adequate information on the pharmacology and the toxicology that served as a basis, what the sponsor used to say that the study was reasonable and safe to conduct.

It says you have a toxicology of appropriate duration and scope to support the planned clinical trial and it says you should have pharmacology data and drug-disposition information if known. That is very general guidance in terms of the regulatory standard.

[Slide.]

About 1994, it was brought to the attention of the senior management within FDA, within CDER and CBER, that initial phase I studies in the United States were not being conducted because of a perceived additional impediment in the U.S. to the datasets that were needed and the way that the information should be packaged and presented.

To address this, the agency actually clarified the intent of the IND regulations. It talked about things, like, for example, that phase I protocols are really investigational outlines and not detailed protocols with every possible endpoint included but only detailed to the point that they addressed the safety elements, that the necessary chemistry information is relatively limited, and I think that Eric will maybe talk about this in a moment, and that pharmacology and distribution data should be summarized, so we are not talking about extensive

information there, and the absence of this was not necessarily cause for a clinical hold, and that the non-clinical safety database really be an integrated toxicology summary with full tabulations of the datasets that were used to draw those summaries on the protocol and, importantly, non-QA's reports would be considered acceptable pending QA audit within 120 days.

[Slide.]

The reason for this is it was stated that it took--just the non-QA's portion alone, would save industry one to four months of time in terms of clinical development, early development, that they could get this human data very quickly by having this non-QA'd report be available.

The fact that we were only asking for summary information, not for complete final reports, would be--not summary information; I'm sorry. I take that back--summaries of the toxicology, not complete final reports of the toxicology. We do require the line listings. I need to be clear about that. This, together, would actually allow industry to enter into those human studies early on and actually get clinical data to feed back into the development program.

I have talked to some industry representatives about this as part of one of our initiatives to try to understand what some of the issues are that industry has

with the regulatory agency in terms of communication. Although it is only an informal survey, most, in fact, think that this allowing non-QA'd reports is useful, although I have to say that, four years after the fact, some companies have said, "Well, we haven't done it yet but we are about to begin doing it."

So it has taken four years from this change to actually be put into the standard processes of some companies. But there are some questions that one could ask about this. First of all, has it, in fact, fostered testing, early testing, in the U.S. and has it been useful to the pharmaceutical companies in a more formal way.

I guess one would still have to ask, to the extent that it is answerable, what are the issues that, in fact, limit early testing in the United States, what are some of the barriers and, in fact, what are the deciding factors that could be addressed. I think that this is a data question, not a toxicology study-design question. But I think it is an important question if we are going to understand how to facilitate drug development.

[Slide.]

So, to conclude, I would just like to say that there are clearly areas of non-clinical and clinical research that could inform the agency and industry on guidance and other types of decisions, that it can be the

types we talked about today earlier, the very specific methods. They could be talking about general changes in toxicology study design, trying to collect data to support those.

In either case, both the identification, the focus areas, the approaches that one needs to take and the types of research that will answer these questions are really going to necessitate a broad cooperative effort. I think this is a starting point for that effort.

Thank you.

DR. DOULL: I think we can go ahead and finish up the presentations if that is agreeable.

Dr. Sheinin?

Quality Issues

DR. SHEININ: Good afternoon.

[Slide.]

As Joe indicated, what I am going to talk about today will focus on CMC or chemistry, manufacturing and controls issues. I call it CMC issues for screening INDs. It is really immaterial from the chemistry standpoint whether we consider this a screening IND, early introduction into man, phase I or however we want to term it.

It is the information that would be needed in the CMC section of the application before a drug is introduced into man for the first time. I am going to focus almost

entirely on that phase I guidance that Joe mentioned because it very clearly spells out what type of information is needed for chemistry.

Again, as Joe showed, there have been very few screening INDs over the years, but if you do want to do a screening IND and however many compounds you are going to look at, we would need the same kind of information for each one because each one is judged on its own merits; is it safe to give this product to humans. That is the whole driving force of everything that the chemists are looking for.

[Slide.]

Again, this is the title of the guidance. It was issued in November of 1995 and you had that from what Joe was speaking of.

[Slide.]

It says in the introduction to this guidance that any drug that has not been authorized for marketing, has not been approved in the U.S. for marketing as a prescription or over-the-counter, if it requires an NDA, if it is going to be introduced into man, it requires an IND or an investigational new drug application.

It also talks about in the regulations there are certain exemptions, certain criteria, certain types of studies that do not need an IND. But we are going to focus on ones that do require an IND and these would be products

that somebody would eventually be interested in marketing.

[Slide.]

From the chemistry standpoint, the amount of information that is needed, and everything that we are looking at focusses on the identity, strength, quality, purity and potency of that drug and how do those characteristics of the drug, from the CMC perspective, impact or reflect on the safety and effectiveness of that product.

The amount of data that we would need, or that an applicant or sponsor would want to put into their application, is going to vary based on the phase, so these early studies, generally, are done in phase I but as the drug-development process is streamlined, the clear distinction that we used to have between phase I, phase II and phase III is kind of disappearing and, many times, they are running together.

But, still, we are talking about the early introduction into man so that the amount of data that is going to be needed in that type of study is going to be different than what type of information would be needed in the chemistry section if you are going into your well-controlled and adequate trials that are going to form the basis for whether or not that product is safe and effectiveness and allows the sponsor to determine if they

want to go on to an NDA.

So the chemistry information is evolving while the IND is going on, as you are going through the various phases and the various types of trials that are being performed in man. Everything should be finalized at some point during what used to be considered phase III but we will call it during these "pivotal trials," although we are not really talking about pivotal trials anymore.

It is also going to depend on the dosage form. A tablet dosage form is going to require different type of information and generally less information to support the safety aspects than a sterile injectable because there are different considerations, different concerns, that come up when you are injecting a product into a person as opposed to taking it orally.

It is also going to depend on how much information is available. Sometimes, sponsors may have a lot of information available from the CMC perspective and sometimes they may not. At least one interpretation of our regulations implies that if you have information available, it should be submitted to the agency for evaluation.

The emphasis on everything the chemist and the microbiologist are looking at focusses on the safety aspect; are there any reasons that are apparent in the data that we are looking at that would make us come to the conclusion

that it is not safe at this point to go forward with the trial.

[Slide.]

The guidance actually spells out several areas or points that could lead to a recommendation of a clinical hold. I don't know if you have talked about what a clinical hold is. The agency had 30 days from the time you submit an IND to make a determination whether or not it is safe to go forward with that study.

If you don't hear from us within 30 days, then you assume it is safe to go forward. If you will hear from us, what it is called is, we would tell you that we are putting this IND on clinical hold which means you can't introduce that product into man until you clear up the problems that we have uncovered.

So these are the areas that might lead us to make a determination that it is not safe to go forward. If the product is made with components that are not given to us, if we have no idea what is in this product or if the products are impure and, based on consultation with the toxicologist, we have a concern about a possible toxicity of these materials, of what make them impure.

If there is a product that has components, and generally, this would be the active ingredient but it could be the inactive components as well, if their chemical

structures are not known to us. So a sponsor needs to have at least some basic chemistry information about what is in this product that is going to be given to man or, if based on the chemical structure and, again, consultation with the toxicologist, is this a structure that is likely to have a toxic effect on man. That might be a reason to say don't go forward with that study at this point in time.

If there is evidence that the product is not going to be chemically stable throughout the intended study; if it is a one-month study, you want to have some assurance that the product is stable for at least a month. If it is a longer-term study, if it is a six-month study in man, we want to have some assurance that the product will be stable in man for six months.

Some of this information can be generated during the study so it is not always necessary, if it is--I wouldn't call six months a long-term study but if it is, say, a six-month study and a sponsor comes in with one month worth of data, that material would stay on stability and would be studied while that clinical trial is going on so that the data could be generated concurrently with the experiment. But we do need to have some assurance that it is chemically stable.

If there is data that shows whether it is unstable or whether there are impurities that are introduced during

the synthesis or the manufacturer of that product and we have some knowledge about the structure of those impurities and it might be indicative that it could be a potential health hazard. Again, this would be in consultation with the toxicologist. That would be a reason to recommend a clinical hold.

Or if there is not enough information for us to assess whether or not there might be a problem from the safety aspect. And, for biotech-type products, if there is a poorly characterized master cell bank or working cell bank.

One area that the guidance does not mention which could come into play is, again, for sterile products. If we have some concern about the sterility assurance of that material and how it is being made, it might be a reason for us to recommend not going forward with that study until the problem is cleared up.

[Slide.]

The other thing it talks about that, I think, is critical to what Joe was just speaking of; the sponsor should have some data that relate the drug product that is proposed for use in these trials to the material that was studied in animals.

If it is the same material, that's great. Generally, there may be some differences and those

differences have to be explained and there needs to be something that relates that material.

[Slide.]

As far as the specific type of information that would be needed, it talks about the IND in general and the drug substance or the active ingredient and then the drug product. So, are there any signals in the information that is available to us of potential human risk? If there is any information like this, the sponsor should include that information in the IND and discuss it and also propose what they are going to do to monitor those risks, to try and minimize those risks, or, if they have some reason to believe that even through the are signals of potential human risk, it is really not pertinent to the study that they are going to do. They can discuss that in the IND as well.

One of the things that Joe talked about was that pre-IND meeting where you have an opportunity to come in and discuss with us what your plans are for these early studies. This type of information, if it is known at that time, could be discussed with the review team and it would be a way of possibly avoiding problems down the road when the IND does come in, again, any differences between the proposed clinical material and the material that was used in the animal trials.

From the safety aspect, do the differences in any

way affect the potential safety of going forward with that study. So I come back again and again and again to the safety aspects.

If any of you have had experience in the past with submitting INDs to us, even a phase I IND quite often had that much or that much chemistry information. Our reviewers used to do a very in-depth review of that and look at all aspects of the chemistry, manufacturing and controls portion.

We have gotten away from that with the issuance of that guidance in 1995 so we are really focussing just on the safety now.

[Slide.]

Now, again, this is minimum type of information that should be included in the IND. We need to know something about the drug substance and if it is not a new molecular entity, if there is a USP monograph for it, quite often the information that would be needed would be just to reference that it is a USP material and that might suffice, or at least would go a long way toward satisfying the needs of the chemistry reviewers.

If it is one of the inactive ingredients, generally there will be an NF monograph for that. If somebody wanted to do an IND and they wanted to use an inactive ingredient that has never been used in humans

before, that is essentially the same as introducing a new molecular entity active ingredient into humans. If it is something that we don't know anything about, we are going to have some concern about it and we would expect to see the type of information that I am talking about for the drug substance for that inactive ingredient, also.

[Slide.]

A couple of places I am underlining "brief." A brief description of the physical, chemical and biological characteristics of that material just so that we know that it has been characterized and that the structure of that material is what you think it is. This would be like structure elucidation information.

The name and address of the manufacturer; you might say why is that a safety concern. It is expected that any material that is given to humans in the U.S. is manufactured under good manufacturing practices. This goes for even a phase I IND.

