FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

8:37 a.m.

Friday, October 20, 2000

Jack Masur Auditorium
Clinical Center, Building 10
National Institutes of Health
900 Rockville Pike
Bethesda, Maryland

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C O N T E N T S

P R O C E E D I N G S

(8:37 a.m.)

DR. PACKER: This is the 91st meeting of the Cardiovascular and Renal Drug Products Advisory Committee. Today's topic is a discussion on the need and mechanisms of defining dose-response relationships in the evaluation of drugs for the treatment of hypertension.

The nature of today's discussion does not deal with a specific product, although there will be examples of data that has been collected from earlier development programs, although the drugs involved in these earlier development programs will not be specifically identified. So, there is no approval or nonapproval that is required from the committee in terms of a recommendation.

That is being sought from the committee today is a sense as to what direction this area should be moving towards, and we will have a very good discussion about the principles involved, the issues involved, and we will try to address many, perhaps most of the questions which have been posed to us in the time that is allotted to us.

I will have Joan read the conflict of interest and the administrative matters for today's meeting.

MS. STANDAERT: Thank you.

The following announcement addresses the issue of conflict of interest with regard to this meeting and is

made a part of the record to preclude even the appearance of such at this meeting.

In accordance with U.S.C. 208(b), general matters waivers have been granted to all committee participants who have interests in companies or organizations which could be affected by the committee's discussion of dose-response. Copies of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, room 12A-30, Parklawn Building.

With respect to FDA's invited guests, Dr. Donald Rubin has reported interests which we believe should be made public to allow the participants to objectively evaluate his comments. Dr. Rubin would like to disclose that he has minor holdings in various drug companies. He consults for Amgen, Pfizer, Merck, and Roche. He also speaks for Pfizer, Merck, and Roche, and serves as a scientific advisor to Pharsight.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask

in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

This is part of the public record on the 20th of October 2000.

DR. PACKER: The committee needs to receive a charge and an introduction about the events that will unfold today, and I'll ask Ray to introduce today's topic and describe to us what is going to happen and what he expects from the committee.

DR. LIPICKY: I think I can do it from sitting here, but I will need to see the slides that start at 60. If you can show the first slide please, and then I'll ask you to advance the slide because the podium is occupied.

We have three individuals who have agreed to come to a rather loosely structured meeting that has no singular objective, but rather to get involved in a discussion of the need for dose-response and how one might go about evaluating dose-response. I thank them for that because they've taken time to come as far as from California with really no real agenda and no real purpose except to get involved in some intellectual discussion about stuff that we're not sure anybody is interested in.

So, that is the purpose of the meeting, and if we can see the next slide. The reason that it's the

purpose of the meeting is because when one writes a prescription, there are really only two parts. You have to decide what drug you want to use and ordinarily the committee is involved in deciding whether a drug can be used or not. But once that decision is made, the only other decision left is the dose and/or dosing interval. I hope that we will be able to convince the committee that current developing programs don't define that and that if one thinks they do, they don't know what they're talking about. And there has to be something new and different thought about and done in order to handle that properly.

So, we'll be talking about development programs, and in particular, we'll be talking about, I hope, what properties of the drug with respect to dose ought to be defined in a development program. I don't think that's very clear at the moment, and maybe by the end of the day, it will be a little clearer.

The notion is to evolve a framework of reference. I know my framework of reference. Each individual up here knows their framework of reference. How do you approach this? How do you look at it? What do you want to get? What do you want to know? How should you go about getting it? And the question is whether anybody's framework of reference is the same. We want to explore that and find out whether what is where and what is how.

I think that there are no rules. There's an agenda, but I'm not sure we'll stick to it. There are questions. I'm not sure they'll get asked. But I think the notion is that whatever interaction seems to be necessary ought to occur, and if anybody who is talking says something stupid, they ought to be called on it. Otherwise, the framework of references won't evolve properly.

And that is the purpose of the meeting.

DR. PACKER: Does anyone on the committee have any questions about what this is all about? If you do, you'll find out shortly.

We'll move forward to the first presentation, which is by Carl Peck. It's going to focus on does the current development find the right dose.

DR. PECK: Thank you, Dr. Packer and Dr. Ray Lipicky, for inviting me to present my views about this important subject today.

I've been challenged to lead off with a brief discussion concerning the question, does current drug development find the right dose? I'm going to answer that question in the end, but first I'm going to pose five sort of leading questions that I think provide a background for being able to provide an answer. These questions will be: What do we mean by "right" dose? Is there regulatory

encouragement for finding the right dose? How good are approved doses? How good are dose-response studies? What might be the consequences of getting the dose wrong? And after I've answered those questions, I'll then provide my view of how well we're doing.

What is the right dose? Well, my personal view -- and this reflects practice of medicine many years ago and several decades of trying to get the right dose for others -- is that right dose will be a range, not a single dose, but a range of safe and effective doses which is accompanied by information for achieving benefit in individual patients. So, the emphasis here is on a range of doses and on individualization of the dosage.

That leads to the desirable features of an adequate drug label. In my view, there ought to be quality dose-response information displayed prominently in the label so that the practitioner can understand the linkage between dose and effect and the covariates that affect that.

There should be specific instructions relating to a safe starting dose that are keyed to individual patient characteristics when appropriate, such as age, gender, body size, ethnicity, concurrent medications, concurrent medical conditions, and severity of the disease being treated.

After the dose is started and monitoring has occurred, then there ought to be some advice as to how to adjust the dosage upwards, in the case of inadequate effectiveness, or downwards in the case of an adverse reaction.

Finally, in italics I've got that labeled dosage should remain stable. In other words, there shouldn't be a dosage recommendation that's changing over time. I'll get back to that because this comes closest to what we've discovered as a method for evaluating the adequacy of current approved dosages.

The second question is, is there regulatory encouragement for getting the dose right? Well, in fact, there's at least a century of regulatory encouragement that began at the beginning of the last century with requirements for truthful labeling and, more particularly, in the mid part of the century, the emphasis on safety; in the 1960s, the emphasis on effectiveness; and during the last several decades, a move toward emphasis on individualization. Perhaps in the future, there will be an even greater step when genomic information becomes importantly available for personalization.

But this is just not a theoretical concept. There are literally tens of thousands of pages of regulatory guidance in this country and in Europe that give

instruction and counsel on how to get the dose right.

FDA realized in the late 1970s that there were severe imperfections in dose finding in drug development, and that led Bob Temple and Ray and others in the early 1980s to begin to publicly discuss the matter and to move toward written regulatory guidance. I'm citing here a DIA journal article that Bob wrote in 1982 and a chapter that he wrote in 1989, which are rich in information advising on the qualities of titration in parallel dose-response trials that, surprisingly, don't seem to be well-recognized even today.

There's a multitude of FDA guidelines. The ones that I would cite here that are particularly applicable are the guidelines for format and content of the clinical statistical sections of the new drug applications published in 1988 and the geriatric guidelines published a couple of years before, specific information on dose-response trials. And several International Committee on Harmonization guidelines that basically reflect the FDA guidelines, the geriatrics guidelines, general considerations for clinical trials, ethnic factors, and one specifically entitled dose-response information to support drug registration.

In my view, any serious practitioner of drug development science ought to have read this document, the

dose-response document, and know it really well, because it contains contemporary knowledge on this subject.

Here's the way that document starts out. It says, the purpose of dose-response information is to express knowledge of the relationships among dose concentration and clinical response, the importance being that it leads to safe and effective use of drugs in individual patients. It goes on to say that this can help to identify the appropriate starting dose, the best way to adjust the dose to the needs of the individual patient, and increases or decreases as needed.

Now, the next question I wanted to consider was how good are the first approved doses. Remember I said that a desirable feature of a drug label would be that it doesn't change over time. Well, here you're going to see some real data, not just hortatory comments.

We've been undertaking a study in our Center for Drug Development Science at Georgetown University of drug doses as first approved. The principal investigator on this is sitting in the audience, Mr. Jamie Cross. He's been assisted with this study by several other post-doctoral fellows and faculty and staff of our center.

The purpose of this study was to evaluate all 499 approved new molecular entities that were approved from January 1980 to December 1999. These are U.S. approvals.

The study has a very simple design. It seeks to capture the dosage recommendations for the first approved indication in the first approved label and to compare that dosage recommendation with the current recommendation in the approved label. Not so simply done, however. Of the 499 drugs, we've only been able to find actually both labels for 354 evaluable drugs. We've used every possible source of information I believe known. We've gone to the Physicians' Desk Reference. We've gone to FDA. We've gone to multiple Internet sources. Some of these simply fade away. Ray and I were discussing and confirming that between us this morning.

Nevertheless, we've got over a 70 percent representation here. What we've found is that 1 in 5 of the approved dosages during this two-decade period have undergone a dosing change. That's 79 out of 354, 80 percent of which were dosage reductions. So, there's a systematic error in dose finding, it appears, that's leading to a dosage reduction. We concluded from this cohort as a whole that premarketing drug development is improvable with regards to safe doses.

Now, that might not interest you as much as antihypertensive drugs, which is in fact the focus of this particular committee's work at present. During this period of time, there were at least 34 new antihypertensive drugs

approved. This is probably a pretty accurate figure. There were at least 9 label dosing changes, which is about 1 in 4. 8 of those resulted in dosage reductions of 33 to 50 percent, or a contraindication from a previously approved cohort of subjects, or a full-market withdrawal because any dosage was considered to be unsafe.

This is the list of those 9. The panel on your left contains those labels that show a change in dosage of the starting dose. You can see, surprisingly, there's one in which the dosage has been increased. That is, there's been an expansion of the dosage allowed for the first dosage. But the other 5 have had a 30 to 50 percent decrease, two of which Ray tells me -- these are the asterisks, captopril and indapamide -- were a result of competent dose-response trials done following marketing approval.

