subcommittee but that will be the topic of the next meeting, but the three that are on the table for discussion are the screening IND, the general area of molecular biomarkers of safety, with focus on the safety rather than the efficacy side initially, and then among the non-invasive technology area high resolution magnetic imaging as a technology that we feel might hold some promise

for allowing biomarkers to be better measured in the human, as well as in animal models, and also where the technology has come to a point where it might be applicable to both nonclinical animal studies and the human to provide what I like to call the bridge between the nonclinical and the clinical studies, and a way to get a handle on the principal endpoint that we, in fact, use in the nonclinical studies, which is tissue pathology, because magnetic imaging has now come to a point where it is beginning to be feasible to look at tissue pathology in live animals. If we can do that, we can make the same measurement in human and animals, which we do not do the way we now do nonclinical toxicology.

DR. BYRN: We are now being asked to comment on these three areas, the SIND, biomarkers for safety studies, and MRI microscopy for tissue pathology. This is maybe a slight change from what Jim said but I think it is general. Those are the three areas. Would people like to comment on those or suggest any other areas?

DR. BRANCH: I would like to endorse those areas. I just wonder if you are taking imaging whether you should broaden it out a little bit because I think that PET has really some very attractive opportunities, but it has some technological barriers which, in some cases, are just the logistics of making the isotopes for the drugs. If resources can be targeted for that, that would really allow that

technology to take off.

DR. REYNOLDS: So perhaps you might be one of our first experts that we tap into to help us focus our thoughts on that.

DR. MACGREGOR: PET is something that the previous technical committee had discussed and, in a way, may have been, say, a close second to magnetic imaging as a first choice of something to do. In fact, we are looking into that technology in our own laboratories, and there is actually an active industry group, the Society for Nuclear Imaging and Drug Development, which is an industry consortium of people that focused on imaging technology in general but with heavy emphasis on PET. So, there are some existing organizations you could tie into, and I think it is a very good suggestion for something we should think about because it would be easy to tie into and we, at FDA, are looking into that area already as well.

DR. BYRN: A suggestion I would have on the SIND, obviously, I am really interested in this concept of minimally characterized drug substances, which I think can be worked out in committee, but also there may need to be some, and I don't think this is a show-stopping issue, consideration of formulations -- what type of formulations are used? Are they liquid formulations? Injectables? Probably there needs to be a little bit of attention on that

in that committee.

DR. REYNOLDS: As you well know, the formulations are driven by the physical chemical properties of the molecule but, yes, clearly that is a consideration because the more complicated the formulation, obviously the more drug substance it takes, the longer it takes to come up with that. Absolutely.

DR. BYRN: So, it sounds like there is an endorsement of these three topics, with a couple of additions to those. Are there any other topics that the committee is aware of? Yes, Robert?

DR. BRANCH: Sorry to keep coming back. Clearly, CBER and CDER have joint interests in this whole area because a lot of the genomics is being driven through biological product. It sounds as though what you are thinking and generating would be useful for both aspects. Is there any discussion about that particular integration?

DR. REYNOLDS: Well, clearly we have good representation from CBER in David Essayan at the onset, but I think we have always viewed this activity, in the months that I have been associated with it, to encompass CBER and CDER as well as maybe other companies or interest groups that deal with drugs.

DR. MACGREGOR: It is moving back to that issue of representation I guess, and the logic of the representation

is pretty obvious, that PhRMA and Bio represent the two trade organizations that deal with the kind of scientific research that goes into pioneer development. So that is why they were chosen, and CBER and CDER are the two centers that are involved in therapeutic development. So, that is basically our rationale for the initial composition. So, I guess I could kick that back to the committee for your thoughts. Is that the way we should go, or are there other organizations that we should consider having involved at this stage?

DR. BRANCH: In terms of the regulatory input, you are coming back to this group but I presume that is an equivalent group for CBER. Would there be joint reporting? The deliberations could be as relevant for them as they are for this group here.

The other question I had was in terms of your areas of selection. It sounded as though you had actually included informatics. That sort of raises up a whole another array of questions. Is that intentionally going to be part of your purview as well, or is that going to be a separate issue?