Generally, we will not inspect any of the facilities that are involved in INDs but if it is being made by somebody who we don't know anything about or if it is a manufacturer that we have on record, we know that we have had problems from the GMP standpoint with that manufacturer, we might send an investigator out and do an inspection. So that is why we need to know the name and address of the

manufacturer, and a very brief description of the manufacturing process. This could be a detailed flow diagram, just going through the various steps. It doesn't have to get into tremendous detail about amounts or time or anything like that.

If it is a biotech product, quite often, the reviewers would like to have at least some more detailed information about the process that is being used to manufacturer that material. The same thing if it is a drug substance that was extracted from either human or from animal sources.

[Slide.]

A brief description of the analytical procedures that will be used to monitor the identity, strength, quality, purity and potency of that material and some proposed acceptance criteria. This doesn't have to go into great detail. It may suffice to say, for the assay of the drug substance, we are going to do an HPLC and we expect the material to be between 95 and 105 percent pure, something like that.

There should be a copy of a certification of analysis or, if there is more than one drug substance, if it is a combination product, certificates of analysis for each of the active ingredients. Quite often, the drug substances are being purchased from somebody else, from another

company. If you are the sponsor of the IND, you should be getting a certificate of analysis from your supplier.

We have been asked many times in the past, is it necessary to validate these analytical procedures in an IND. What the guidance talks about is that it is not ordinarily needed to have validation data and establish specifications or acceptance criteria in the IND except for some of these well characterized biotech-type products, but you should have at least some validation of those procedures because you want to know--if I think this is a pure material, is it really pure.

What if your method is such that 10 percent of an impurity doesn't show up and you go ahead and you do the clinical trial or this initial trial, and you don't know that 10 percent impurity is there. And, later on, you get a more pure material so it is down to 1 percent or a half percent or a tenth percent and it was that impurity that caused the activity.

So you need to have some confidence in what you are measuring. It is not a full validation as is recommended in the ICH guidances but at least some confidence that that method is going to do what you think it is going to do.

[Slide.]

A brief description of what you are going to do to

demonstrate the stability and what analytical procedures will be used to monitor those characteristics that are indicative of the stability of the drug substance. What the guidance suggests is it could be presented in a table for each of the drug substances or each of the batches that you have used and it specifically says that detailed data in a stability protocol are not needed at phase I.

So that really doesn't impact the safety as long as we have some idea of what you are doing.

[Slide.]

For the drug product, there should be a list of all of the components that are used to manufacture that drug product including any reasonable alternatives for inactive. So you might want to use mag stearate. You might want to use something else. That should be explained in the IND.

It is sufficient just to say what the quality is, is it National Formulary or NF grade. Is it American Chemical Society grade? Is it something else? There should be a quantitative composition listing how much of each component is used to manufacture that drug product.

That includes materials that show up in the drug product and materials that are used during manufacturing that are removed before you have your final drug product. And, again, the name and address of the manufacturer of the drug product for the same reasons that I discussed earlier.

[Slide.]

Just like with the drug substance, again, a brief description of the manufacturing process. This could be a diagrammatic presentation, a flow diagram. It doesn't have to be anything very elaborate but just so that we have some sense of how the product is being made.

Now, if it is a sterile product, then we would want to have some detailed information on how that material is being sterilized so that we have assurance that we would not be introducing a product that might cause infection or might have bacterial endotoxins in it.

So we do have a lot more concern with a sterile product than with, again, for example, a solid oral dosage form. And a brief description of the stability studies, just as we had for the drug substance. This would be for the drug product, again showing that the drug product is stable, at least for the life of the intended study.

[Slide.]

A brief description of the analytical procedures. A very similar discussion in the guidance as was held for the drug substance. I won't belabor that but, again, it is that at least a minimum amount of validation should have been performed. It does say for the biotech-derived products that data should be available, which means is should be available at the sponsor site. It doesn't

necessarily have to be submitted to the agency.

[Slide.]

If you are using a placebo in your study, then there should be some brief information on the composition, the manufacturing process, the analytical procedures used to control the placebo quality as well.

Not a safety concern, but there should be a copy of all labels and labeling and any IND that is being used should have on its label "Caution; new drug. Limited by Federal or United States Law to investigational use." If it is not on there, it is certainly not a reason to hold up the study but it is discussed in the regulations.

And last but not least, there should be, in most cases, a request for a categorical exclusion from the portion of our regulations that say you have to have an environmental assessment. I don't know what I can say about that.

About two years ago, our regulations were revised and, for an NDA, almost every NDA can now claim a categorical exclusion as well. INDs have always been able to.

[Slide.]

I guess just for completeness, I should mention guidance that we are working on. CMC guidance for phase II and phase III INDs. It is a continuation of what was in

that phase I guidance. We published a draft in February of this year for public comment and we are now in the process of evaluating those comments and revising the guidance which, hopefully, will be out in the first quarter of 2000.

[Slide.]

Again, even in phase II and phase III, the focus from the CMC aspect is on safety. We talk about any new safety information and data, safety updates, would come into the IND as an information amendment. So if there is something that has been changed or new information that is determined--and this applies during phase I as well--if you determine information that could impact on the safety, it should be submitted to us immediately as an amendment to the IND.

If there are changes that are made that don't affect the safety, then it comes in an the annual update. Every IND is expected to have an annual report filed for it.

[Slide.]

Finally, things that might be changed that could affect safety include these. It is not necessarily limited to those. Number one, change in the method of sterilization. If you are going from a terminal sterilization process to an aseptic fill process, we would have a lot of concern about that and we would certainly want to have information that showed that you are still able to

maintain the sterility of that material.

If there is a change in the container closure system that could affect the product quality, that should be submitted to us immediately. Changes in synthesis that result in a different impurity profile. Again, as different impurities are introduced, this would require consultation with our toxicologists and could lead to a recommendation that the IND be put on clinical hold.

We do have the authority to put an IND on hold at any point during the IND studies. It could be phase I, phase II, phase III. It really doesn't matter. If we have a safety concern or something has arisen, data have been submitted to us that lead us to believe that there might be a safety concern, we could recommend a hold at any time. And changing from a synthetic process to a biological sources for the drug substance.

Those are the considerations that affect the potential safety of a study that is being performed, whether it is phase I or whatever, from the chemistry, manufacturing and controls aspect.

Thank you.

DR. DOULL: Thank you, Dr. Sheinin.

Why don't we take a ten-minute break and then we will come back and do the general discussion of biomarkers and the remaining aspects.

[Break.]

Subcommittee Discussion

DR. DOULL: We are at the point, now, where we are ready to come to the general discussion by the subcommittee. There are many of you in the audience, I know, who have great interest and knowledge and wisdom in some of these areas. Dr. MacGregor and I were talking and we think that it would be nice to utilize that if at all feasible.

We also have some questions which were sent to the subcommittee previously which we probably also could go through. Why don't we, at this point, take a few minutes and let Dr. MacGregor kind of outline a plan of attack for our discussion.

DR. MacGREGOR: I guess maybe I could raise some issues and maybe reiterate where we started in the beginning and what I hope we might see by the end of our discussion. Let me first start by saying that the agenda, itself, and the focused topics that we discussed in depth were essentially chosen for two principle reasons.

One is that all of the areas are, in fact, areas where we, in the Center for Drugs, have already committed some level of resources to pursuing the areas because we think they are important to our programs and to the future. I guess the first question is are there areas that are overlooked or are there other priority areas that we would

be considering and are those topics that were chosen really the highest priority areas that we should be discussing in the context of this committee.

And then, within the context of the things that were discussed, I think, throughout the course of the day, we have heard the comment that a lot of things that we would call maybe "gee whiz" science with tremendous potential but lots of questions were presented, and, in addition, some of the speakers presented some very specific recommendations.

So, hopefully, we can come to grips, before the end of the day, within these areas that we did discuss today, what are the priorities and what are the specific things that, within the context of our vision for this subcommittee, should we try to pursue and, in particular, can we come to consensus on some issues that we see as, a priori, so important that we want to move them ahead through the mechanisms that we have discussed by bringing together an expert group to pursue then.

Then, if we did get to that stage, we might even want to set aside a little bit of time to talk about the process that was presented in the beginning, what has already been discussed as a possible process for bringing together the appropriate experts. There is not a lot of point in discussing that if we don't agree that we want to do that. But if we do agree that we want to do that, I

think it might be important to just discuss the process on how we are going about that to be sure everybody is in agreement that we are doing that in an appropriate way.

So I guess those are really my general comments and, as far as the best way to approach the specific recommendations and priority areas, I will leave that up to the chair.

DR. DOULL: In regard to people from the audience who want to make comments, it is very important, Kimberly reminds me, that you come to the microphone and that you give your name so that we get it on the record, and give your affiliation, so that way we comply with all the rules.

Let me start by defining some areas. We started out this afternoon with a discussion of the imaging, the PET scan area, and the MRI and MRM, I guess, areas. I would propose, if the subcommittee agrees, that we kind of group that as an area if we are going to make recommendations since there is some overlap between those different imaging procedures and talk about that as an area, if we make recommendations for that.

Then, in the early afternoon, we focused primarily in the biomarkers area. We had two speakers who talked about that and I would suggest that we also focus on that as a potential area in which we might wish to make some recommendations.

What is the wish of the subcommittee? Shall we start out with biomarkers or imaging, do you think? Biomarkers? One of the things that was mentioned in the biomarkers area when Dr. Morgan was talking, he reviewed what is going on with the ILSI proposal. I guess I didn't ask Dr. Robinson if there is--do you have anything that you would like to add in regard to the ILSI project?

DR. ROBINSON: Not specifically. I think that Gwyn covered the goals and objectives of that project quite well, but just, I guess, to make the point that this is an opportunity for collaboration with FDA and, particularly, CDER and the scientists there and the research arm of FDA and that we really do welcome input into process as we develop our project and, hopefully, direct experimental collaboration as we get our program up and running.

DR. DOULL: That is Dr. Denise Robinson from ILSI. One of the things that I noted in the presentation was that they divided biomarkers into early biomarkers and then talked about the different kinds of biomarkers. All of those were dynamic biomarkers.

There was no mention in there of kinetic biomarkers. I would have thought that the ability to actually measure the drugs in fluids and so on, as a kinetic marker, would be a useful marker. I just kind of wondered why that wasn't included. Isn't that something that we need

to touch on?

DR. SISTARE: I totally agree that it is something we need to touch on. I view that as a biomarker of exposure and my focus was biomarkers of effect. But I did make a point several times, and I think it is really critical that as we investigate these biomarkers of effect, the biomarkers of response, they have to be done in the context of exposure and it has to be linked to exposure. I guess I didn't make that point strongly enough but I totally agree, exposure to both parent and metabolites.

DR. DOULL: I also liked Dr. Morgan, the presentation about the dose response and the fact that the low-level effects are the--we tend to talk about pharmacokinetics and toxicokinetics as if they are two different things, in a sense. Really, they are all part of the same dose response.

When you are down in the pharmacologic range, you tend to be in the lower dose-response ranges as opposed to the toxic where you get up to see those effects. So I think it is artificial for us to make that kind of distinction. It is more useful to talk, as you did, about effect, totally, effect at different levels.

In fact, there is probably no real difference between toxicity and pharmacologic manifestations and that they are both effects, just different kinds.

I guess in terms of the biomarkers--does the committee have questions about biomarkers or shall we talk about the questions?