Now, the other 3 you might find arguably included here. Maybe these are oranges rather than apples. Mibefradil you know only too well was completely withdrawn from the market because of its liability in certain drug-drug interactions, especially for lipid-lowering agents, and lisinopril and enalopril have had a specific contraindication announced for subjects that have angioedema with ACE inhibitors. Even if we take these out, this still results in a 17 percent of new antihypertensives

that have undergone a dosing reduction.

So, in summary, for antihypertensive drugs, 26 percent underwent a dosing change, which is about the same as the 22 percent for all drugs. 90 percent were reductions, which is comparable to the 81 among all drugs. So, I would propose that antihypertensive drug development is no better than or no worse than drugs in general. So, there's perhaps a systematic error in dose finding across the whole of drug development.

Now, the question is how good are dose-response trials. Let me say that I believe that there were few proper dose-response trials done before the decade of the 1980s. I think that's what motivated Bob Temple's articles and the plethora of regulatory guidance.

In our center, we study contemporary drug development practices, and to date we've had an experience in over 160 IND programs with over 60 companies. So, we get a peak into how many clinical trials are being done, what the nature of those trials are, and here's a snapshot.

Current NDAs continue to employ very large numbers of clinical trials, typically 25 to 100. It's phase I and phase II and phase III. We're seeing a remarkable fraction of phase IIb -- that's the dose finding in phase II trials -- are randomized, blinded, controlled, dose-response trials, typically parallel dose-response

trials. What's amazing to us is that most of them are analyzed as hypothesis-testing trials using only comparisons of each assigned dose against placebo or sometimes against each other. Few studies are thoroughly analyzed for the shape and location of the dose-response relationship or for covariate influences even though the studies are designed in such a way as to make that an appropriate statistical assessment.

A few years ago, Hans Melander of the Swedish Medical Products Agency presented a study undertaken in his own statistical section of dose-response trials submitted to their agency in the early 1990s. They documented 46 dose-response trials that were submitted during this time period. 20 of the 36 used only pair-wise comparisons in the analysis of the data. 19 of those 20 used unadjusted multiple comparisons in arriving at their p values. Almost all of them were overpowered for assessing the significance of a dose response, a linear dose response, and only 10 of them actually had any kind of a dose-response analysis or regression analysis undertaken to evaluate the shape and location of the dose response.

Informally, I've heard from colleagues at FDA that the situation is very little different here, and we certainly see this in the companies that we work with, a very inadequate analysis of dose-response trial data.

The next question, what will be the consequences of poor selection of dose for the label? Well, clearly patients who get the wrong dose, especially if it's high and if 80 percent of that quarter that undergo a dosing change are high, then there's injury. Moreover there may be suboptimal effectiveness. Some patients may be denied the opportunity to benefit from the drug if they're withdrawn from the drug because the dose was too high.

Manufacturers encounter liability.

Erosion of pricing, and I would think at this moment in time, this should be particularly important to manufacturers since pricing is often based on the first marketed dosage, and if you must reduce the dosage, you can take the bottom out of your profit margin.

Increased costs by having multiple dose-response trials that are not fully exploited for the subsequent trials, and then, of course, the post-approval costs.

Regulatory agencies can be subject to criticism and loss of public confidence with drug withdrawals or drug dosage changes.

So, the question I was asked to answer, does current drug development find the right dose? Well, you could say most of the time, although let me say that the

study that Jamie Cross and the rest of us are undertaking is not clear on that yet. This 20 to 25 percent dosing change rate is for the whole two decades, but we're doing some Cox regression analysis on these data using epoch or decade as a covariate. And we're discovering that the rate of dose changes is higher in the decade of the 1990s than in the decade of the 1980s. That doesn't mean necessarily that the effort is any worse, but we're picking up dosing imperfections and making label changes seemingly more frequently.

Dose changes that are too high can harm patients. There's no doubt about that.

The rate of dose approval changes, 20 to 25 percent, including antihypertensive drugs, can be improved, and it's the purpose of this day to discuss some approaches for doing that.

Finally, regulatory guidance is ubiquitous, but for some reason these trials continue to be inadequately analyzed and that information is inadequately exploited.

Thank you very much.

DR. PACKER: Does anyone on the committee have questions for Dr. Peck?

I have a question. The definition you use in your study of determining whether the right dose was found is a ratio of a denominator over a numerator where the

denominator is all of the new chemical entities, for example, approved for the treatment of hypertension and the numerator is all of the drugs that have undergone labeling changes.

Excluding the three drugs for which a dosing change was not really part of what happened -- it really was withdrawal or some other major event -- you have six drugs that underwent labeling changes. Were the labeling changes, in terms of dose, for the general population or for subpopulations?

DR. PECK: Those five --

DR. PACKER: It's six I think. I think it was six and three.

DR. PECK: Six. One was an increase, yes.

That was in the first dose section of the label, and that would apply to all patients. I think that two of them actually referenced patients with renal dysfunction and so there was significant dosing adjustments for renal dysfunction. So, it was, in effect, a discovery postmarketing of a significant covariate that had not been taken into account. So, in my view that's part of the dose-response issue, identifying the right dose for the right subpopulation.

DR. PACKER: The reason for asking the question is it was also my impression, by just looking at the

examples and relying on memory, that many if not most of the six examples or five examples were dosing adjustments in sub populations as opposed to an overall population, which now addresses another layer of complexity. It's not dose response for the general population; it's dose response for an increasing number of populations of interest. So, it's not only patients with underlying comorbid disorders, it's not just demographic distinctions amongst populations, and that increases the number of complexities. And frequently the development program for dose response is not a development program for dose response in subpopulations. It's for the general population. So, we wouldn't be too surprised to see that there may be tweaking of doses in subpopulations.

So, a more interesting or perhaps more targeted question is, how many times were there adjustments in the general population in dose response. Just looking at this, my sense is that it only applied to maybe two of the examples. That would make the denominator now quite small.

DR. PECK: Well, you're more forgiving than I am. Actually the data is that of the six dosing changes, only two were in the subpopulation of patients with renal dysfunction. The other four were for all comers.

However, this particular subpopulation, patients with renal dysfunction, we've known for three

decades is a special population, that any drug that has any significant excretion to the kidney should be taken care of. So, it's not so much, I think, a layer of complexity. It's routine clinical pharmacology. It's what most development programs discover in the phase I and, for some reason, forget when they get to phase II and phase III. So, I think it's a matter of awareness and interpretation of this knowledge rather than anticipating an increase complexity.

DR. PACKER: Okay. Lew, do you want to start, in terms of the discussion?

DR. SHEINER: I just wanted to make the point that I think this study is a useful study, but I think we have to regard it as sort of the tip of the iceberg in the following sense, than an official label change of dosage is unlikely to occur unless there's a safety issue. So, a drug, if it's essentially nontoxic, that comes out at a dose that's three times larger than you need and then gets lowered and winds up having economic consequences for the manufacturer and in some sense we'd like to use the least dose that will do the job because there's a general bias against giving excessive doses, but I don't know that they would show up as labeling changes.

DR. PACKER: Ray?

DR. LIPICKY: Well, the other thing is I think

the idea that renal problems or deficiencies in eliminating the drug are well known, and sometimes at the time of writing the initial label, one forgets to put that in. I guess there are people in the audience who might know the answer for the ones where there was dosage reduction. I don't know if that came from studies, adverse events, or, geez, we just forgot to put that in, we ought to. Does anybody recall?

DR. PACKER: I'm not certain that we can poll the audience.

DR. LIPICKY: Well, no. The audience could too because probably somebody knows the answer to that.

DR. PACKER: The one thing that strikes me as being interesting about the renally impaired subpopulation is the fact that this committee, to my knowledge, although we've seen a fair number of dose-response studies, we have never seen a dose-response study in patients who have renal disease.

DR. LIPICKY: Right, but you do see biopharmaceutics, pharmacokinetic studies in people with renal disease, and every question you are asked asks you to think will this influence the dose response, but you never do.

DR. PACKER: But what we see are studies in an extremely small number of patients with renal disease,

usually like 20 or 30. George is saying, well, even less than that, but that's okay. Usually all the patients who have renal disease are lumped together as if they were one kind of patient, and some formula based on creatinine clearance or something else is determined that allows for "dosing adjustment." We don't get dose-response information. We just get crude reductions in dose based on reductions in renal clearance of a drug. My sense is that that has been "satisfactory" up to now. Is that wrong?

DR. LIPICKY: Well, I think we are here to ask you whether that's wrong. You have described the practice properly.

DR. PACKER: George?

DR. BAKRIS: Since Milton threw the question down, Ray, I'll answer it. I would agree with Milton a thousand-fold and say that, in fact, the papers that I've reviewed for clinical pharmacology journals do exactly what you said, Ray. They look at pharmacokinetics and they look at mathematical models and they look at n's -- I thought Milton was being very generous talking about 30 and 40 patients. I'm used to seeing single digits in each arm. That's totally inappropriate.

Frankly, the renal insufficiency seen in diabetes is totally different than the renal insufficiency seen in heart failure in the sense of the mechanisms may be

but the duration and natural history is different. Certain drugs, for example, ACE inhibitors, to my knowledge, that are renally cleared may accumulate more, but I'm unaware that there's any substantial side effect profile seen. Other drugs clearly do have that, and certainly in the transplant setting, that's important.

So, I think Milton is right to say this is extremely complicated, and I think the whole focus on patients with renal insufficiency needs to be looked at as a separate entity practically or at least a parallel entity to the general population rather than doing these certainly inadequately powered window-dressing type studies that are put in there just to give you some pharmacokinetic data because the pharmacodynamics is absolutely important in those people longer term.