DR. REYNOLDS: Maybe I will respond first since I made the comment. To me, it wasn't so much that it would be part of these activities, I think we certainly have to be mindful of dealing with this information. The pharmaceutical

companies obviously have most of the resources we need in place to deal with informatics, but I think even from a regulatory side, they are probably less prepared to deal with this information than the industry is, and I think we need to be mindful of that. There would be significant lead time for the FDA and others to build this infrastructure to handle this information. So, it is just something I think we need to be mindful of when we are doing this.

But it certainly wasn't my intention, and Jim may think differently, but it certainly wasn't my intention that we would deal specifically with informatics, other than knowing it is a very critical part for this area.

DR. BYRN: Do you want us to endorse this list of members for the nonclinical studies subcommittee? Would that be helpful?

DR. MACGREGOR: I think that would be helpful.

DR. BYRN: I will turn to the second page of the handout. We have a list of members. I don't know whether we need to take a vote or just try to make sure that we think that this is an appropriate and broad enough representation for this nonclinical study subcommittee.

DR. DOULL: Yes, you mentioned NIH and, clearly, I think that is an option you ought to consider, and there are some other options too. I am not sure we should buy into a rigid list. I think we need to say that you need

representation from the stakeholders, and that you appear to be headed in that direction and should be encouraged to do so. That may mean you may add additional groups, and so on, if necessary.

DR. REYNOLDS: Yes, John, we certainly saw the NIH to be one of the major and probably one of the initial collaborators, and you will see that reflected in the minutes. It was just a matter of timing when we would partner with them. But you are exactly right, and I think we do reflect the committee's mind set that NIH is a very important collaborator for us, and we will get them involved sooner than later I am sure.

DR. BYRN: So, you could report back to us at one of your reports whether you decide to expand. But other than NIH, are there others that you think ought to be contacted right away?

DR. DOULL: Well, I was thinking about the European Society of Toxicology, but I don't know. But I think as we think about it other ideas may come along that you might like to think about.

DR. BYRN: Are there any other suggestions from anybody else on the committee? Can we just take it that this membership is endorsed with these additional comments? Is that enough endorsement, Roger, for this committee?

DR. WILLIAMS: Sure.

Jim, next question or any other questions? We are getting close; I am just making sure. This is one of the advantages of Friday afternoon. You can get a lot of work done in a very short period of time --

[Laughter]

-- and there is generally a movement towards consensus at this time also.

DR. WILLIAMS: I will be extremely brief. Again, thanks to the committee for the discussion and I will say some more general words in a minute about that.

I always want to focus this committee on the science and technical issues because policies and procedures I think are not within their mandate. Is that right, Kimberly? So, I am glad to hear everything the committee said. For example, when you endorse the membership, you are endorsing them in terms of their science and technical skills. So, that is a very powerful endorsement coming from you as experts.

We could talk a long time about why we are doing this, but there is a motivation here which is that it makes it appropriate. If the agency meets with people, you know, behind closed doors -- and I think it is more than ten or something like that -- we start to violate the Federal Advisory Committee Act. So, what Jim has done here with Jack very creatively is figure out a mechanism to allow this to

happen. I think it is a wonderful collaborative idea.

I will just tell you this, that when I came to the agency in nine years ago there was, and sometimes there continues to be, a very strong feeling in the agency that there is "us" and there is "them" and you have to maintain that distance. And, I can tell you some people feel that that is the appropriate thing to do.

There was another view when I came into the agency, people were being accused of collaborating too much and taking bribes, which is another way of collaboration --

[Laughter]

-- that we certainly don't want to encourage. So, I think we are striking an excellent balance here, and I can't imagine turning back from this because we have worked so hard to do it appropriately, and I think the payoffs have been so remarkable, not just in this environment but in ICH and PQRI and Site Specific Stability. I mean, it is really a good way to work, and I think we have to give it a lot of enthusiasm, support and endorsement.