DR. CAVAGNARO: I just had one comment as we, again, talk about each of these various areas whether or not we will make a distinction, generally applicable versus specifically applicable, screening versus mechanistic, so we can better understand what we are talking about.

For example, some of the biomarkers, focus on, as we try to implement them or include them in various toxicity study designs, whether or not some make more sense to include across compounds initially for screening, if you will, and then those that we might reserve for more mechanistic down studies. I don't know. David is shaking is head, so maybe he understands what I am speaking to--just so that we don't lump everything together as--it is the same point I made before.

Some of these technologies are driven based upon a question that we want to ask and you don't ask that of every product class. We want to make sure we use these judiciously where they make sense to use them and, in those cases, we have a better opportunity, I think, for them to be used and to be implemented, more readily implemented.

So that is just a general comment to, I think, both the imaging technologies as well as the biomarkers.

Do you want to say anything, David?

DR. ESSAYEN: No; only that I agree with your conceptualization here and for focussing the use of the various markers.

DR. DOULL: When Dr. DeGeorge gave his presentation, talked about the tox screen, went through the outline, two species and all of that and so on--the question would be, I think, how one would incorporate biomarkers into that scheme; where would they go and how would one use that information in interpreting where you are at with that screen and so on.

I think the is a difficult area and, as you say, Joy, needs to be tailored to case by case, so you would put in there whatever really was most helpful for that particular case.

Let's look at some of these questions, then.

DR. MacGREGOR: Could I make a comment on biomarkers?

DR. DOULL: I'm sorry; Jim.

DR. MacGREGOR: I am wondering if we might want to address Dr. Sistare's recommendations directly. I think he did make an effort to make some specific proposals. Just going back to my presentation, I think that the comments that Joy and David Essayen just made about deciding whether you want to focus on a class of response related to a

therapeutic group of agents that is of interest or a general set of biomarkers that is damage-specific.

They are different questions and we need to come to grips with whatever path we might want to take or focus on. I think, Frank--maybe he can correct me here--but my understanding of what I think he put out as proposals was that we might want to think about a general approach where we use proteomics to look at tissue-specific damage by using 2D gel electrophoresis, for example, in a consortium type of approach to see could we find protein biomarkers that looked like they would be useful for specific types of tissue damage. So that would be one kind of proposal.

Another was focused on the particular problem of vasculitis and should we focus there and look for vasculitis biomarkers for reasons that he presented why that would be useful to do. The other was photocarcinogenicity and the other was a very specific validation of troponins. Frank said troponin T but maybe that could even be generalized because there is a little work going on with troponin I and other subclasses, but troponins as an established--to really cement in their use as a routine biomarker for cardiac damage in nonclinical studies.

So, again, he made the argument why it is close but not quite at that stage. So there are some very specific recommendations there.

I guess to add my own comment, I would say it follows on the logic that the ILSI consortium is going to look at two or three types of toxicity and try to take a genomics approach to looking at genomic responses to hepatotoxicity, genetic damage, and they may or may not end up including nephrotoxicity.

So, because they were doing that, the proteomic approach would be complementary, number one, and, number two, if successful, would give us biomarkers that would be usable in readily assessable tissue compartments and, therefore, have the potential to be used in a variety of different settings.

Do you want to add to that? Did I get it right?

DR. DOULL: Hopefully, the recommendation that one would make would be most helpful to doing exactly what you want. Whether or not we can make specific recommendations, Jim, for a specific area requires careful consideration.

I guess the thing is the subcommittee has the option of recommending that here is a field that has progressed to the point where a group looking at it carefully could probably figure out things to do that would be helpful to the agency in doing the preclinical and tox testing and so on.

Then, if we agreed that we were at that stage, we could still recommend that we would go ahead and do that and

then that group would go ahead and, hopefully, develop some kind of recommendations and guidelines and so on that would be helpful to do that.

So I guess the first question is are we at the stage, with biomarkers, where, in fact, it would be useful for the subcommittee to consider that to be an area that we would focus on and take the next step which, I guess, would be appointing some kind of committee or something.

DR. CAVAGNARO: I guess my comments are, you have to start somewhere. I think today we have seen that there is a sufficient database to at least start.

I guess the question that I had was ILSI has an initiative and then this would be a separate initiative. Is there a way to have some baseline standard. Joe talked about the two-week rat model, et cetera, as the two- to four-week. That helps in the facilitation of early clinical development as the model where you would now ask the question about troponin.

So you would always have some reference point. It is a two-week study and, in that study, you would measure traditional markers, the standard, if you will, and then build on that as a framework so when you are assessing troponin or some of these--because what you would like to do is bridge all these studies, again, bridge the studies that, if these are the studies for--biomark troponin and the ones

that you had suggested and that Frank had suggested.

Somehow, you would like to correlate that database, once that is assembled, to the ILSI database which is just measuring a different endpoint biomarker. So, if you agree on the backbone of the study--do you understand what I am saying?

If ILSI does things in single-dose studies and somebody does things in three-month studies versus six-month studies versus one-month studies, then we are always going to question the relevance of duration. So, if we could establish--could you envision a standard treatment or duration or species where you could, now, ask these questions and then be able to leverage the data.

DR. DOULL: Maybe what we need to do for that, Joy, would be to have a link--if we were to form a committee, for example, would could have somebody from the ILSI committee talking to that group or a part of it to insure that we did cover it.

There was also mention of the European effort which--I don't know how we would encompass that, but, clearly, we don't want to go off in all directions so we need to do whatever is facilitating.

DR. DEAN: John, it seems to me that the starting point might be where are there information gaps or biomarkers needed in terms of toxicities that we are not

predicting well from the animal or that we are seeing in the animal that we are not predicting well for man is a place to start because you can either start with a list of biomarkers and you will get everyone's favorite biomarker, or you could start with a list of what are the problems we run into the clinic that we don't predict well from preclinical testing.

Then what are the most likely biomarkers that would predict those effects. That might be a way to conceptualize this without making a long list of biomarkers to go validate or evaluate.

DR. MacGREGOR: I would agree but I would reiterate a point that Gwyn Morgan made that I think is a very important one, and that is that a lot of these things that happen in clinic that we don't predict very well from the laboratory models may, in fact, not be the fault of the laboratory models but individual variation in the human population.

We could get into trouble if we pick those and then try to go into an animal model to answer the question. So we need to be careful about that, I think.

DR. ESSAYEN: I would echo a couple of the comments that have already been made. I think as we go forward with something like this, the couple of other things that we are going to be need to cognizant of are achieving of samples so that, given a particular protocol and

standardization of assay today, should a different database be necessary to be acquired, we have the proper samples stored in order to recreate databases using evolving technology, standardization of assays that we use today to create the present databases and, as best as possible, to make them consistent with the ILSI initiative or other parallel initiatives to make the data comparable.

And then the last thing we are going to need to be cognizant of, as we would set up a committee to look at these things, is the possibility that, in looking for biomarkers, we may actually identify potential therapeutic targets and that will raise issues of intellectual property which will need to be dealt with within the committee.

I think it will be important to have NIH representation on that committee because a lot of the issues related to acquisition of intellectual property have already been worked out by the NIH and other initiatives that they have participated in that are analogous to this one.

DR. REYNOLDS: I think one focus we could look at in the area of biomarkers, and I heard someone quote, I think it was Gwyn, whether biomarkers would become a badge of honor or a stigma that becomes associated with a class of compounds or other treatments.

I think, with biomarkers, we have the ability to generate an awful lot of information a lot of which may not

have any relevance whatsoever to, really, the questions that we are asking. So I think it is important that we focus on what do we do with that information that we can generate that it not really relevant to the questions that we are asking, especially as it pertains to reporting requirements and pursuit of other things that may be indicated for toxicity.

So I think whereas we rely upon the traditional OECD type of toxicology studies, the in vivo studies, are we talking about layering upon those studies, then, additional biomarker endpoints or are we going to talk about the ability to do biomarkers in lieu of some of these additional studies because I can see us causing ourselves a lot of work here that may not mean very much.

I think, also, one of the things we should focus on in terms of the, shall we see, nonspecific biomarkers that we might generate or even the specific ones, that what do we do when we uncover ability to measure things like QT interval prolongation? Does that mean that every time we see this response, that we have to have some clinical outcome that will validate the relevance or lack thereof of this--there is not a general answer, but I think we have to be cognizant of those escalating non-value-added types of things that we can do.

DR. DOULL: Who was it that said, "Tox deaths are

like old generals; they don't fade away. They just keep on doing whatever they do."

Let me go through these questions that were submitted to us. Maybe they will stimulate some thoughts in regard to this. What is the current state of science on the predictive value of biomarkers for use in assessing risk on NMEs? Is there a correlation between changes in the value of biomarkers and untoward outcomes in cells, tissues, organs that can be used in both preclinical and clinical studies; that is, is there a consistent pattern with the biomarkers.

Third; what questions need to be addressed in order to use biomarkers in risk assessment? We have heard a number of comments about risk assessment today.

Fourth, what recommendations about the use of biomarker technology should sponsors and the agency consider in their deliberations of risk assessment for MMEs?

I think what we are talking about is, perhaps, to get a group together to ask the question that you are saying. Is there a value of overlaying, say, the standard tox procedures that we now do with some additional tests that have to do with biomarkers and are there ones that would be general enough that we would, in fact, recommend them fairly uniformly or are they case-by-case recommendations which would fit the kind of adverse effects

that one would see.

Presumably, a group that would say, "Hey, we are just not at that stage yet. Biomarkers is a developing technology and we need to have this kind of information before we really are ready to make that recommendation." Or, "Here are a list of biomarkers which generally are informative and predictive and could be included as a part of a general tox screen that would be useful and informative and predictive and, hopefully, would help in risk assessment, whatever that is."

DR. MacGREGOR: Just to add one further, I think, requirement. I guess, in my mind, this point has been made a couple of different times in several different ways, but that it is important to define fairly specifically the biomarker problem and issue that we might address, that the questions just posed are very general ones and, for example, if you were going to constitute an expert group to address the three or four issues that I just named, say, proteomic approaches to tissue damage or vasculitis or photocarcinogenicity, those would be very different expert groups.

So you have to decide, I think, which areas you want to pursue if you are going to pursue it via an expert group so that you get the appropriate groups of experts. If you get people who are too general, which I would say, for

the most part, are those of us around the table who, I think, have a perspective of the field but are not really experts in how we would solve the vasculitis problem, for example, that we won't really get to the specific level that we need to make real progress.

DR. DOULL: I agree.

DR. DeGEORGE: I just want to comment that I think it is important that you address whether you are going to go after issues that have already been identified--and I tried to make that point in my talk and I don't think I did a very good job--issues where there are areas where we already there are problems; for example, the vasculitis.

Clearly, it has been said to be a normal pathology of the dog through it is an indicator of potential toxicity in humans that we can't readily monitor. And there is a broad spectrum on that. Answering those kinds of questions, are there ways to identify--are there distinctions, in fact, maybe both are correct, maybe both positions are correct, but are there ways we can distinguish that through biomarkers, for example, that this is a dog pathology and not relevant to humans, and this is a pathology in the animal that may translate to humans.