DR. LIPICKY: Well, there is an important distinction to make and I think we need to have that out in the beginning. Clearly defining dose response for anything, whether it's an antihypertensive or anything else, might be able to be done in a fairly efficient way so that for the molecule and for some patient population, one knows what's going on.

Clearly the business of what is the "clinically relevant" outcome isn't known from those studies. So, if the notion is that one needs to know the clinically

relevant outcome with respect to dose, we will talk about that, hopefully, today somewhere late on.

But for the moment -- and maybe that's what the complaint is for the renal problems -- I'd like to keep the discussion focused around how you tell dose response, because with the clear recognition that that tells you one very small part of what you really want to know. The question is, do you want dose response in every subpopulation? If that is the issue that's in front of us.

DR. PACKER: Jeff?

DR. BORER: I'd like to ask what information you have, Carl, about the problem or situation that you touched on but didn't give us any data about, probably because there aren't any, and that is the other end of the spectrum, that is, labels that are written for doses that actually are less than, could be safely given, at least to some people, with increasing benefit.

You noted that one of the drugs on your list actually had a labeling change to increase the dose. My perception is that there are other drugs -- I won't say many -- for which the dose that's commonly used probably exceeds the label as it was first written. I'm thinking, for example, of diltiazem particularly, but there are others. That may not seem like so much of a problem, but it sort of is because there are potential benefits that

aren't known and there are patients who don't benefit optimally, though they're taking a drug, because the dose-response curve hasn't been explored to the high level.

The usual argument seems to be, well, we know there are side effects up there, so won't be marketing at that level because if 50 percent of the people have side effects, they won't take it. Or we have to study too many people at too many doses to be able to determine safety at the high level, which is different from determining the dose-response curve.

So, I wonder if you have any information about how many drugs -- this may be impossible to determine -- are being used commonly at doses higher than the label because of experience plus published literature. The label may not have been changed, so it wouldn't show up on your chart, but it would still be the wrong dose and it would be unfortunate that that is the case. I believe it's the case. What do you think about that?

DR. PECK: Our study would capture a label dose increase.

DR. BORER: No, no. I'm saying you would only capture a label dose increase.

DR. PECK: I'm affirming your comment. It would not be able to capture the practice of deviations from the labeled dosage. I'm sure you're correct, that

there are wide deviations from the labeled dose that are being practiced.

DR. BORER: Well, my question really is, is there something we should be doing about that in terms of guidance or requirements or whatever so that the upper levels of the dose-response curve are explored more fully, even just to provide information, even if the company isn't going to market at that level?

DR. PACKER: I'd like the committee to, in general, until the next discussion period, hold questions about potential discordances between what a drug is labeled for and how it is used by practitioners. I think that's an important issue, but it is more appropriately handled in the next discussion period rather than this discussion period. So, Jeff, hold that thought. There are many related thoughts to that.

DR. BORER: It's held.

DR. PACKER: We'll bring it up.

Marv and then Tom. Carl, I'm sorry. You wanted to answer the question?

DR. PECK: I have a comment to make but I'll take my turn.

DR. PACKER: Okay. Then Marv, Tom, Carl.

DR. KONSTAM: I'd like to understand how much of the problem is a function of population dose response

and inadequate exploration of population dose response and, therefore, fixable with full exploration of population dose response, and how much of the problem might be related to distribution of responses within the population. I don't necessarily mean definable subpopulations.

But actually in one of your constructs, you talked about individualization and maybe you could expand on that because dose response with regard to hypertension was a really good example. Dose response of a population with regard to a certain millimeter mercury change in blood pressure in no way really describes what's really going on from patient to patient. There may be huge variations in response within an individual. I wonder if that kind of information is being fully captured in NDAs, and is it important?

DR. PECK: My view is that the data is being collected. Contemporary clinical trials are extremely burdened with data. The analyses are pitifully meager relative to the data that's collected. The typical phase III trial is viewed as an intention-to-treat hypothesis test with literally thousands of data items collected per patient but only a very small fraction actually used in the statistical test of interest. Not that that's not unimportant. Confirmation of effectiveness and documentation of safety is important, but there's a gold

mine of relationships that is typically unexplored. We'll hear a lot about that as the day proceeds. It's subject to issues of causality and randomization and so forth. But nevertheless, your basic point I think that I'm supporting is that there's a huge amount of data available for evaluation that is simply left alone.

DR. SHEINER: Let me just make a quick response to that, as I'll define later. I think we should, in fact, take the point of view that you're taking. That's the entire distribution of responses to doses that we're after, not just the mean. And how we might get that is a more technical issue, and Carl is saying the data might already exist or we might have to change what we do. But there's no question that the distribution is what's of interest, not just the center.

DR. PACKER: Tom?

DR. FLEMING: Carl, I'd like to maybe expand on your opening summary here in terms of maybe defining what the problem is and defining what the strategies or approaches would be. Some of these elements you have already identified.

It seems to me the challenge is quite broad. Certainly part of that challenge is finding the right dose. As you pointed out, though, it might actually be a reformulated, though, as what is the right dose

concentration in blood. There's also the question of what's the right schedule. What's the right route of administration? Within schedule, what is the right frequency or what's the right duration of administration of an intervention? Related to the drug concentration in the blood, it might actually be do you dose to a given achieved normalization of a marker like hematocrit.

There is a huge array of specific challenges that I've seen in various settings, and often when we think what's the right dose, we're really just looking at one element of a huge array that define the options that one could use in formulating a regimen. So, I'd like to just expand on what you've already articulated to say that the challenge is enormous in coming up with the right specific regimen formulation.

In terms of the solution, certainly the strategies that are in place right now are attacking this problem, obviously as you would point out, not fully efficiently at an array of stages, at the preclinical stage in phase I and IIa with PK and early safety and biologic activity measures and in phase IIb and in phase III. So, the question is, as I see it, ultimately as you're attacking this very broad problem of identifying the right regimen, there is the whole myriad of the drug development phases that could be approached in terms of defining how to

best do this.

Very much too, it becomes an issue of confirmatory versus exploratory which was also just pointed out. I think what we do frequently in the phase III trial is we do try to focus, if at all possible, on an intention-to-treat or hypothesis testing stage. At least in my experience, the myriad of issues that have to be addressed in formulating the right regimen are, as much as possible, relegated to the stages that precede the confirmatory step. Right or wrong. But that's in fact the way I've seen the strategy approached.

So, ultimately today it seems to me that we ought to be looking at the totality of this issue of finding the right regimen and then also recognizing that the strategies that we use ought not be focused just on what we do in phase IIb or phase III but in all of the phases.

DR. PACKER: I think that's true.

Carl, I know you wanted to add something, but my sense is that all of the points that have been raised thus far are just the first step in a much greater process that will unfold quite quickly. With everyone's indulgence, what I would like to do is for everyone to hold their thoughts and go on to the next presentation when these ideas will be developed more fully. We will have

more specific examples of issues we can focus on going forward.

So, Ray?

DR. LIPICKY: Thanks.

Can I have the first slide please? I guess what I'm going to try to do -- and I don't know whether I will do it very well is to say that our guidance in this area, whether it be explicit in words or implicit in written or spoken, what we're doing is giving bad guidance. The question is whether in the final discussions today you'll agree with that.

In particular, for hypertension, we focused on it because it's an easy thing to measure. It's a continuous variable. You can play games all you want, and it's not an irreversible thing that one is dealing with. But I think the principles that apply here are the same as you would apply in any other field for any other purpose. So, it is focused on hypertension, but it isn't meant to be exclusive to hypertension.

There is no such thing, I will assert, as a phase III trial for antihypertensive drugs. Antihypertensive drugs get approved for dose-ranging trials. That's classically thought of as phase II and there is no morbid/mortal trial that is required to get an antihypertensive drug approved.

So, I think the thinking process should change from what do we do in phase I, in phase II, phase III, to what are we trying to accomplish in this development program. Indeed, one of the major things is to define dose response. That indeed is one parameter. Maybe then there should be a phase III in antihypertensives, but at the moment, the whole development program devotes itself to finding a dose.

So, what we did, with the help of the Office of Clinical Pharmacology and the two individuals that are named there, is embarked on looking at what we have gotten in the way of dose response from our trials. What we generally recommend is parallel fixed dose, placebo-controlled trials. There are 15 million other trials that could be done conceptually designed, but this is generally what we do.

If I show a slide, it is X, 3X, 10X, 30X, and usually everybody laughs. They say, yes, X, 50 percent more, 50 percent more, and 50 percent more. Basically they go from X to about 1.75X in the three arms, and that is a trial. So, then they do another and they do another and then they do another.

A successful development program looks like this where basically there isn't any question about what's going on, and there is an effect here and these data points

out here because these are called phase III even though they're dose response, are indeed statistically significant from placebo. So, basically the drug clearly works.

But the limitations of the drug as a clinical tool are very obvious: the side effects of the dose-limiting problem. Indeed, this point is statistically significantly different from that point.

But the thing that is convincing here is that the shape tells you the whole thing. The question is, is this point different from placebo or is this point different from placebo? The thing you get here is that this is the limiting factor and that there is a relationship to what you want in relationship to dose. I'll assert that, given a figure like this, I can make all the decisions I need to without a p value.

So, in fact, it leads to doses that say the usual dose is 5, the maximum dose is 10. The adverse reactions list adverse reactions for 2.5, 5, and 10. But since 15 milligrams is not part of the dosing information, the 15 milligrams adverse reactions are absent. In fact, that data point is the one that really convinces you something is going on. So, the most important part of this development program is left out of labeling. Our choice. We do that and I agree to doing that.