DR. REYNOLDS: If I may make just one comment to echo what Roger had said, I think working for an international pharmaceutical company for a large number of years, and also seeing even in the public press comments of pharmaceutical industry in Europe especially, one of the real advantages that we have had in the U.S., and I have had

as a drug development specialist, is in fact this open and very constructive dialogue with the regulatory agency. I think it has benefited all of us, and has really benefited the U.S. base and also the entire pharmaceutical industry with the kind of things that Roger has mentioned. I too see this subcommittee activity to embrace that, and I think it should be very productive.

DR. BYRN: We are now almost concluded, unless there are any other comments that anyone would like to make. This concludes our discussion. We wish you luck and we will look forward to hearing from you in this very exciting endeavor.

There has been a request just to go on and conclude. I think that is what Roger is really to do. So we will move to the 3:30 entry, which is entitled committee function and awards.

Committee Function and Wards

DR. WILLIAMS: Thank you, Steve. I could probably stand up here and talk a long time but I will try to be brief.

First of all, I want to thank all the committee. Thanks to advisors and consultants, you do a terrific job and, from the heart, I really mean it.

I am about to thank Antiretroviral because he is departing the committee and I will have some special thanks

there, but before we get to that I want to just speak generally about the advisory committee process in the FDA, and I think it is one of our glories.

I am reminded of something my parents sometimes say to me. They are both ninety. I am very lucky to have ninety-year old parents. Every now and then they fuss about age and I say, "well, consider the alternative." And, I feel that way sometimes about we do here. You know, advisory committees are burdensome and you all do so much work to come here and spend two days with us and we deeply appreciate it. The alternative of not doing something like this, to me, is so awful. I just really love the advisory committee process and I have enjoyed every meeting we have had over the last nine years.

We always speak to our constituencies, but the real constituency out there are 275 million Americans. So, you guys are helping them. I think because so much of what we do becomes globalized, you are helping the global community as well which is -- what? -- about six billion. So, don't think the fact that you don't have a lot of constituencies sitting in here this afternoon on a beautiful day -- you really have a lot of people riding on your shoulders.

With that in mind, I will say we always like to celebrate people who are completing their term of service on

the advisory committee. And, Kimberly, what is that term of service? Three years? Four. Basically it is a four-year term -- a lot of work. We try to meet once or twice a year so you can see there are hundreds and hundreds of hours that people to commit to be an advisory committee member.

We are losing three now. We are losing our chair, Bob Taylor, who is here, in Washington, a very distinguished clinical pharmacologist and pharmacologist I believe down in Howard University. We are also losing Jim Stewart, who is an expert analytical chemist at the University of Georgia, in Athens. And, Arthur, I am very said to say we are losing you as well but we have been delighted to have you here. You have been a very thoughtful, articulate commentor on what we do. Of course, we have a plaque -- I won't say suitable for framing because it already has sort of a frame, and a very nice congratulatory letter of thanks from our Commissioner, Dr. Jane Henney.

So, congratulations and thank you very much for helping us.

[Applause]

With that, Steve, I will turn it back to you, and thank you especially for being a chairman on short notice.

DR. GOLDBERG: I would like to thank Roger and the FDA staff for affording me the privilege of serving on this committee. It is not often that somebody is asked to serve

and then feels served. I think that the interaction of the staff here and the advisory committee brings a wide diversity and it has been very enlightening to me, and I thank you all for that enlightenment.

DR. BYRN: Thanks very much, Arthur, and I know on behalf of the committee we all wish you well, and I am sure we will see you at several meetings. Roger?

DR. WILLIAMS: I also want to thank Norm Pound. Norm has been a very patient witness observer to our events. Norm is from the Therapeutic Products Programme, in Canada, and whenever we can we would like to reach out to our regulatory counterparts. Norm has sat here, as I said, very patiently listening to us, and we are delighted you came, Norm. So, thanks very much.

DR. POUND: Thank you for having me.

DR. BYRN: Are there any other comments? If not, I think we can assume that there is a unanimous motion to adjourn. Is that correct? And, we wish everybody safe travel and we will see you at the next meeting.

[Whereupon, at 2:47 p.m. the proceedings were adjourned.]

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CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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