Clearly, that would be important to have an answer to. One can talk about general toxicology screens and layering and all of that. I think, initially, it is either

going to have to be layering or stand alone by itself and not use it in any regulatory setting until there is such confidence built up.

On the other hand, once you get confidence in it, either by incorporating it somehow or by having a large stand-alone database, then, perhaps,we don't need the other markers anymore. We may have the same problems with these markers as we have with the current ones but, hopefully, in the choice of the markers, that won't occur.

The other thing is the tools, and this is the other point. If you just want to say, okay, we have a tool that we can now use, let's try to find a way to use it, I think that is something you have to think about if that is really what this group can help. I really think it would be good to try to focus on very specific questions where everyone feels there is an interest to be served by getting a better answer than we currently get from our models and testing programs.

If you do that, it may be that, in some cases, it is used only for drugs that cause, potentially cause, cardiac toxicity, that you would always want that included. After you do that, maybe you generally say, well, maybe we can replace our current methods to look at this as a general toxicologic effect. But I think you need to focus on those areas where we know we have problems today to get everybody

interested in trying to solve the problem.

DR. DOULL: Let me just refer to a little history. When Bruce Ames came along with his Ames test, a lot of us who were doing two-year oncogenicity studies thought, hey; that is great. That is going to save us an awful lot of money, a lot of rats, and what have you. So there was a lot enthusiasm for the Ames test as a biomarker for cancer early on.

It took us a while to realize that there were problems with that biomarker, it didn't always give us the right answers and we ended up doing not only the two-year oncogenicity study but the Ames test and a whole lot of other gene-tox studies, a battery of gene-tox studies.

We need to have as much wisdom as possible going in to that to do exactly what you are saying. There is a group which is discussing right now, for example, the use of adducts as an indicator for carcinogenicity. There are a lot of questions about whether we should use those adducts and which adducts should be used and what do they mean, and so on.

Jim Swinberg, for example, gave a talk recently. I think the jury is still out. We really can't tell which adducts are the most predictive and which would be most useful and whether they should just be added onto the current protocol or not.

I suspect we are probably going to have that problem with a lot of those things that we would like to add, whether it is the test for vasculitis and so on, as to how predictive they really are and how well they move us along and how one can utilize that information without getting boxed in by some kind of requirement.

I don't know whether we could get a committee that would have the skills and the wisdom to do that or not. That is a tough job.

DR. DEAN: I want to kind of echo what Joe is saying because I think we are saying the same thing. I think it is going to be more important to focus first on what are the toxicities where there are the gaps in our predictivity.

If you read the charge on 12 for the way this was framed, on page 12--it says, "to examine new biomarkers for improved predictivity of nonclinical studies and at providing a better interface between nonclinical and clinical studies." And then Frank has done a very nice job of outlining some of the toxicities, hepatotoxicity, cardiotoxicity, et cetera.

I think we would have to first get a group to agree on what those toxicities are then convene the working groups because if you bring the working groups together without defining the toxicity, then we are going to go off

in 100 different directions chasing everyone's favorite biomarker as opposed to focusing in.

The beauty of the agency's involvement is because there is always a gap in what industry knows and what the agency knows, I think, because they see everyone's compounds and they see everything that everybody submitted. The problem that individual companies have is going out and looking at a new biomarker, or putting it in, assessing it now knowing what the agency, one, is going to think about it or not knowing whether it has any validity.

So this way, by working together with the academic people who have new biomarkers, I think you have the best of all of the worlds. You have the agency which has a history of knowing what biomarkers may be relevant to start with and you have experts who have those methods.

But I think we ought to focus on maybe just a couple of toxicities that we would like to go out and try to evaluate biomarkers for.

DR. DOULL: But you are also suggesting, Jack, that maybe we need a group to figure out what are the ones we really ought to focus on rather than just deciding, say, de novo, at this time.

DR. DEAN: Unless we think we could hear from people in the agency who have pretty much framed this. If Frank has the correct list, then maybe that is the starting

point. Maybe we should just focus on the one slide where he named four different toxicities where he thought we lacked enough information.

Is that the appropriate list or do we need to get another group of experts to go off and frame the list?

DR. CAVAGNARO: I think the list is probably derived from some careful review of data. I think that is a reason why it was presented. I would add that, perhaps, there might be one area to get bio more involved in and, perhaps, one of the major issues that faces many of the new biological is the whole concern about drug-induced immunosuppression, et cetera, et cetera.

So if we could add something that might be more relevant to bio, and maybe David can add to that. But I think that I would submit that these markers were proposed based upon review of internal data that the agency has and that it represents a good place to start.

DR. DOULL: When you were talking about that group of four, Frank, I wrote down there neurotox because I was thinking about we really do need some biomarkers there. Whether any of those things are far enough along--it used to be when we were talking about what do we really need in tox to evaluate what we are seeing in the clinic. One of the things we really need is CNS depressant kinds of things.

We have no way of finding out if a rat has a

headache, for example, and yet we see a lot of headaches when we are testing drugs.

Let me give this as a proposal. What I hear the committee saying is we need to first explore what we have in the way of areas where biomarkers could be helpful if incorporated or made a part of the kind of the tox screens that we have, as a first step, to kind of identify where we might focus and then, second, to figure out how we might move ahead and get the knowledge together that would facilitate what we are going.

Everybody wants to talk.

DR. MacGREGOR: Actually, I didn't want to talk but I was going to suggest that we call on the audience to comment on Joy's supposition because we have, within CDER, a research subcommittee of the Pharm-Tox Coordinating Committee which is the committee that deals with these toxicology problem cases. Joe DeGeorge and Frank Sistare are co-chairs of that committee.

So I think they could comment on the degree to which these issues are appropriate choices.

DR. DeGEORGE: I first of all want to comment that I think part of the last the Frank brought up, actually, is a focus of FDA-CDER research activities and not necessarily a prioritization of general interest. It is who is there and who can do what that helps drive some of that list.

I think there is another area, another forum that has actually brought up some of the toxicology questions that are unanswered, or unanswered with our current standards. I would, again, mention the ILSI project which is looking at how well animal toxicology studies identify human toxicities. The lists would not necessarily correlate.

You picked up a good one, neurotox, which is one of the ones that is not well defined by the animal models that we currently use because animals can't tell you if they have a headache or nausea, necessarily.

Another one that was important was immunotoxicity. It was almost missed 90 percent of the time by our animal toxicology studies. That is one, actually, I think the bio people would be very interested in because of the impact and because of the fact that it is missed until very late in clinical development when you have already spent $300 million developing a drug.

So I think there are some other areas. I think Frank's list--these are things that we are doing because, one, we have the resources to investigate these. They are also areas of importance to us. I would go along with the vasculitis which may have an immune component as one of the effects there.

But I am not so sure everything on that list is a

driving force based on a need as much as a need and ability. So I would not make the assumption that that list is the agency's specific need.

DR. DOULL: We are not buying this as the final list. We are saying that this is a moving target. We are going to add details and details.

DR. DEAN: John, can I just ask a question of Joe before he leaves?

DR. DOULL: Oh, sure.

DR. DEAN: The specific issue relative to the ILSI project on productivity, that was systemic allergy, Joe, inability to predict systemic allergy?

DR. DeGEORGE: I believe we don't have enough data on the cutaneous to actually make a distinction but, clearly, we know that how well we can predict systemic-based hypersensitivity responses and other immune toxicities is not--our animal models are not terribly good at identifying those which we detect late. We may have ruled out a bunch of them but they can still cost an awful lot of money and resources when detected in marketing.

DR. ESSAYEN: There are a number of other groups who are chipping away at the immunotox issue. One of them I would mention is the Immune Tolerance Network which is being funded in large part by the NIAID which is going to be assembling a very large database for immunomodulatory

signalling molecules. That is going to be a seven-year project which was initiated this past October.

I am actually one of the representatives to that so I can keep the subcommittee up to date on the progress there.

The other type of toxicity, per se, and I have to put toxicity in quotes for this one, that the committee may wish to entertain as a possible focus area would be tissue remodeling in fibrosis and markers of that.

DR. DOULL: Those are both good suggestions.

DR. SISTARE: The only other comment I wanted to add was, to some extent, Joe is correct, that we are focusing on things that we can do within our research group so part of a reflection of those four things are initiatives that we are undertaking.

But we are undertaking those because they have been identified as priorities of the agency. So there is that component. The second one is the focus was on biomarkers of response. The focus was on biomarkers of response. The neurotox, I think, could be better addressed using one of the imaging modalities. You heard David Lester from our group who is focused on neurotoxicity.

So, yes, that is a biomarker but no really what we are calling as an accessible protein-based biomarker of molecule-based biomarker approach. It falls in the category

of what Jim referred to as maybe an upregulated or downregulated membrane protein which is accessible using, like, a PET probe or using an MRM imaging modality.

So I agree with you, neurotox is a high priority. It is one that we are focussed on. It wasn't in my talk because I don't view that as something that can be used as an accessible tissue thing to go across species.

The other thing is there was a careful elucidation of biomarkers versus alternative model systems. We are interested in being better able to predict immunotoxicity or hypersensitivity. And there is some discussion, some effort is under way, to look at alternative model systems that might be better animal model systems to what is currently being used to predict hypersensitivity reactions because, I agree, that the ILSI effort showed that that was a weak area for animal-to-man kind of predictivity.

Whether or not a biomarker approach in the clinic is the way to address that, I don't know. I think we need to refine the animal model, maybe look at alternative endpoints within animal models, but we want to define it in the animal before we go into the clinic.

My focus is on areas where we can do the experience in animal and in man and draw interspecies extrapolation and paradigms. So when we pick the areas that we want to focus on, I think we have to keep these kinds of

things in mind. What modality do we want to approach these things with and is it best answered using an alternative model or is it better answered using the biomarker approach?

But I totally agree. Those four things I put up there are examples that were based on my experience from my vantage point. We are doing those because we think they are important; that's true. There may be other ones and I do invite the committee to bring anything to the table that they think might be more important.

DR. DOULL: Two things. First, we are thinking very broadly of biomarkers so we would include PET scan, other things in there as biomarkers, because they would serve that function. And the other thing, I think, is exactly what you said. These are things that you have identified where you need some information. Certainly, one could expand that list significantly and add other things.

But the question, hopefully, that you would first ask is would it be helpful and is there enough ground work done that we could move ahead in this area by putting together some kind of a list and then exploring how these things might be used in a predictive sort of fashion.

DR. SISTARE: I agree. Establish the need first. Where is the biggest need? Where are the biggest questions that need to be answered. But one thing that you brought up earlier, too. You referred to the Ames assay as a biomarker

but I don't view that--that is an in vitro assay that is being used to predict something that is going to happen later.

Another thing was the DNA adduct. I view that as a sort of biomarker of exposure. One could argue that it does reflect an effect as well. But the other point I tried to make is if we are going to look at biomarkers, if we look at very early biomarkers, there is a lot of complex biology to sort through to tell you whether that early biomarker is really linked to the later event.

But if we choose biomarkers that are a little more proximate to the toxic event, I think our chances of success are greater; like, for example, a troponin leakage. It is not the same as a gad 153 gene expression induction as predicting cancer this far down the line. That could be reflecting endoplasmic reticulum stress or DNA damage or some general toxicity.