Then you get a thing that looks like this,

where there's dose here and decrease in blood pressure. All of the data you'll been seeing is parallel placebo-controlled, fixed dose stuff where the placebo arm's mean is subtracted from dose 1's mean, and then it's the delta of deltas. So, that's the data that is shown in all of this stuff.

Clearly there's a dose-response curve here. Every single dose, almost, with a couple of exceptions, as you go up is sort of bigger, and it even looks like it reaches the maximum effect. Then you just do a silly thing. You plot that same thing on a log axis, and all of a sudden, it looks like it's not increasing to a maximum. It looks like it would keep going up forever. All that's been done here is to go from a linear axis to a log axis.

So, you say how should I look at this. What's going on here? How come these two graphs look so different, if you're graphically oriented? Did it really get to a maximum effect? I don't know.

But indeed, what we do is we look at this data point and we say, before that data point might be approved, how many people received that dose? It might only be 50. In the event that only 50 people received that dose, we say, it's smaller than that, the point estimate. That dose can't be approved. So, we do some kind of funny stuff here even though this is all one nice continuous curve and there

isn't a dose-related side effect in the database. This is an ACE inhibitor. There isn't any such thing as there being a dose-related side effect that I'm aware of.

So, then you get to another guy, and again plotted there linearly, the data is all over the place. It's a bunch of trials, different dosing regimens, q.d., b.i.d., and so on and so forth. But the sense you get here is that it reaches a maximum. Semi-log doesn't really tell you much and you get very confused. At least I do. What's the framework of reference here? How should you plot this stuff? Is it really going to a maximum? Where are we on the dose-response curve?

But, indeed, some kind of dosing recommendation gets made, usual starting dose. Ignore the 9. That's a typo, and the total daily dose is from there to there. There isn't any data that justifies that outside of the fact that that's all the doses that were studied, so that's all you have information about. But it has nothing to do with the drug or the drug's intrinsic properties.

So, I need a framework of reference, and I say to myself -- and I have a problem. I use a Mac and when you put a Mac Power Point thing into IBM Power Point, the electrons don't flow right.

(Laughter.)

DR. LIPICKY: So, this is the number of drug

molecules here. There's supposed to be a drug there. This RD is supposed to be over there. So, it's the number of drug molecules interacting with a receptor with two first order reversible rate constants, because the universe operates that way. Right? Everything is first order. That leads to a dose-response combination, and it may be and drug-response, and that that's identical to the effect.

So, we can write that model. You can write equations for that model. You can put them in a computer and you get curves where you can vary the ratio of K1 to K2, and that's the affinity constant. So, as you change the affinity constant, the curve moves, but the distance from here to there stays constant, but the ED50 changes, if you would, or the affinity constant changes.

The thing to point out is nothing funny that has been done here. This model goes over a range of from here to one, two, three, four orders of magnitude. Not four times. Orders of magnitude.

Indeed, you can vary the number of drugs that attaches to the receptor, and then you get changes in slope. So, this model you can worry about where its affinity constant is and what its slope is. Those are the things that you can worry about.

If you have this kind of conceptualization in your head, you can say, well, this is the effect that I

care about. These are the bad effects. There are some red points there. And the distance in the ED50 between these two guys basically gives me the safety margin. Indeed, this starts here, so with this particular drug you'd have a pretty good effect before you got any adverse effects.

Now, the problem is that we see data that looks like this, and these four data points are those four data points from the previous curves. So, my worry is that if you don't see the whole curve, you don't know where you are because this looks terrific.

So, we said, well, the way you make decisions nowadays when you don't know what to do, you ask a computer. But computers want numbers and with numbers you've got to have equations.

So, we said, well, the simplest thing you can do is say that sum Y is equal to mX plus b, a straight line. That translates to an effect equals an effect at 0 dose plus a slope times the dose.

So, you can use this model to see if the data you have collected is consistent with the model. The behavior of this, when you plot it linearly, dose versus effect, look like that. If you plot that as log of dose -- the same data, log of dose -- versus effect, the curve looks like that.

Well, you can also say the effect is equal to

the slope times the log of the dose plus b. I should have written that differently. That translates to that equation that was put into the package that was sent to you. Now you have dose effect. That curve looks like that. If you plot it on a log axis, it looks like that.

Now, those are very different looking curves. So, you say to yourself, geez, I ought to be able to tell whether this model or this model applies to the data that I've obtained.

But then you say to yourself, yes, but this is stupid. This says that as long as the dose keeps going up, the effect will keep going up. And you know that's not true. You could be a walking crystal of an ACE inhibitor and your blood pressure is still finite. Right? So, that can't be a relevant model. That's just a stupid model. But it's reasonable to ask yourself can I tell that that model that isn't operative.

This guy has similar properties. As long as the dose goes up, the effect is going to keep going up forever. It has the unusual property that the 0 effect is not at 0 dose because there isn't any 0 dose on a log scale. So, you've got numerical problems here, and people who do numerical things don't like that.

So, you say, okay, it must be some nonlinear thing like the effect is equal to the effect at 0 dose plus

some complicated thing that contains the maximum effect and the ED50 and the dose. You can tell the computer for this model, that this is my data. I know this and I know this. Tell me what this is and this is, both E0 and slope.

Similarly, for the log thing. And here the effect is equal to this. So, you know this and you know this and that, and you tell the computer, tell me what the other things are. That's called overspecifying the model sometimes. That is, the data we're analyzing is placebo subtracted. So, we know what that number is, or it is part of the observations if we assign it that way.

But we didn't do that in this first pass, and I can say we have a second pass of the data that we sent out to you that, in fact, did not have an intercept term for either the linear or log linear or the Emax model. And the qualitative information you get out of looking at this data is exactly the same. The numbers are different and so on.

One minute longer here. When you tell the computer I know this and I know this, tell me what this is and what this is, the computer gives that to you with a confidence limit. So, from the data you have and this equation, you can tell how well you know that number, and you can tell how well you know that number. If you have two sets of data, you can even ask the question, is this number for the one set of data different from that same

number for another set of data with some confidence that you can, in fact, answer that question.

So, if you buy the Emax model, you can simulate it. In fact, the Emax model is here where this is a drug that looks like that from 0 effect to 100 percent effect, a drug that is less potent, but equally effective, that looks like that, then another pair of drugs that are less effective and they look like that and they look like that. But all of those drugs have the same ED50, if you would. So, you know what effectiveness is. This is less effective than that. You know what potency is. This is more potent than that.

And if one studies this drug at that dose and that drug at that dose, and finds that the two point estimates are different from one another, you know that that has absolutely nothing to do with effectiveness. And if you really wanted to know whether something was more effective than the other, you've got to have an appreciable part of the two curves to be able to make that differentiation. Otherwise, you are guessing at what is going on.

Now, this is exactly the same simulation, the same equation, the same ED50, everything else, but 10 percent of the baseline blood pressure was added as noise to every point estimate. Boy, you're less able to make

differentiations there. In particular, if you take any one section down here and you have three data points, you tell me that anyone would be able to tell you what's going on. That is, however, what we do and we label drugs because someone has three points there and gives that to us and we make sense out of it.

Then why do we want to know anything about what the maximum effect of a drug is? Well, in the hypertension area, our policy with fixed dose combination labeling is you should never use a second drug until you have explored the entire range of the effects of the first drug because you shouldn't expose people to two sets of the independent side effects. So, if we're serious about this statement, we ought to be equally serious about knowing what dose gets the maximal effect.

So, the notion then was to take the data we had and see what we have. So, if we could see the first overhead please. This is a graph of whatever the number of drugs that we had. This is all approved ACE inhibitors and/or angiotensin 2 receptor blocking agents. Don't pay any attention to the lines that are present on any of these graphs. This is linear scale.

A lot of these guys, data point-wise, look like they've hit a maximum effect. It happens to be that this line is a linear fit, and if you happen to do a linear fit,

in fact, the line goes through the points. Not too bad.

But if the same data is plotted semi-log, all of a sudden all of them straighten out. Indeed, the line that goes through the data points that is a log dose line, to my eye this all looks better than the first set of graphs did.

Then if you want to look at the Emax model, now you should pay attention to the line on a linear scale. Well, the Emax model line goes through the data points, more or less, when it's plotted on a linear scale, and it even looks like it curves. That's what we want to see.

Then when you plot it semi-log, it stills goes through the data points, but now the curvature in the wrong direction. What the hell is going on? So, then you say to yourself, well, how am I going to decide? This doesn't make sense to me at all. I'm at a loss. What does this data show?

Well, you go back to the computer and you say, tell me which of these models fits the data the best, because that's supposed to answer your question. You say, I ought to be able to tell a log-linear, linear, or Emax model from the data because the linear and log-linear models are obviously nonsense. They can't be applicable.

So, one of the ways you try to decide is to look at the objective function from this program and a

smaller number says you have fit the data better. Your model is more consistent with the data. Well, you tell me that any of those models are more consistent with the data than another. Maybe out here Emax does a little bit better, but otherwise any of those models are applicable. So, the data will not allow us to reject or accept a model.

You can look at another kind of how well does the data fit, which is the Akaike criteria. Here it's the same thing. You just cannot tell the difference between those models by criteria. You can look at the standard error of your parameter estimates, and all of those numbers were sent to you. The standard error of the parameter estimates are pretty big, so you'll have a lot of confidence in the parameter estimates you got.

So, the long and short of it is when you look at the data and you try to do something very simple but crude -- we did the wrong thing. We had the intercept in for all of this stuff. We shouldn't have had the intercept in. When you take the intercept out, it looks a little better but the qualitative thing doesn't change. Well, it says you can't tell. So, I hope you didn't spend a lot of time trying to figure out what those things tell you because you can't tell anything from them.

What that means to me is the data is not collected. The data you need you don't have. We have not

planned the experiment properly. We haven't made the proper observations.