We don't know what that means but a troponin leakage makes us think. Is it coming from the heart? How did it come out? Is it an active secretory process or was there tissue damage there. There are not too many things you have to sort through. That is why I think we have to be careful in terms of where we focus our attention in biomarkers.

Clearly, from the industry perspective, they want

early biomarkers of effect to be able to make good decisions on what drugs to continue down the pipeline. Clearly, that is a very important thing to do and to be able to sort out those patterns is going to be extremely beneficial.

From where we are sitting, I think FDA kind of enters the realm when it gets into the animal. And then from the animal, it gets into the clinic. So, from my perspective, I will speak personally here--from my perspective, I think it is much more beneficial from our perspective to look at things that are more proximate to the toxicity that is going to be seen in the animal and in the clinic.

I think that is going to have more impact on human health. We have to do our job. Our job it to make sure that these things are safe in the clinic and when they get wider exposure. Industry has a much bigger job to do. They have got to sort through a bazillion compounds and pick the right one and then make sure it is safe, just like we do. So they have got a bigger focus.

DR. DOULL: I think the committee that is selecting the biomarkers also needs to give some thought to the lexicon, to defining the things. I agree. DNA adduct is not the same as a biomarker--well, I was thinking about metallothioneine. Is metallothioneine a biomarker or is it a cause of cadmium toxicity.

There are some fuzzy lines there that really need to be talked about in order to define these issues. You talked about apoptosis, for example, apoptosis as a biomarker or apoptosis as a cause of disease. It is a difficult area.

I think I hear some consensus which is that we think this needs to be explored, and the way to explore it is to initially put together a group which would give some thought to defining what a biomarker is and how this might be used and looking at some of the potential biomarkers that might be included in this to decide whether, then, we could go ahead with a more full-scale effort which would be to get experts in those different areas to advise us.

This committee is not defining the trees. We are defining the forest, hopefully, and, therefore, we don't have to get down to the nitty gritty. The expert group would probably have to get down to the nitty gritty. Our chore is to report to the Pharmaceutical Sciences Panel the forest, not the trees, as I understand it.

DR. MacGREGOR: I think, and Kimberly can keep me on the right track here as far as what these subcommittees can do, but my understanding is that we do need to report back periodically to the full committee and get their endorsement on the tracks that we are taking but that, in fact, because we do hold fully public open meetings, we can,

in fact, proceed ahead to form groups and perform activities on our own without going back to the committee every time.

So if we did have consensus that we should pursue a particular area, we could begin to do that and then report back to the committee periodically.

DR. REYNOLDS: Maybe I will just kind of surmise what I viewed as maybe where the committee is at and what our activities should be. I think there is consensus that we need to drill down and focus on specific areas where we can model biomarkers and show the utility.

I like what Dr. Sistare said; we need to find biomarkers that are in close proximity to the toxicity and what we can see in the clinics, but I think we need to spend some time as a committee focusing on what are those specific projects or pilots we should do.

I heard two areas where we can maybe seek advice. One is in the ILSI activity in looking at the predictivity. I think that database, there is a lot of controversy on what the database means, but I think one of the things that it can point out to us, or I think what Jack means, is where are the gaps, where are the areas of clinical toxicities that we are not doing well with the existing models of predicting.

So I think there are some important learnings and potential topics there, but I think also what was said about

the FDA's database and perspective on what the gaps are I think is very important. So I would suggest that this committee partner with the right members of FDA to look at whatever the knowledge gaps are but also maybe talk to several of the people from ILSI on what that survey at least pointed out and maybe tee up a number of specific projects that we can focus on.

I am not sure, then, in terms of process whether the committee would make a decision or whether it would come back to a forum like this to actually decide on what those specific projects are. But at least I think we could begin to focus, then, on what are the important high-value types of projects that we could work on.

So I guess that is where I have heard the consensus on where this should go. I would just put that on the table as a proposal.

DR. DOULL: I think that sums it up pretty well. That is what I am hearing. Are you all hearing that? I think we can make the point that, in the best of all worlds, biomarker will certainly facilitate prediction. And if they do that well, then I think that is where we want--how to use biomarkers, is that they help us make better predictions from animals to man.

They also will help us define the doses, the time of exposure, all these sorts of things. Biomarkers have the

potential to do a lot of good things in those areas and we ought to keep that in mind.

I think, then, in terms of the biomarker thing, we are fairly agreed that we would move forward in a general sort of way to define the area and to then define the next step which might be the formation of an expert group.

DR. MacGREGOR: I think it would be well at this point to define how specific we can be in terms of the focus of this biomarker group. For example, I think we need to be explicit whether we are talking about just safety or efficacy, whether we want to focus the group on biomarkers, molecular markers, that could be used in both animals and, ultimately, in the clinic or whether we want to focus more on the discovery end.

I would say, for example, that the ILSI genomics effort is focussing more toward the discovery end using genomics technology. We are going to be faced with the problem, when we go out to solicit experts, we are going to have to face up to those questions.

Do you want people that know something about vasculitis? Do you want people that know something about proteomics? You can't have everybody if you are going to have a workable committee. So I think, in my perspective, before we leave this, we should try to be as defined as we can by about the focus.

I guess I think we are talking about safety biomarkers with the flexibility to be used in animal models and, potentially, in clinic. But we want to be sure we are in agreement.

DR. DOULL: I am not sure we are at the place where we can make that selection. I think what we are saying is we are going to rely on this small group to massage--you have these four; the troponin test, the skin photocarcinogenicity, the vasculitis predictor and the hepatotoxicity.

We have added a couple of other potential ones that you might consider. I think what we are saying to you is talk to the OC group, talk to the European group, talk to the immuno one that Dave mentioned and find out from a list, hopefully, a relatively small list of potential biomarkers which ones could profitably be explored in a way that would facilitate what the agency is really trying to do with biomarkers.

And, then, at that stage, if you want, you can come back and, perhaps, the committee can give you some help in terms of recommending people and so on that might be helpful in this point.

The committee agrees with that? Let's move on, then, to the other issue which is the imaging issue. I think it was clear from what all four of our speakers said

is that we have a situation where science is really moving ahead at a galloping rate. It is incredible how much has happened in a relatively short time.

The difficulty is that, somehow the technology, all the things that are going on in terms of drug development, don't seem to have kept up with all that. We have that high throughput screen, for example, which is turning out all kinds of potential candidates.

We have no real quick way to--we can't do the conventional toxi, acute, subchronic and two-year study on all of those agents. We need the ability to somehow facilitate that kind of testing in a way that helps us deal with those kinds of problems; databases, predicting structures that have activity, and so on.

Certainly, the imaging thing, I think, offers potential for dealing with some of those things and it is a powerful kind of technique. But my feeling was that it is really not at the stage where you can bring it into your own laboratory, in a sense, and add it to what you are doing in a very profitable way.

It is a highly tailored situation. If I were going to bring PET scan, for example, in to do my rats, I would have to spend a year at Duke or wherever figuring out how to do all that stuff. It is a very complex technique, a very expensive technique, and one that I think we need to

figure out how to move toward getting it into the main stream of toxicology.

But I didn't hear any easy answer to do that in the presentation this morning. How about the committee? Gloria, you are an imaging person. Did you hear how we can do this?

DR. ANDERSON: I am not sure that is a major problem. I think the technology is going to continue to grow and, at some point, we have to catch up. The question I would have is how much do we know about what I might call the safety of these noninvasive imaging technologies. When I say "safety," I am talking about the--if I call it NMR, forgive me, people, because that is what I have been calling it for thirty years--you are talking about putting a human or you are talking about putting cells in a magnetic field.

I didn't understand the engineer's and physicist's units that he used, but I don't particularly like to go in the room where my 200 megahertz FTNMR is. I am not sure that we even know what the long-term effects of those kinds of things are. So the question I am asking, I guess, is how much do we know and before we go down that road, should not we try to begin to collect some data, not only on the MR but the PET as well because they are daily talking about radioactivity and do we do more harm than good especially when you come to the human trials.

I am not against, it, now, because I think we have to catch up with it. But I think we probably need to know more about the effect of these technologies, particularly on human beings.

DR. DOULL: I think it was Dr. Frank, wasn't he the one who showed us the slide that says, "Here are some of the potential disadvantages of the procedure." One of those, of course, was the radioactivity.

DR. ANDERSON: I don't remember but you have got, basically, in PET, as I understand it, to use radioactive labeling. That, to me, is a concern if we haven't really studied any effects, any long-term effects of that.

I don't recall whether or not that was there, but I do think that if, in fact, these represent techniques that could get us to where we want to be more quickly, that certainly they should be looked at. It may very well be that when you are talking about the development of drugs, you may really be talking about something else, like you may be talking about F19 instead of F18 that is used in PET.

F19 is used in a different way, but it can do some things.

DR. DOULL: The issue, then, is what can we do about the imaging thing. Should we deal with PET scan separate from the nonimaging or deal with those together? Let me read you the question for that. Oh; they have got

them together. Imaging technology; are the current preclinical guidances available for demonstrating or assessing the potential risk of noninvasive technology suitable for the first time utilization in humans." That is what you were saying, Dr. Anderson, part of that concern.

"Can the risk of using these technologies in combination with new medical entities be adequately predicted?" I guess that is more for the PET scan than for the NMR. "If not, what questions must be addressed or studied, or what studies need to be conducted to demonstrate the safety and utility of these technologies?

"Are new imaging technologies adequately developed to reliably assess cellular tissue and/or organ perturbation? What biological level of integration can imaging technologies detect changes, molecular, subcellular, cellular, tissue or organ?" We heard some pretty good description of all of that.

"What studies need to be done, or what data should be provided to the FDA, to determine the predictive value or validation of imaging or noninvasive technology? What are the opportunities for utilization of imaging technologies across species to support the safety and efficacy of drugs in development?"

That was the same issue, Dr. Morgan, that you were really talking about as you move across dose response in a

species, how well can you make those kinds of steps. It would be the same thing for imaging.

"What recommendations about the use of imaging technology should sponsors and the agency consider in their deliberation of risk assessment for new medical entities?" Those are the questions that were sent out to the subcommittee to consider and I think they focus on a number of the issues that remain with imaging technology.

The question is how best should we proceed with that area. The problem is if we don't do anything at all, that area is going like a house afire and it is going to be down the road and it is going to leave us in the dust.

At least, we probably need some kind of mechanism whereby we can keep track of what is going on in it.

DR. DEAN: John, can I put a stake in the ground as an absolute novice in this area. But it seems, from what we have heard today, that the nuclear magnetic microscope would be a very interesting kind of tool because you could look at the whole organ. You then could come back, as we saw in the presentation--you can look at that and the comparison with the histopathology or the various stains.

You get a three-dimensional picture as opposed to three sections or five sections, normally. That would seem to be something that might be more easily validated. One, it would take fewer animals. Two, you would get tremendous

resolution from what we have seen today--maybe not validated isn't correct, but at least evaluated against standard pathology and see if there is an advantage over this method versus standard pathology, in those lesions that are hard the characterize, or even very early in the process of the lesion being formed and the pathogenesis equation.

That, to me, makes more sense than to look at whole-animal imaging at this point in time when the machines are so scarce and you have got to put an issue in the machine for eight hours or so.