So, then you say, I'm going to make the proper observations. I'm going to take this thing.

I forgot to point out. If you look at those data, most of that data goes over several orders of magnitude. We have one of those drugs that goes over three orders of magnitude. Three orders of magnitude wasn't good enough.

So, you start looking at what you got. You got a few orders of magnitude, and you're going to change dose by 50 percent increases. How many arms is that? Well, people tell you to go home, you're crazy.

Well, you can cover that same range with just six doses if you increase things by a factors of three. So, maybe that's how we should be thinking. If you're doing to do a dose-ranging trial, at least use factors of three because you can cover a wider range, if you think you need to cover a wide range. In fact, we have told people who just want to do two three-arm trials, placebo, dose, two times dose, don't do the two times dose. Pick dose or two times dose and put all your resources into a two-arm trial so you really know whether you found something or not because you're wasting your time studying two doses that are the same.

Now, I said things aren't planned right. Well, how should they be planned? The first statement is, why dose range? Whole curve. Big increments between doses. The second is, where on the curve should you collect that data? Over the whole curve or parts of the curve? So, if you have a model like Emax, and data that has error in it, you can say, if I pick this dose and this dose and this dose over the whole curve, does that give me better information than if I pick this dose, this dose, this dose or this dose, this dose, this dose, or this dose, this dose, this dose?

When you boil it all down, if the question you're asking is, I know this is an Emax model, because that's how I made the data -- it's got to be an Emax model -- and I introduce some error in the point estimates that is generated, and I want to reject a linear model or reject the log-linear model, because I know this is an Emax model, it turns out simulation 4, putting your doses there -- you only want to pick 3 -- gives you your best chance at being able to have data with noise in it that, in fact, allows you to make some decision. Any of the others are less adequate.

This just lays it out graphically where if you have an Emax model that you believe and you want to know the probability of rejecting the linear model, pick the

Emax model over the linear model. If you have simulation 4, and you do some Monte-Carlo simulations, you need a smaller sample size to have pretty good chance of rejecting it. If you do this simulation 2, this guy, you're not so well off, and the thing that you think would make you well off -- you have the whole limits together, the simulation 1 -- is not bad but not as good as if you just concentrate in some part.

Now, I'm not offering is as this being meaningful. In fact, it probably isn't and we probably should have done a different simulation, and we probably should do more work and so on and so forth. What I'm offering this for is that if you think you are going to analyze the data with a model, you think you know the model, in fact you have a pretty good idea of where you want to concentrate your efforts, and to put it in Lew Sheiner's terms, if you tell me what you want to know and you tell me the accuracy with which you want to know it, I will be able to tell you what you have to do.

So, the discussion today is sort of going to be you telling us what you want to know, and Lew Sheiner and Don Rubin telling us what you have to do to get it.

I'm open to questions.

DR. PACKER: I think what we need to do is pause and consider the issues that Ray has put forward

because, I think as Ray concluded in his closing remark, it would not be useful to go on to the next presentations until the committee concluded what it wanted to know. So, we need to focus on what we want to know. I think that the illustrations that have been made by Ray clearly identifies some of the inadequacies of the databases which have been presented for approval to date and the difficulties that are encountered in writing labeling based on the data which is presented.

There are, as I can see it, two somewhat different situations that the agency faces in looking at adequacy of dose response.

There are databases where the range of doses is limited by an identifiable and prohibitive adverse reaction, and you gave us one example of that. I think you emphasized that in spite of the fact that that development program did not cover a wide range of doses, it clearly identified a "safety margin," a relationship between the doses that define efficacy and the doses that produce an adverse reaction.

My sense, Ray, is that to the extent that most of the drugs that we have available for the treatment of hypertension have such dose-limiting side effects, that you have not been unhappy with the dose-response information that has been developed for those drugs that have dose-

limiting side effects. Is that a fair statement?

DR. LIPICKY: Right. I must admit that we generally ask people, although they don't actually always do it, to find a dose that hurts people and to clearly demonstrate it.

DR. PACKER: But I think that that's the point. Up to now, in order to qualify for what might be called the easier path, the path in which there is a dose-response relationship or any useful dose range, defined by a dose which produces an adverse reaction profile which is unsatisfactory, companies actually were somewhat grateful when they had a drug that produced a problem. I know that sounds a little strange, but their development was simplified when they identified a drug that produced a dose-limiting side effect that essentially capped the upper range of the dosing curve.

However, in order to identify that, they had to make some people sick, and the hope was they had to make as few people sick as possible, and that if they could do so and they could do so early in the development program, then the delineation of dose response was simplified.

DR. LIPICKY: Right.

DR. PACKER: The problem that comes to the fore is that to the extent that the pharmaceutical industry has now been increasingly able to develop drugs that may not

have dose-limiting side effects like ACE inhibitors and A2 antagonists, then the previous model of trying to define or guess at a dose that produced a problem was not workable.

DR. LIPICKY: Right.

DR. PACKER: And that is really part of the problem that we have today.

Let me just ask two questions so we can define the questions for the committee. In the model which is the more common of the two, where there is an AE that limits dosing, you can write labeling for use.

DR. LIPICKY: Correct.

DR. PACKER: However, to an increasing degree, industry is also interested in determining whether their drug is better than another drug, something that you hinted at when you showed two dose-response curves that had different effectiveness. And they want to say, well, our drug is better than another drug, and your response is, well, it's hard for you to say that unless you have defined the entire shape of the curve for both drugs and have shown me that your drug has a higher plateau, a higher Emax, that the slope of the curve is different than the slope of the competitive curve.

DR. LIPICKY: Correct. That is what my response would be as an individual. The agency's response, however, is that if a dose of a drug gives a better effect

than another dose of another drug, that is reasonable information to communicate. And if you show me two trials of such nature, you can communicate that. That is mistaken by many people as a difference in effectiveness.

DR. PACKER: Right. Your concept that, in order for a company to claim superiority, you need to define the entire shape of both curves --

DR. LIPICKY: Yes. You assert that.

DR. PACKER: How should that concept be modified when you have a development plan for both drugs that has a dose-limiting AE? In other words, since it isn't, as I understand it, necessary to define the entire shape of the dose-response curve, if you have a dose-limiting adverse reaction, can a sponsor claim superiority? You can clearly write labeling if you have a dose-limiting AE. Can you claim superiority if you have a dose-limiting AE if you compare the new drug to an old drug at the highest recommended dose?

DR. LIPICKY: Yes, I think so. To me the thing that you're asking is very complicated because it would require your knowing that the effect that you get at the best usable dose of the drug that has dose-limiting side effects, you'd have to have a pretty precise estimate of the magnitude of that effect. Then you would have to say that at some range in the dosing of the new drug that has

no adverse effect, dose-limiting side effect, that you know at what range in that dosing regimen you indeed exceed the effect of the other drug. Then you'd be able to say, I can produce a bigger effect than this drug, and more than that, I don't produce side effects, so you don't have to worry about it.

Did I answer the question you asked?

DR. PACKER: No. You may have, but I wouldn't know yet.

(Laughter.)

DR. PACKER: Let me try it a different way. It is possible for a sponsor to say that their drug is better than another drug -- and let's just say it has to be in two trials and it has to be persuasive, internally consistent -- either because the shape of their sigmoid curves are different and their Emax's are different or, in fact, their Emax's may be the same. But since one can push the dose of one drug higher than another because of the absence of adverse reactions, would you allow a company to claim superiority even if the shape of the curves were the same if in fact one could push to a higher dose with a drug that had fewer AEs?

DR. LIPICKY: I think so. What I was addressing was the difficulty one would have in getting that information. That would be hard to get that

information. But, indeed, I think if one showed that, that would be claimable.

DR. PACKER: So, the problem is not in the validity of the concept, but in the ability to get there.

DR. LIPICKY: The design and the analysis that would allow you to conclude that you, in fact, had that data.

DR. PACKER: And one couldn't simply do that by going after the highest dose of the comparator drug which is in their labeling? Because presumably you made an educated --

DR. LIPICKY: I would assert that that would not be an appropriate thing to do, but I would probably lose the argument if it went to the place -- here's what I'm saying I guess.

Incidentally, for conversations, there is transparency in ink and overheads because sometimes you've got to have the curves you're looking at because you don't know you're talking about the same thing.

But if drug A has the dose-limiting side effects and drug B does not, and drug B's dose-response curve goes to effect sizes that are substantively greater than the effect size of the usable dose of drug A, that would be fine. But it's the question of how would you tell it is substantively greater.

You're suggesting studying a dose of drug A and then a dose of drug B and then doing a pair-wise comparison on that. I think if I were pushed to the wall, I'd have to say, sure, that would be okay, but I'd try to convince you not to do that because that just seems slovenly.

DR. PACKER: Slovenly but not inaccurate.

DR. LIPICKY: Not inaccurate, right.

DR. PACKER: Okay. So, in fact, the development program that has a dose-limiting AE is not the issue before us today because you are comfortable with how a sponsor would define the appropriateness of use and therefore the labeling, and it therefore also becomes reasonable how one at least operationally, not ideally, would define differences between usable doses.

DR. LIPICKY: Right.

DR. PACKER: So, the issue before us today is what happens with the drug doesn't have a dose-limiting AE.

DR. LIPICKY: That is one issue and it is a real problem.

The second is, what are the properties of the drug, as it affects the effect in relationship to dose, that you want to know about? Because, in fact, if you boil all of this down, all we're doing in this antihypertensive stuff is saying we will approve you if you beat placebo. And that's the nuts of what we're doing. I would

personally like to see that changed but I don't have any support.