What I heard today is you could lay out several organs and image five organs simultaneously with some machines you have got today.

DR. MacGREGOR: Just to clarify, my understanding was that David made the proposal that, in fact, while his proposal was there could be an in vivo component and a tissue in vitro component, but that tissue in vitro component might be based on preserved tissues from previous studies. It might not take animals or pathologic characterization but maybe go out and find lesions that have already been characterized and then assess the capability of the technology to see those characterized lesions.

I would say that would be one thing to think about, is that worth doing with all the caveats about the cost and the expense and so on that I would like to have

feedback on. That is one of the things we have previously discussed a year ago, possibly initiating something, and it has kind of been in abeyance.

DR. ESSAYEN: We are talking in somewhat general terms here about what we would do with these imaging modalities. I think one of the initial things that probably should be focused on is getting the clinicians together with imagers and trying to figure out what the data gaps are, what specific areas to pursue that are technically feasible, and decide on the focus areas, similar to what we are talking about with biomarkers, similar to what Frank has alluded to, push the front on focussed areas and then hope the rest of the front pulls along with it.

I am very concerned in all of these endeavors about the dilution effect if we try to do too much too quickly.

DR. DOULL: When you talk to clinicians who use PET scan for diagnosis of different kinds of tumors and so on, one of clear powers of that technique is what Jack mentioned, the ability to visualize that tumor in site and to turn it around and to manipulate it so you can figure out exactly how best to treat it or to remove it or whatever.

That is an incredibly powerful tool and it is one that the clinicians have been using for some time and are very comfortable with and are very familiar with. That is a

concept which we haven't incorporated at all into what we are doing and which could give us a whole avenue of investigation which we do not have.

But there are all the other problems that go with that. The question is would that particular imaging capability add that much to what we now do that it would be unique and special and would justify the effort it would take and the expense it would take. That is a tough question.

DR. REYNOLDS: I think to kind of build on what David teed up and what you said, I think that if we look at imaging technologies, they have been used in terms of focussing on disease states and response to disease states, diagnostic kinds of things.

I think that maybe what this committee can do in its wisdom as well as ability to gather information from broad-based groups is maybe to help us focus on models or applications of these technologies where there are knowledge gaps.

I think one of the things we heard was in the area of neuropathology. I think there is a lot there that we might be able to do with some of these here. So I think, maybe, as a proposal for the initial activity of the committee, and I would just echo what David said. I really think that if we can focus on areas of where we can show

benefit and show the utility of this, I think we have done a real service.

So I think that the committee maybe could spend some time, as we have proposed with biomarkers, looking at the collective wisdom of us and our networks but also what FDA and other groups like NIH know about the knowledge gaps and maybe come back here and propose specific examples of where these new technologies may have utility would be of benefit.

DR. ESSAYEN: What I am hearing from the imaging people is that actually we may be taking the word "imaging" a little bit too literally. I think the power of this technique is not just using FDG to be able to look at a tumor but to actually come up with other agents in order to do functional analysis of tissues.

I think that is really where I would be looking to direct a lot of the interest. I agree, just another way of looking at a specimen of cancer in three dimensions is probably not a cost-effective use of resources but to develop very specific disease-process-focused functional correlates using this kind of technology particularly in tissues or loci that are not otherwise accessible through other efforts and biomarkers may be the niche for this type of work.

DR. DOULL: Clearly, that is a possibility. They

talked about using the technique, for example, to do precisely that sort of thing. In that material that you sent to us, there is the use of it in knockout mice, for example, to determine whether you are upgrading or downgrading in those particular cases.

Just to look at metabolism, for example, is something you simply cannot do with any other kind of radioisotope use in the drug. So that is all powerful and could add significantly to what it is we are now doing.

DR. SISTARE: I just want to point out that there are at least a couple of instances where I think these new technologies can be very important. Actually, I was saying at lunch, about five or six years ago, we actually had a question addressed to look at kinetics because there was this whole argument about animals showing neurotoxicity and the question about what was the accumulation in the animal brain versus what was the accumulation of the target site in humans and actually going out and collecting the data.

The data was collected PET imaging in humans, anyway. So there is a case of taking an animal toxicity and a risk assessment and trying to find out, do we have a risk or not, in a very difficult area to detect to humans.

But, more importantly, from the general perspective, I can think of several cases for pharmaceuticals that went even to advisory committees on FDA

where they had neurotoxicity. I remember one case was intermyelonic edema which would seem to be a very useful technique, perhaps, with MRN to see can you measure it in the animal with that technique, and, if you can measure it in the animal, does it occur in humans.

This advisory committee met several times to try to sort out how to actually assessment that potential toxicity in humans for this very important therapeutic class. I think, in the end, it was evoked potentials which no one ever knew if that was actually even something that would monitor the toxicity.

So I think there are some areas of neurotox where there are clearly cases where one could use these techniques focused but for particular kinds of effects. Does it happen, and can we detect in the animal, a toxicity which we know we would not want to have happening in a great extent in the human and can we do early testing and what is the sensitivity in the animal model versus the long-term toxic effects that we identify only after histopathology.

So I think that there are some real uses that could be pursued in focussing on those areas where there is potentially big benefit to understanding whether that drug is doing that in humans or not.

DR. DOULL: You are saying case-by-case? I certainly agree with that.

There are a couple of things which the agency can do uniquely. One this is that the agency has the ability to facilitate communication in this area. We were talking at lunch about the fact that, in the SOT meetings, we have never had, as far as I know, a symposium or a discussion of the new techniques, these imaging techniques.

Clearly, they have great potential application in toxicology. As far as we, Jack and I, at least, can determine, nobody is talking about it. They ought to be because this is the toxicology of tomorrow. It is probably as important as molecular biology. At least we need to be aware of it.

The agency has the ability, by doing a joint effort and collaborating with various groups and so on, to facilitate communication about this technique as a means of exploring, enhancing prediction, exploring adverse effects and so on. That is one thing which they clearly could do and I would suggest that maybe the subcommittee would encourage the agency, somehow, to look into this and to figure out how they might be able to do it.

The other thing that the agency can do is uniquely provide collaboration between industry and academia and NIH and ATSDR and whoever to facilitate an exchange of information and to keep up to date, so to speak, on what is going on in the various places.

I think what was presented here was, for many of us, a revelation of how much has gone on in this area and how powerful it is and how interesting it is and how exciting it is. I think would could begin to do that for the scientific community and that would be an immense help to facilitating the implementation of these techniques into the scientific community.

The question is whether we should explore beyond that. I think Jack's recommendation is that we could find a very focused area which would be to use the imaging techniques together with pathology, for example, as a validation of that kind of procedure to provide us with information which you really can't get in any other way.

It is expensive and it is complex but, in many cases, that is the only way you can get that exact kind of information. There is no alternative as far as we know.

DR. ANDERSON: As I understand it, one of the things that we are interested in doing is having a better success rate when we get to clinical trials. If that is, in fact, the case, it seems to me like it would be helpful to know if these imaging devices have been used in any instances prior to clinical trials.

I don't know if that information is available, but that would be helpful to me because that, apparently, would establish a link between what we are interested in and what

it appears that most of the people who are involved in this type of research are interested in.

I would like to know. I looked through but I didn't find it. I didn't find all the answers I wanted. I think there are some projections in there but the question is are there actual cases or examples where people have shown that this kind of link can exist or can be made to exist because that would directly correlate with the objectives of this committee.

DR. DOULL: That is a good point and we could certainly, if we asked the agency to explore these areas, they could certainly look to see--look for instances where there is a specific benefit in terms of drug development.

Actually, that is both areas that are covered in the questions. Did you charge the subcommittee with additional tasks, Jim?

DR. MacGREGOR: I am not sure I understand. There is still one area we haven't addressed.

DR. DOULL: Tell us about that.

DR. MacGREGOR: The efficient entry to trials issue. Do you want to go on to that?

DR. DOULL: Let me give you the three questions that have to do with this early clinical development. "The preclinical underpinnings and approach to conducting early human clinical trials has not changed substantially in the

past few years." That is like saying we are still doing tox the same way we did it when Arnold Lehmann first made is recommendation, which is true. I guess it is the same thing for clinical testing.

The question is, "Are there alternative or emerging approaches that would facilitate the conduct of early clinical trials that the FDA has proposed or accepted?" You have talked about some of those, Jack.

"What would be the scientific and regulatory issues for studies and data requirements that could be used in designing preclinical programs to support these alternative approaches to early clinical development?" That is what Joe talked about, and Frank.

"What are the factors used by global pharmaceutical companies in determining where or in what country the initial human clinical trials will be conducted?" I thought you said they are not being tested here so they must be being done in Europe, or something. But I didn't hear an answer to that question.

Did you give us one, Joe?

DR. DeGEORGE: Actually, I think industry has to answer that question, but four years ago, or in 1994, there was this notion that most phase I studies were going to be moving from the United States to Europe. That is when we started having this discussion about, because we think we

can contribute even in phase I from the regulatory review process in the U.S.

That is, in fact, why we first made that change about the IND format and conduct which talked about making sure it is clear what chemistry data was needed and it wasn't an excessive burden and what toxicology data was needed and that that wasn't an excessive burden in allowing the non-QA'd reports to see if, in fact, that would be helpful in keeping the studies in an area where we could actually contribute to them.

I don't think we know the answer back on that although I did point out that even though that document has been around since 1995, some companies have not availed themselves of one of the more beneficial aspects of that until very recently.

But that is a data question that only the industry can tell us where they are doing their drug development and why they are doing it in various places.

DR. DOULL: Actually, I was pretty impressed when you gave these requirements for the single human dose study. That sounded to me like a pretty good tox database for a compound. I think I would be pretty comfortable with that. If we had all that data and I had to go take it to a patient, that would sure reassure me.

Also the chemistry data, I thought, with that kind

of a data background, I would find that very reassuring.

DR. CAVAGNARO: I was hoping to have the opportunity, now, since I am still unclear about a screening IND and, despite your efforts, Joe. The reason that this is so difficult during ICH discussions and why N3 doesn't have a standard, what you need for phase I trials, is because there is no clear definition of phase I trials.

I would like to go backwards from that. Normal volunteer studies in some countries are not considered phase I trials. Clinical pharmacology studies to assess bioavailability which is discussed as an obvious rationale to move forward in the screening IND and that is selecting based upon bioavailability weren't defined as phase I trials.

So it was difficult for a global approach for understanding what is needed to support single introduction, much less the screening IND. So I guess the question I have for you is, for these proposals where there are 18 INDs, and three INDs, and they were proposed and accepted, et cetera, what was the clinical study? Was it in normal volunteers? Was it just a bioavailability study?

Was it really an MTD study? And then, after having understood that, what is the screen, a animal study? Is it a single high dose for five different compounds? Do you understand the dose response of toxicity for the five

different compounds that you are not introducing into the clinic?

DR. DeGEORGE: The answer to the last question is it is the same for all the compounds, much as Eric said. You don't have to make very large molecular structure changes to actually significantly change the toxicology. We all know that and so, clearly, knowing that, the standard tox package on each one of them is part of it. It is an administrative process, that I talked about previously, that allows a single clinical protocol, whatever that protocol is, to be evaluated and to bring all that data in.