DR. PACKER: Yes, let me just make sure. Just so that we clearly have defined this, sponsors in the past have pursued with great justification development of drugs that have the least possible side effects and the greatest safety. What you're saying is that with the increasing ability to develop agents that have that profile, there should be an increasing responsibility on the part of the sponsor to develop a much more complete database on dose response. In other words, although they can celebrate that they have a better tolerated agent, there should be an enhanced responsibility that goes along with that.

DR. LIPICKY: And, in fact, one of the drugs that might have come to the advisory committee at one point, which is what this whole orientation was meant to address, was it could be that for ACE inhibitors, angioedema is dose-related. And one just hasn't figured out that because there isn't a large enough dose that's been studied. One will find that out by experience and by postmarketing and all that sort of stuff, or maybe that's not the case.

But the problem is I feel uncomfortable, in fact, if people have not identified the dose-limiting side effects. That was the problem with rhabdomyolysis in

whatever those drugs are that lower cholesterol.

DR. PACKER: Statins.

DR. LIPICKY: Yes, statins.

That that was related to the dose of statin was not known until mibefradil came along and clarified it. Now, that's a drug development problem that should have been known at the time it was approved. It wasn't. I do think that that ought to be considered to be necessary, although what do you ask people to do, and that's what we're talking about.

DR. PACKER: So, what we need to do is have a discussion using what might be called the non-AE model, the example of drugs that they may or may not have side effects. The idea is we're not talking about drugs which are free of side effects, but which at least from the data which can be collected and are available for analysis do not have a relationship between the frequency of a specific AE and dose.

DR. LIPICKY: Right, because that is the hardest problem, and that's the one to address.

DR. PACKER: So, let me ask the committee. I hope that this has been clarified sufficiently. The reason that this has come to the committee -- it never came to the committee before because we always were plagued with drugs that had dose-limiting side effects, and so no one had to

talk about this. Now we've got an increasing ability for industry to develop drugs that may or appear not to have dose-limiting side effects. In an era where there were dose-limiting side effects, it was relatively easy to write instructions for use and define doses that could be used for comparative studies. Now we're in an era where the appearance of -- there's got to be some relationship between AE and dose, but I guess not over the useful range. Under those circumstances, how well should one define and how broadly and precisely should one define the relationship between dose and effect.

So, I just want everyone to focus on this because no one is suggesting here -- and the division is not even putting forward for discussion defining six orders of magnitude of dose for a drug that has dose-related side effects. The focus today is for drugs that appear not to have dose-related side effects and the responsibilities on a sponsor to define a broader range of doses than they have conventionally defined in previous development programs. I just want to make sure we've accurately focused on the question. Ray, is that fair?

DR. LIPICKY: Yes.

DR. PACKER: Lew?

DR. SHEINER: I just want to say I think that is a particularly difficult question, as you bring up, and

may be it's a good metaphor for us to consider because if we can answer that question, we perhaps can answer others. But I don't want to say that the only situation that we're not handling adequately with respect to dose response is that case. I think there's an argument that can be made for finding something about dose response even for a drug where clearly the upper limit -- we don't dose aspirin until we have tinnitus anymore. We don't dose digoxin until you throw up. So, we would like to find the right dose response. But I agree, this is a nice metaphor to talk about because it presents a wider range for --

DR. PACKER: The reason, Lew, for framing it this way is because if we don't frame it this way, we're going to get lost today. We will get lost not only in the broadness of the scope of what we can discuss, but also in our unlimited ability to have our clinical judgment intercede here, especially when it comes to the use of multiple drugs for the treatment of hypertension because we will commonly say, of course, we'll use a second drug, and it is no problem in using a second drug. There's no reason to define the range of useful doses for a first drug because we will always put the second drug in place. That's a very appropriate clinical response because invariably the reason that we're going to the second drug is because the first drug has a dose-limiting side effect

we do not want to encounter.

The discussion is far more interesting if the first drug doesn't have a dose-limiting side effect that we want to avoid and then the argument becomes more interesting as to why one would go to a second drug if one hasn't fully utilized the first drug. So, we've got to discard the first paradigm because we can find all sorts of excuses for not looking at the dose-response curve for the first paradigm. If we don't focus on the second paradigm, we won't have a useful discussion.

Jeff.

DR. BORER: I would like to get back to Lew's statement here for a minute because I think that there's something very important that we need to focus on here. Following the line of reasoning we've begun to discuss, I think it is important to attempt to define the dose-response curve even in drugs that have side effects at the upper limits, at some high level because, first of all, in theory -- well, there are several thoughts here. So, let me try and put them in order.

Number one, for the sponsor, to define a drug as effective, the demonstration of a dose-response curve is one form of acceptable evidence. So, if you define that a dose-response curve exists -- forget about the relation to safety for a moment -- you've shown efficacy for

approvability purposes.

Now, a problem, it seems to me, is the assertion that we're in an era where there's a class of drugs that doesn't have dose-limiting side effects. It may be true, but I don't know how you know that until you give high doses of the drug. That means you've got to expose a certain number of people to the drug at high doses, and how are you going to predict that there will be a problem? Well, you do animal studies at high doses, but maybe you don't see what you're looking for in the animals.

I'm going to bet, because I've heard Lew speak before, that he will show us mathematical models or methods that would allow us to use relatively small numbers of data points so that you don't have to expose too many people to very high doses that might be deleterious in order to define the shape of the dose-response curve. If we have the shape of the dose-response curve, the only other thing we'd need to write a label would be the dose-related side effects and what the side effects are at each dose. That's what we'd need.

So, I think it is important to define the dose-response curve throughout its entirety or as high as you can go without running into side effects that potentially kill people or are irreversibly damaging because, without that, in fact we really don't have any starting point for

determining the level at which we want to look for dose-limiting side effects. So, I think it's probably wrong and probably a little naive to suggest that we're now developing drugs that don't have dose-limiting side effects because we don't know that until we test it.

So, anyway, I would argue that we ought to be looking at a larger segment of the curve, that we probably can do it with relatively small numbers of patients, that that is a basis for approvability, so it's not a lose-lose situation for a sponsor, and that then we have to figure out somehow at what level we want to start looking for dose-limiting side effects. I would say that part of that decision would be based on the increment of effect as you increase the dose, which you'd know if you did the D-R curve.

DR. PACKER: Jeff, I think what you're saying is that the two paradigms may not be different, the one which has AE-limiting and the other one has no AE-limiting. It's just that maybe it would be better to say that a dose-limiting AE has been identified in paradigm 1 and has not been identified in paradigm 2, not that it doesn't exist, but it hasn't been identified.

DR. BORER: I would agree with that.

The other point is the one that I was beginning to ask about before and now I'm glad you told me to hold it

till now. The issue is that, of course, not all individuals respond identically to all drugs in all situations. So, even if there is a side effect that's nonlethal or non-permanently damaging, that would preclude the use of the drug in 70 percent of the population. If you knew what the D-R curve was, you could titrate up that D-R curve to get the extra increment that you know might be there until you hit that side effect. Why be limited by the fact that 70 percent of people are going to have a side effect?

So, I think I'm arguing just what you say. The paradigms aren't different, and what we ought to do is what's being suggested here, study the whole D-R curve.

DR. PACKER: Well, it's not clear that the committee would agree with that.

DR. BORER: They may not.

DR. PACKER: So, what we need to do is to define what we want to know. Let me pose to the committee a specific point of discussion which is very important. It's a very specific example.

Just suppose you had a drug that the sponsor had shown reduced blood pressure by what is conventionally referred to as a meaningful degree. Let's assume that the identified doses that lowered blood pressure in the realm of 5 to 8 millimeters of mercury, which is the common

range. There are no dose-limiting side effects. Is that database adequate based on everything that you have heard today? Because clearly, the question that arises, based on the data presented today, is you could maybe get more -- you could get 10 millimeters, 12 millimeters, 15 millimeters -- if you went up and avoid the need for a second drug entirely in patients who require a greater antihypertensive effect.

Or should we congratulate the sponsor for having developed a drug which does a reasonably good job based on conventional criteria and that they should relax and feel good and be approved?

That is really the question because if we say that the second response is appropriate and that drug is approvable, everything else being equal, then we don't have to discuss how we're going to define the dose-response curve because we're saying we don't want to define the dose-response curve.

So, this is really a pivotal point of discussion right now. It deals not only with questions 3, 4, and 5, but it deals with the whole purpose of going on with the further presentations. If we say we don't care, then we can go home.

DR. LIPICKY: No. You'd have to listen to Lew and Don anyhow.

(Laughter.)

DR. PACKER: But if we say we should care, then we need to find out how we should care. I really want the committee to focus on that. It's a very important question. Each member really needs to think through this. We need to have a full discussion on this issue and all of the issues that pertain to it, and we'll begin with Marv.

DR. KONSTAM: I think, Milton, you've broadened the question from an intellectual question to getting into the realm of practical drug approvability. I am becoming increasingly convinced that dose responses are not being adequately explored and we need to move toward adequate exploration of them. So, I think that's going to wind up being my conclusion.

I think, though, you're pushing it because getting into the question of, okay, but now you've got an NDA in front of you and there is a set of doses. That set of doses clearly achieves a response at a very acceptable side effect profile. So, by definition, that range of doses is safe and effective. Now, in my experience on the committee, we've never been asked anything beyond that. Yes, it's safe and effective, but we don't know that the drug might not be more effective at a higher dose. So, this is the first time at least I'm involved in getting into that.

Now, I don't know whether we're going to be able to, at the end of the day, really answer that question. I wonder whether this discussion is really specific for hypertension. It makes more sense in hypertension because, after all, there are so many antihypertensive agents, and for the next antihypertensive agent to come along, let's get more information. We don't need another antihypertensive agent necessarily to be approved.

But let's say we were talking about a disease that didn't have 500 drugs treating it. Let's say it really is the next big thing in heart failure or some other area where there clearly is an added benefit shown, but the full dose response has not been defined. I guess I would begin to get very shaky in saying I don't think a drug is approvable until the full dose response is defined under that circumstance.

DR. LIPICKY: Just for Marvin's sake, limit it to antihypertensives, because that will make it easier. I think you do need to generalize it, but limit it because that is the easier setting and it's where you can be most rigorous.

I guess what I'm looking for is what your intellectual sense is. You can tell us, well, you shouldn't approve this. It's not worked up right. Yes,

it's safe and effective, but you shouldn't approve it. We won't follow that recommendation probably, but if you say do the bad things, we'll keep doing the bad things. So, I'm asking you what you think. We don't care so much what you think in the sense of the actions we take.

(Laughter.)

DR. LIPICKY: But if you tell us to do things that are not meaningful, it's very hard for us to argue that we should do things that are meaningful. If the dose response is important and you tell us, ignore it, well, then how can we say, no, we're not going to? Say what you think. Don't worry about the practical parts here.

DR. PACKER: Ray, in all fairness, I had toyed with the idea of asking the committee to take a poll, so to speak, and ask them whether they thought that antihypertensive development programs up to now were adequate in terms of defining dose response. And I thought that that was sort of a silly question because my sense is that each of us would look at the presentation that you've shown us and say, no, it's not adequate. I don't know if that's a very meaningful question.

The real question is, to the extent that it is not adequate, are we prepared to say it is not adequate and are we prepared to hold sponsors or recommend that sponsors be held to the conclusion that it is not adequate because,

otherwise if we say, well, it's not adequate -- but I would still approve a drug which lowers blood pressure 5 to 8 millimeters and doesn't produce side effects -- then there's no meaningfulness to the declaration of inadequacy. Then we will simply say, you know, you're right, Ray. The whole thing is a mess and they should do better, but we really don't think that that sentiment should be translated into any action.

DR. LIPICKY: So, I will make an assertion then to help you in your deliberations because I want you to enunciate what you think. I will pledge -- if you say you've got to have the whole dose response to be approved -- to try to stick to that, and I'll fight to make that happen. If you say I don't want to see the whole dose response and it would be all right if it didn't, then I'll say, what the hell do I care? How's that for terms?

DR. PACKER: Well, I think those are fair terms, which is why I presume we're here today because otherwise this is just an analytical, theoretical, and potentially meaningless discussion, and all of us will scratch our heads and say, this was pretty interesting, but nothing will change.

Lew has been arguing for years that lip service is paid to this, nothing ever changes. Nothing ever changes. So, why should today be different than any other

day. Is that right, Lew?

DR. SHEINER: Yes.

DR. PACKER: I'm not saying today is going to be different than any other day, but I think what we should do is take the matter seriously and determine how we feel about this because that's what we're here for. We're not here to have an elucidation and description of the failures of previous drug development.

Lew?

DR. SHEINER: Just a very quick comment. I think one of the things that may help us think about this -- and I think you are on the right track of what you should be thinking about -- is to remember that you don't want to make the best be the enemy of the good, recognizing that it is extremely difficult, as Tom has pointed out, as others have pointed out, to understand the entire distribution of dose responses, conditional upon all the varieties of things that could be different among patients. That doesn't mean you should give up, which is fundamentally I think what we've done. So, I think there will always be a judgment of how much do you need to know.

Ray has abstracted the three questions that I will present to you that I think you need to answer before you do anything, the first of which is, what do you want to know? But there are two others, and we can talk about

those. But they bear on the issue of essentially what it's going to cost and how much you're going to demand. So, I think we can recognize that we could do better than we're doing without necessarily doing everything that was possible.

DR. PACKER: I anticipate that every single member on the committee, whether they have their hand up or not, has something important to say and contribute to this. What I want to do is have some general discussion, and then I want to move rapidly to addressing questions 3, 4, and 5.

I'm going to skip questions 1 and 2 because my sense is that whether we admit to it or not, we use models, and that frequently those models are intuitive and frequently they are quantitative, and we will use both kinds of models. Does anyone not use models? We all use models. We do all use models. Right, Tom?

DR. FLEMING: The fact that the answer to that is yes is leaving out a huge part of this though. I.e., there is a huge range in the level of model assumptions that are made and, in turn, the robustness of those model assumptions. The real interesting discussion then comes down to how dependent on model assumptions are you willing to be because certainly the more dependent you are, the smaller the amount of patients or doses or whatever that you have to look at. So, the essence of the issue here

goes beyond just saying, do you use models, yes or no, but how reliant on model assumptions are you willing to be and what are the tradeoffs for what you gain by being more reliant against the lack of robustness or reliability of your conclusions.

DR. PACKER: The only reason I think that this question -- and it's 1 and 2 -- is being asked is that, in fact, if we don't use models at all, then elucidation of dose-response relationships is impossible because they're all model dependent. So, let me set aside the degree of dependency on the assumptions of models for a moment because that relates to the feasibility as opposed to the desirability.

DR. FLEMING: But this gets down to one of the real philosophical issues, and actually I really would like to hear the other presentations as well because there will be important input, I'm sure, from Lew and Don's presentations.

But one of the philosophical difficulties, as I encounter all this, is in phase III are you looking still at an exploratory stage or a confirmatory stage. It's not to say that you can't be doing both, but if you are still heavily relying on models, as you point out that you are, when you're looking at dose response, when you get to the confirmatory stage, are you at a point where you want to be

able to say something that is less model dependent? It's one of the reasons that in phase III studies, as Carl pointed out, people are frequently looking at pair-wise comparisons because they're trying to confirm whether a given specific dose is proven to be efficacious against a control.

DR. LIPICKY: Just to follow that, I have seven slides I didn't show because I thought I had formulated the problem okay. It sort of tends to address what Tom is saying now with respect to where in the stage of drug development do you get what information. I wonder if I ought to do that now or wait until some later time.

DR. PACKER: Maybe one should wait.

Before opening this up for discussion -- it's a very important discussion -- can we just have one other point of clarification on the paradigm that we're not focusing on today, which is the paradigm where there is a dose-limiting side effect which has been clearly identified, what might be called the old model. I hate to use that because there are lots of new drugs that fall into the old model, the AE-limiting model.

A lot of sponsors will say, well, we have identified a dose or range of doses which lower blood pressure and have an acceptable safety profile. We have gone higher than that and we've gotten into problems. Do

we need to go lower than that and identify the minimally effective dose of a drug that has dose-limiting AEs? That is not something specifically that we are likely to address in the next few minutes because we're focusing on the model and all the questions before us are in the model in which dose-limiting AEs have not been identified.

So, let us just complete the picture of the model where dose-limiting AEs have been identified if a sponsor has identified a range of dosing which they believe is useful and the agency would be likely to recommend that range for purposes of labeling. There's a clearly identified dose or dosing which would not be recommended. Do they have to now identify what is commonly referred to as the minimally effective dose or a no-effect dose?

DR. LIPICKY: Are you asking me?

DR. PACKER: Yes.

DR. LIPICKY: I'm sorry. Well, I don't think those words are useful words because they imply value judgments. Is a half a millimeter important? And they also imply sample size; that is, the minimally effective dose, if you're doing a pair-wise comparison, the difference will not be different from placebo unless the dose is pretty big if you have a small sample size. If you have a large sample size, you can detect a smaller thing. So, the concept of minimally effective or no-effect dose is

very difficult and not a very meaningful concept.

I think a better concept is you know where the ED50 is because you have defined the entire curve and you know what model is applicable, so that then you can, in fact, intelligently say, well, some dose down here really isn't going to do much and that that should not be an empirically derived property. At the moment, we do require it to be an empirically derived property.

DR. PACKER: Right. In fact, we commonly see sponsors that make presentations in front of this committee where they do a pair-wise comparison between a low dose and placebo. The p value is .07. They say, see, we've identified a noneffective dose.

DR. LIPICKY: But I think that whole conceptualization is just totally misleading and isn't worth the time it takes to discuss it, which we could discuss for a long time. It's really a matter of you've got the whole curve. You know what the curve is. You feel confident in the model. I'm making an argument that you may not accept. Then you, in fact, have the information you need to be able to make rational, reasonable choices.

DR. PACKER: Then let us set that question aside because what you're saying is that the principles that we are discussing for the model which has no identifiable AE-limiting side effect is just generally

applicable to both models. It's just that the first model is just easier to execute.

DR. LIPICKY: Right.

DR. PACKER: All right, terrific.

Now, I want to have an open discussion on the example that I put forward because, although we can have a wonderful theoretical discussion on the desirability of dose-response relationships -- and my sense is that everyone would say that the history has been inadequate and we should do a better job. So, I'm going to assume that everyone thinks we should do a better job. The question is, how much better a job should we recommend to the division that they hold sponsors to?

The best example I can come up with, the most striking example, is development of an agent which lowers blood pressure to what might be called a meaningful degree, in which the side effect profile in that range is very, very good, let's say comparable to placebo. And the dose has not been pushed to a range where the possibility is the drug may be even more effective with the possibility that dose-limiting AEs might be identified. Is that kind of database adequate for approval? Because that is question number 3 and that goes to the heart of identifying what we want to know today.

We'll start. Ileana, please, lead off.

DR. PINA: I'll state one of my biases that I've had for a long time about choosing dosages of drugs, and that is that I don't think we choose dosages adequately. I am interested in a comment that Dr. Peck made that there are numerous data points that are never analyzed, and I'm not as interested in that mean as I am in the people that it didn't work on. And if the people that it didn't work on, it's maybe that they need the higher dose and maybe that's the population that we need to push the dose to finding out a side effect. We dose children by weight and by body mass. Why don't we dose adults the same? So, I have a problem with this initial basic starting dose, which as a clinician has never helped me.