It is minimal but it is still substantial enough I think to assure the safety of everyone being exposed. The screening IND is actually, again, more than one and less than some large number of compounds that are closely related being put into a clinical setting to collect data.

The specifics for, I think, most of those cases may have been bioavailability sorts of studies although I think in at least some of those cases, they were the standard phase-I single-dose kind of study to make a decision as to whether or not to go forward.

Some of them we were looking for--were not single-dose and, in fact, looking for some efficacy biomarker that they thought that they had a handle on and they were trying to assess that in looking across products.

DR. CAVAGNARO: All in normal volunteers?

DR. DeGEORGE: I can't say for certain if they were or not. I don't know if they were all normal volunteers. I think they probably were since that is the usual study design outside of very limited indications.

DR. DOULL: Are you asking, Joy, about that animal screening, the adequacy of that?

DR. CAVAGNARO: That is the single-dose to support single-dose studies. It was the screening IND which the explanation has been a little bit kind of--I am unclear of what the phase--to me, the most important is the efficiencies that one gains in the clinical setting. So, the number of patients involved now to answer the question, et cetera, and do we realize any efficiency short of the efficiencies in, I guess, the time involved in making the various materials.

DR. DeGEORGE: As I said, I think that is a little bit in the eye of the beholder. Different people want different kinds of information before they commit to taking products forward into one-month toxicology studies in two species to go into a full exploratory phase I study or even a phase II study.

So I think that there are differences depending on the specific question that the company is trying to ask. A screening IND is a regular IND, as it complies--we only have

one IND structure in the FDA--it is a regular IND that has multiple chemical compounds and multiple rounds of administration or multiple formulations of a particular chemical entity.

Any of those things could be considered screening but, as it is exercised in that list, it is different compounds closely related trying to make a selection based on some parameter of interest to the company, that this is the one we would like now to do a development plan on.

You can call it phase I. I guess maybe I shouldn't call it phase I because they don't have phase I in some countries in Europe. It is initial studies in humans.

DR. REYNOLDS: May part of what I didn't tee up or clarify so well is--I think we talk about surrogates. We talk about imaging technologies. I think these are all ways in which we hope to be able to go into humans, in many cases, and answer a very specific question which may determine whether a chemical entity is appropriate to take into development of not.

I guess what I heard on the one hand is that FDA, in terms of the preclinical toxicology as well as the chemistry, is quite flexible. I guess, having been in the real world and with two different companies, unfortunately, when you go back to your companies in the pharmaceutical industry, at least it is not that clear.

I think that people think that we need to have fully compliant GMP drug substance, we have to have fully GOP toxicology studies and we have to have two-week, one-month kinds of studies to help us go into humans with a single dose, a low dose or several chemicals to try to answer this question.

I am afraid, if that is the message that we send away by not clarifying what one doesn't have to do, I think there are going to be a lot of questions out there that new technology could have answered, but we are not going to be able to facilitate people getting to those answers.

I still don't know if I made that clear. I think we need to define--and one of the stated objectives of the committee was maybe not so much determining policy but communicating what one can do to adapt or apply some of these technologies.

I just think there is a lot that we can do to underpin the ability to go into humans with minimal effort up front to get an answer using the new technologies.

DR. DOULL: When Dr. DeGeorge was talking about this, I was comparing this to the ICH harmonized tripartite guidelines which, I gather, is now all pretty consistent with what you were talking about. It seemed to me that that all fit pretty well and that maybe the problem is we are not communicating that very well, where we are at, in a sense.

It is more complex because you are complying with the OECD or the European recommendations, of course, but that all seems to be pretty consistent.

DR. DeGEORGE: I think that, in terms of multiple-dose study designs to support what actually, in the ICH guidance, says you need two to four weeks of tox in two species to support single doses in humans is a generality. FDA has taken the position that we think we can, provided the single-dose study design is adequate.

I tried to lay out what we consider adequate--go in based on single-dose study designs in animals. So there is the distinction. I also stated that I am informed by some European regulators that they are allowing single-dose studies in humans based on single-dose data also, and that there may be a revisiting of their view which was largely carried forth in the M3 document saying it has got to be two-week and four-week studies

DR. REYNOLDS: Let us stay on that chemical that has a seventeen-step syntheses, that you need to generate a kilogram of material to do the studies that are required under M3 or other guidelines. In fact, the answer that you want is this material going to cause an elevation of troponin in patients because--or some other endpoint.

What we are saying is we have the M3 guidelines and we have other guidelines, and so we need to do that.

And so we have to synthesize a lot of material. The CMC folks will say, "Well, this materials have to meet certain specifications and certain kinds of things."

It becomes very complex back in the world of the pharmaceutical business how we take this first step to simply dose people with a single-dose of this material to measure a very precise biomarker. So I am not sure that we are going to be able to facilitate the assessment of these endpoints in people--by facilitation, I mean being able to find paths to do human studies having less up-front investments.

So I guess in the context of the facility guidelines to support entry into the human clinical trials, I think if we could just step back and say, what is the basis of those scientific regulations, I think it is that we need to characterize late limiting or potential organ toxicities of drugs. Do we need two-week studies to do that? Are there predefined protocols that we need to do that? Or could there be some general statement that there needs to be a scientifically credible way in which we have demonstrated rate limiting or target organ toxicities, the dose responsiveness of that, and that can be done using non-GOP, can be done using whatever to find a very efficient route to do these assessments.

So, again, just to repeat myself for clarity, I

think that in the committee, we have talked and kind of given the impression that it is easier to go forward and do these, but I can speak from experience that when we take that back to our individual companies and projects and project team levels, they don't understand what we are saying and so they default to having met everything from the regulatory guidelines and have all the i's dotted and t's crossed.

I think there are much more efficient and effective ways we can get to those decisions.

DR. DOULL: I guess my question is precisely how could the subcommittee facilitate making that whole procedure work better. What could we do that would really move that significantly forward.

DR. REYNOLDS: I think to focus maybe with expert groups on what are the scientific principles that we need to address in terms of the preclinical studies around safety, what are the issues around the CMC components of that, where are areas that we can maybe defer from or vary from guidelines to help people do these assessments earlier.

I think Eric's presentation around the guidance document, that has been around for a number of years. I still think there are both divisions and sponsors who see that as essentially having a fully GMP and GOP-compliant package to go into even early human clinical studies.

So I think we could provide some clarity around what are the scientific underpinnings of the CMC package, what are the things that need to be in there to demonstrate safety of the drug substance or drug product, what are the issues around toxicity and toxicology that need to be addressed without being prescriptive and without looking to the guidelines, because I think there are general principles or high-level concepts.

DR. DeGEORGE: Could I get some clarification from Jack? Are you trying to say that the companies turn to the N3 document and say, you have to do two-week to four-week studies or are you saying that the Federal Register document, which talks about single-dose acute studies, is an issue in terms of what you need to do, other than the GMP issue.

DR. REYNOLDS: I think there is a real lack of clarity of what can be done--not what you need to do but what can be done--because I think that many companies defer to doing the maximum because they don't want to do this work and then have an IND not be allowed to go forward.

So I think some discussion around what are the concepts that need to be addressed to support single-dose or low-dose or screening kinds of things, so not so much the guidelines as much as what are the scientific concepts there.

DR. SHEININ: I think, speaking from the chemistry aspect, we would certainly welcome any input this subcommittee could come up with. I really feel that the amount of information that the guidance talks about that I presented today is a minimal amount of information. Scientifically, I guess I have a hard time trying to justify saying a company could have less than this amount of information and give it to a human being.

I would say to you, would you volunteer for one of these studies if you knew that the company had not done a minimal amount of work to even know what it is that they are going to put inside your body. I think, yeah, we want to try to encourage drug development, but if you could come up, as a committee or subcommittee, or have a group working with you that could scientifically justify coming in with less information, we would certainly listen to you and we could also encourage, as I indicated and Joe indicated--talk to us at your pre-IND meeting.

What are your plans? What kind of information are you going to have and is it possible that we could live with less information. But our primary objective in asking for this is to protect the volunteer or the patient or the healthy volunteer, whoever is going to be given that material for the first time.

We would be remiss in our duties if we let

somebody do a trial like that and there were serious adverse reactions because there was a problem with that material that we didn't know about because of a lack of information that, if we would have had adequate information, we would have said, "Wait a minute; let's step back and not do this right now."

DR. REYNOLDS: Eric, I would just respond, I wasn't meaning to imply how little can we do. It is what is the appropriate thing should we do. I think that one thing that we need to be mindful of is that facilitating early entry into clinical trials to me implies we want to be able to go into humans single-dose, low-dose, with a minimal amount of material leveraging what we can learn from technologies.

That is all I mean to say. Are there ways in which we can facilitate that? I don't mean to imply that we should lower our standards or require less than what is absolutely essential to fully determine the potential safety of these materials.

But I guess somewhat of a hypothetical is that, to do a low-dose, single-dose, human study, would that mean that the material absolutely has to be synthesized in a GMP pilot plant and would have to be fully GMP compliant in terms of records and documentation? I think it is that, maybe, lack of clarity of what is essential for these early

materials but maybe where the committee can do an important function to try to establish some clarity on where there is room for flexibility there.

DR. SHEININ: I think that would be more than welcome. As I had said earlier, it is expected that anything that is given to humans has been made under GMP conditions, but it is really a compliance issue. For the most part, we do not go out and inspect these facilities unless we have a reason to suspect that there is a problem.

Again, that is something, I think, that we would welcome any input that you have and if there are any ways to expedite the process without compromising safety, we are certainly willing to listen to that.

DR. MacGREGOR: I guess here I am wondering if we are beginning to diverge a little bit from our mandate of identifying the science-based issues that would should be addressing and kind of getting more toward interpretation of existing policy.

I guess I am still, myself, not quite clear what is the specific recommendation for a science-based approach to a specific question. I am not sure I see that formulated in this general context.

Now, Joe, in his presentation, provided some very specific recommendations on how we might do a survey to gather information on the change that allowed non-INDs to be

initiated before the QA was completed and, also, the issue of what are the issues that are related to trials going out of the country.

So those are two very specific things that were presented. The other issues I still don't see. I think we ought to either try to come to grips with the science-based issue or to just go back to the specific questions of what exactly--should we pursue the specific recommendations.

DR. DEAN: In listening to this, now, for several minutes, it strikes me that--and, Jim, you can correct me if I am wrong--it strikes me if this is outside of the brief of the committee, that the brief of the committee is not to modify guidance and regulations or interpret guidance and regulations but to look at novel technologies and how they can be applied because what I heard from the two presentations, it is very clear what you can do and what you can't do, at least my interpretation, and maybe I am wrong.

So the issue that I think you are describing, Jack, is how to sell this back home, I think is what I heard you say. Maybe there is a lack of understanding in the pharmaceutical industry among member companies or in PhRMA on what you can do and what you can't do. Maybe that is an education issue.

I still even think that, interpreting guidelines and guidance is outside the brief of this committee, as far

as I am concerned, or at least that is my interpretation. I am asking--let me ask that as a question.

DR. REYNOLDS: I certainly agree with what Jim has stated. I think that what we heard today, and I think has been of value, is that it is probably hard to define the precise scientific underpinnings of what is needed but that, both in terms of the pharm-tox area as well as the chemistry area, that there is considerable flexibility in what is appropriate to underpin these early studies.

I think it has been stated, but I think, also, we know that, in fact, there is this case-by-case approach and one can, within a specific project that the sponsor has, create the scientific underpinnings for what is being proposed. So I think being the one who, I guess, has thought that this was a good area for us to discuss in terms of facilitating early development, I agree that, probably at this point, hearing what we have heard, probably outside the remit of this committee and that we are not going to be able to do much about discussion interpreting the guidelines.

So I think that is entirely correct that we have probably done what we can there around the guidelines.

DR. DOULL: There are two issues. One is the communication issue. Is the information fully communicated and well communicated so everybody understands it. I guess that is something that could be done if it really needed to

be done although I am not sure this subcommittee is exactly the one to do it.

The other issue, of course, is the scientific basis. What is the scientific basis for animal requirements in order to take that drug to a patient, for example. Those are scientific issues and those are complex, difficult scientific issues. I hear us saying that, at the moment, at least, if we get into that whole area, then we have to deal with everything, what they do in Europe and is the procedure for the food in the agency the same kind of regulation that it is for drugs, for example, the food-safety group. There are a lot of other issues and I am not sure that that is something the subcommittee wants to take a hold of.

DR. ESSAYEN: I am not sure that type of analysis of regulatory issues would necessarily be in the purview of this committee and I think our time and energies and efforts are probably going to be best spent looking at the evolving technologies, both related to biomarkers and imaging. I think we should really focus there. That would be my vote.

DR. CAVAGNARO: I think some of what was presented by Jerry Collins today in terms of identifying the target there, the bridge, the PK/PD, that is a better, I think, focus for this initiative, this early clinical development, because that is the in vitro correlate, the functional--that, to me, was the most useful advancement of this

facilitation of early clinical trials.

The guidelines are set. Whether or not people choose--there is not much that the agency can do in terms of setting--to be more flexible in terms of this approach. The guidelines are out there. ICH is out there. Short of having to go through that and being a member of that working group, that isn't something that you want to reinvent.

But if we can take this early facilitation and couple it with some of Jerry Collins' presentation, then, I think, that brings in the science and that makes this more exciting because, Eric presented--this is a 1995 guideline. This is slides from a 1995 guidance document. Joe's presentation was from guidelines that were out there for four years.

So the fact that sponsors are not meeting the guidance or choosing to--is not a scientific issue.

DR. DOULL: I think whether it would facilitate communication, I don't know whether the subcommittee could enhance that in any way or not, but I think what Joy is saying is let's leave sleeping dogs lie rather than revise the whole tox approach.

I liked what Joe said about if you think it is safe, try a little something. That is an agency perspective that goes clear back to Arnold Lehmann when he used to say, "If you really think it is safe, take it," or at least that

was the rumor that is what he said.

DR. REYNOLDS: One quick comment. I think one of the objectives of this meeting was to look at the at least three potential topics for addressing by the committee. I guess I hear that we would probably want to focus on two and the third, in terms of facilitation, at least in terms of redefining and reinterpreting guidelines outside of the remit of this.

Are there other things that the committee has thought about or were potential topics that maybe we ought to just quickly tee up for the next meeting or think about? Were there other topics that we wanted to maybe look at, Jim?

DR. MacGREGOR: There may be, but if you are addressing that to me, let me just sidestep that one and say that I think I did hear some recommendations. I think we might want to resummarize the areas where we had consensus and then maybe, at that point, address whether there are other issues that we want to tee up for subsequent meetings.

Do you want to do that? Should I try to do that? I think that I heard a consensus that we should formulate a broader expert group in the biomarkers area to help us focus there rather than trying to do that job ourselves.

I had a question, I guess, about the mechanism by which we might do that, whether we are going to do that,

whether we are going to go the full route that I talked about before. I don't know if I should inject a personal opinion at this point, but clearly we had that consensus, that we should move ahead, that we should assemble a broader group of people on biomarkers and then try to have them focus on the areas for sure where we would pursue this formal constitution of specific expert groups via the mechanism that I outlined early, I think.

I think I heard, but I am not 100 percent sure, that we should do a similar thing in the imaging area. I think it was a recommendation that David made that we should pull together people both from the imaging technology area and the clinical application area and try to identify knowledge gaps in areas where these technologies ought to be being applied in the nonclinical area that is our purview.

I think I would add to that, I didn't hear it in the discussion, that we would need to have the appropriate nonclinical people as well to do that, to have an appropriately constituted group.

There was a recommendation about facilitating communication about the imaging technologies. Again, I might ask the committee members to clarify for me this but, I think I heard two different recommendations. In this discussion, I heard that there would be a value to the scientific community to communicating some of these things

out to professional groups like SOT.

During the earlier discussion, there was the issue of internal communication about application and development of these. I am fuzzy on these. I am not sure exactly how that part would be done. We didn't discuss it just now so I don't know if that is a recommendation.

So I guess I see two specific recommendations; that is, to get broader groups of people together to peruse these two general topic areas, the biomarkers and the noninvasive technologies and to come back for the next meeting with some more specific recommendations on specific expert groups to pursue specific things that would come out of this broader group.

I guess I have a question for Kimberly. Can we do that off-line? Can we get experts off-line to make recommendations to us at our next meeting?

MS. TOPPER: Yes; you may, as long as you don't use SGEs in the process of doing it.

DR. ANDERSON: May I ask a question? The groups that you get together, would they have the benefit of the document that we had which lays out the objectives of this committee so that they will understand what we are interested in achieving?

DR. MacGREGOR: Sure. Absolutely. So then, just to restate what I am thinking is that we can do a little bit

of off-line homework and come back to our next formal meeting with some specific recommendations on how to pursue specific expert groups in these two topic areas; is that fair?

DR. DOULL: Let me just add, Jim. I teach pharmacologists. I teach toxicologists. And I know both of those groups are not nearly as knowledgeable--in fact, their level of knowledge about imaging and so on is abysmal compared to what their need for that kind of knowledge down the road will be, clearly, from what we heard.

Those are the groups that I am saying, if that is the disciplines that are lagging behind, we need to begin to figure out ways in which we can help them catch up. I think it has got to be through professional societies, through students, whatever.

But I think we need to try and figure out how we can do a catchup program for those people. They need it.

DR. CAVAGNARO: Now I will add my personal comments. Being an original member of the CDDI committee and on the steering committee, it has been a long hoe. We have been the group that has broken away and has actually accomplished something.

When you say search for another committee to look at something, I guess, I have a little pause because I think that much has gone into the proposals that were on the

table. I just feel like they were--it is always when you don't want to kind of deal with something, you just start another committee.

I don't know if we have voted on it and it is passed, or whatever, but there are a number of initiatives going on. ILSI, we mentioned. And, again, whether or not Frank just has the resources and this is his particular biases, I really think that each of the areas are at least important in some aspect.

How generalizable, I don't know, but I would like to propose that we, as a committee, work with the ILSI or other stakeholders that have some information base. We could look at these particular endpoints as a prototype and set up criteria and then decide that maybe one drops out and, in the meantime, we will have thought about--something else might have come up and we can identify experts.

It is precisely what you mentioned in terms of understanding drug development. We don't only need the experts who understand the nitty-gritty about the technology but, unless they are in a room and understand drug development, we are never going to be able to talk.

And you are right. They not only have to have this book but, if they read this and they are not used to drug development, I am not sure what reading--what are they talking about. It is almost like they need a tutorial about

leveraging discovery research into development and then to provide their expertise.

So I don't know if we made a formal proposal, but I just think that we have come a long way and it scares me to think that now we are going to set up another committee who now has to be educated in terms of what our intent is.

I don't know how--maybe we can be pretty wrong. I don't know. But I think we would be fairly close to at least something useful to put on the table for, again, discussion but I think people in this room, the experts on this committee as well as the ILSI group and other groups have thought about this a long time.

I think to put at least a stab together and then have it massaged or matured or something like that. I don't know what to say. But the thought of leaving here after this work has gone on and all this research and to think that, Frank, you are not going to go troponins or anything but, now, people think you should do nephrotoxicity and neurotoxicity--now we are taking a piece of what is important and that is the FDA research.

That is my personal comment.

DR. DOULL: I hear Jim saying that what we need is to kind to massage what we got today. I am a little hesitant to take the recommendations which we just got today and move them into action until we have had a chance to

think about them a little bit.

That is what I understood Jim to say is that we will look at these--we have a bunch of proposals, as a matter of fact, recommendations and so on. Hopefully, we would coalesce those in some way that would bring together what you are saying. I am sympathetic to what you are saying.

DR. DEAN: To frame the recommendation of Joy a little bit further, because I think she is kind of where I am at, is that maybe we could have a teleconference in the near future of the members of this committee, some of the people who have presented today. It would be nice to know what ILSI considers the gap in the ILSI study. We know that paper is now in draft and some of us have it, what Joe thinks the gaps are, what Frank thinks the gaps are.

There may be others. And then, with a teleconference, we could narrow this down to two or three that we might be able to approach. Then, before the next meeting of this committee, you could actually get the working groups--you could get some names for working groups and decide where to go.

If not, we might miss a whole cycle of getting anything done. The ILSI project has already started going in one direction and I hate to see us--two meetings, now; is that correct, Gwyn? So we could lose another six months.

Maybe we can shorten it with a teleconference.

DR. DOULL: That sounds fine. Can we do that, Jim, go ahead and put together the recommendations that come out of the meeting today, massage them somewhat and then, in a teleconference, talk about those and which ones we would come down on, so to speak.

DR. MacGREGOR: That is absolutely fine with me. Are we permitted to do that?

MS. TOPPER: If you hold a teleconference, everyone in the world who might have any interest in it has to be asked to participate because you have more than two SGEs with this committee. You can work with a couple that are expert in this area, a couple that are expert in that area, any of the industry people because they are not SGEs.

But if you make decisions that are going to affect this process and this subcommittee, it has to be done in public if there are more than two SGE's participating. So you need to make sure that we don't break any of the FACA rules. I will make sure you don't.

DR. MacGREGOR: Let me just say that I purposely have held back a little bit in voicing my opinion on where I think this committee should go at this point because I had a fairly major role in bringing forward the focus areas that are presented. But I would say that I basically do agree with Joy's comments that we have been working on this for

quite a while and there are a few specific things that could move forward.

It would be nice to move forward with things we all felt were pretty strong consensus items although it is important to be on the right track. So I wouldn't want to push the committee past where the committee feels comfortable.

So I guess the mechanism, maybe in rethinking this, I am wondering if we shouldn't try to move to another fairly rapidly scheduled public meeting of this group having solicited the input that was discussed from the internal FDA groups and ILSI and so on that could be considered then, and then maybe we could move forward without having to go to a broader group.

DR. DOULL: That sounds like a motion. That is a motion for a consensus. That would meet your concerns, Joy. I think that is the plan. You will let us know when all this is--Kimberly will let us know when all this takes place.

Any other items from the subcommittee? I thank you all for coming and you are hereby adjourned.

[Whereupon, at 5:26 p.m., the committee was adjourned.]

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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