So, no, I don't think we're exploring the dose response adequately. I think we're taking this range of the middle population and the patient that is going to give us the most problem is the patient that's out there on either side, the patient that is not responding well to that dose that the average population may. Maybe that person needs a higher dose, and yes, I'd like to push it up to a side effect profile that I'm going to have some side effects because I want to know what that maximum dose is, and that may be that maximum dose for that person and not for the small, frail, elderly woman who may do very well at a lower dose. So, going back to the era of

individualization, since we're not at personalization yet, that's where I'd like to see it go.

DR. PACKER: Jeff and then George and then Carl and then whoever.

DR. BORER: Going back to the suggestion or the dichotomy you set up -- that is, do we congratulate and say that's it or not approve -- I think that the straw man with the mutually exclusive choices isn't really the only option. I think that you can conditionally approve and ask for more data. We have to uncouple the approvability and the need for data collection in some way.

So, having said that, I think that there are a couple of options here. If you have an effective and safe dosing range to give a drug, well, it may be reasonable to make that drug available, but to mandate that additional information should be required, for example, in phase IV. The reason I say that is that the real world is there's just so much money to develop drugs with, and a safety database can cost money; whereas the efficacy database, I would maintain, probably doesn't cost as much money if you actually are studying a dose-response curve with polar extremes and a couple of points in between and going across orders of magnitude.

But having said that, I think that it would be useful to point out in a guidance that's easily

understandable exactly what the principles of identifying or defining the dose-response curve are so you can know how many patients might be required, so you can know how to set up such a study appropriately and at the least possible cost. If that option were available to sponsors, my guess is they might use that as part of their initial studies to gain approvability and then the phase IV problem, which could be a mandatory phase IV, would be to define safety at certain dose levels that might not have been defined in the pre-approvability phase.

So, I don't think it's an either/or here. I think we need more information. Perhaps it's time to mandate more information. But you can't mandate so much that drug development stops because people can't afford to do it.

I would also say, just as an aside -- and I'm sure you didn't mean it this way, but I will answer it anyway -- that it is not reasonable to say that because a certain decrement in blood pressure has been achieved, that therefore we have a drug that we know how to use appropriately because our understanding of pathophysiology is changing over time and our understanding of not epidemiology but the utility of certain kinds of interventions is changing, as we gain more information.

For example, 15 years go who knew that in

people over age 55, blood pressure above 140 in systole actually was more important as a predictor of outcome than diastolic blood pressure? Who knew? Nobody knew so nobody was treating for it. Now, the recommendations for hypertension seem to be that in people with coronary disease, systolic pressure ought to be below 130. Well, maybe 10 millimeters of mercury average drop isn't particularly useful, and if we limit the information to doses that do that, we're not really providing the information that would be most useful to treat individual patients.

DR. BAKRIS: If we were in a different forum, I would stand up and applaud what you just said because I wholeheartedly agree, not only with you but with Ileana as well.

I think, listening to this discussion -- and those of you who know me know that I'm not very quiet, but I've been quiet here because I'm trying to assimilate all of this -- it reminds me of the old military service -- I think it was the Army -- motto, "Be all you can be."

One of the problems that physicians have -- and I appreciate the comment that starting dose hasn't helped anybody. It certainly hasn't helped me. Most physicians in practice are scared to go beyond that, and we have a very limited dose range. There are certain drugs that

we're talking about here that in the very few studies where they have been looked at -- and by the way, most of those are animal studies -- the effects are incredibly good in a very few human studies in a very small number of patients. They do quite well. I think the potential is not realized in these agents.

I think Ray presented a very elegant model that needs some tweaking and needs some statistical help to help give us some guidance as to how to do this, but it's a very efficient model that I think will answer a lot of things. You pick three doses in an appropriate mathematical range, and you get a tremendous amount of information across the gamut. And all these other questions about safety and other issues, if they've already been looked at and they're pretty safe already, should be looked at more.

And yes, I do think it should be a precondition of approval because if you don't do that, you'll be going with the putzy definitions that we have right now. I've published papers where we're talking about using three and four different drugs at maximal doses to control blood pressure because that's what it's taking. Who knows, if we actually use the doses in higher quantities?

Milton, I know you know this. The cardiologists know this and even the nephrologists know this, that super high doses of particular classes of drugs

have very good benefits. The GPs are terrified if you talk about these. They think we're insane. We should be locked up. That's because there's no data to give us guidance. So, I think this is a very important point.

DR. PACKER: Carl?

DR. PECK: One thing that nags at me, and perhaps some others, about this discussion is that I think the FDA actually doesn't have the legal authority to withhold approval if you have demonstrated safety and effectiveness. Now, the FDA often gets more out of sponsors than that sort of simple rule, using a bully pulpit or using their influence. But this could be challenged legally. The legal department of a company could come and say, look, we've done what everbody else did before us. We've demonstrated safety and effectiveness with adequate and well-controlled trials. Why are you withholding this?

So, I think I would challenge the committee to consider what compelling medical or public health rationale can you add to this interest in a broader range of dose-response information. I think you can come up with that. Ray made a very interesting comment earlier that the clinical pharmacology of Posicor, or mibefradil, was well-known but it was the lack of knowledge of an interacting drug that actually resulted in its withdrawal from the

market.

So, drugs are exposed to patients at much higher levels than they are ever studied during drug development and there are a wide variety of circumstances. Patients take overdoses. Patients dose themselves higher. Physicians dose off label at higher levels, or they encounter interacting drugs, which cause the effective dose to be much higher.

So, I would urge you to think about what is the medical or the public health rationale for this as the foundation, and then I think you'll have full authority.

DR. PACKER: Carl, let me just add one minor response to that from a public health or medical point of view. With the increasing evidence that previously recommended target levels of blood pressure are inadequate and that there is a need to lower blood pressure to levels that we previously had not imagined should be targeted but now should be targets -- and that may be particularly true in high risk patients like diabetics -- that there is a uniform sense that monotherapy, given the way that single drugs are used now, is going to generally not be adequate to achieve those targets and that we are going to have to rely on two or three or four drugs.

Therefore, a very cogent position could be put forward that the individual as well as public interests are

best served by trying to minimize the number of drugs which would be required to achieve the new targets of blood pressure lowering that we are now hearing being recommended to physicians. It is difficult for patients to take four drugs. It is expensive for patients to take four drugs, and it may be unrealistic for patients to take four drugs. And if a drug can be identified that would achieve those target blood pressures more effectively as a single agent, then in fact an individual as well as public health purpose could be served. Does that seem reasonable?

DR. PECK: That's exactly what I think would serve your purposes best, to identify and inventory the strong public health and medical rationale for having the full dose-response curve available at the time of approval.

DR. LINDENFELD: To add to that too, I think we can then know the side effects that we might anticipate with a full dose of a single drug, but we can't possibly know the side effects from a combination of four drugs that people would have to use. So, that's a very major advantage of getting these dose-response curves for a single drug.

DR. BAKRIS: Let me just chime in on this. Certainly we have the data from the NHANES. There's a paper I recently reviewed that will be coming out in JAMA that actually looked at the diabetics, as Milton brought

up, and we all know that the goal blood pressure there is lower. Only 11 percent of the diabetics with hypertension are actually achieving the goal recommended by the JNC-6. So, there's a multitude of reasons for that, but we're not helping the situation by not providing adequate information about single agents that potentially could give you a lot more power than they currently are.

DR. PACKER: Marv, Paul, and Ileana.

DR. KONSTAM: I guess I'm thinking somebody has to put in a word of balance in the discussion. I'm very sympathetic to this discussion and we may well want to move in this direction. But I'm troubled by it. I guess I'm thinking that we are potentially setting a precedent for asking something of a pharmaceutical company that really is very different from what we've ever asked before in the sense that previously we've been say, well, just show that your drug is safe and effective.

Now, we're beginning to develop rationale, for example, saying, well, in an era where we need multiple drugs to manage hypertension, I want you to show us maybe you can help in that regard. Maybe this drug could have an economic impact on that or other kinds of impacts if we really knew the full dose range. I guess I'm hearing this argument for the first time and I'm troubled by the precedent that that establishes.

Let's expand it. For example, I've never heard any serious discussion about cost effectiveness, at least on the panel and I think within the agency. Now, I'm in favor of cost effectiveness, but it's beginning to sound a little bit like moving in that direction to me. I just want to point that out. I think there is potential precedent being set here.

DR. LIPICKY: It's not as big a leap as you think it is. Although it is true we approve because it beats placebo currently, all of the guidelines, ICH guidelines, the draft guidelines that exist from FDA, guidelines that Bob Temple has in draft, the European guidelines, all say for an antihypertensive drug there has to be adequate exploration of dose response. So, really you can view this as one step further; that is, you're defining adequate. They left adequate undefined. So, it isn't that much of a leap.

DR. KONSTAM: That's fine and I guess I'm comfortable with that. I guess just as the discussion has begun to expand, that's really what I'm beginning to get a little bit uncomfortable with. I think there could be a significant precedent for saying, well, the company really has a greater responsibility well beyond showing that a drug is safe and effective. Maybe that is a direction to go, but I just want to point out that that seems like it

could be precedent setting.

DR. PACKER: First of all, I think it would be safe to say that a level of uneasiness exists for every member of this committee. This can't be viewed by anyone as being a no-brainer because I don't think that that would be appropriate. I think this is hard at many, many different levels and you've identified a few of them.

I'm not a 100 percent certain that this represents necessarily either an incremental burden or a disadvantage to sponsors. Let me just outline what I mean.

Sponsors now, on a regular basis, do dose-response studies. The only question is not whether they should do dose-response studies, but what should be the doses that they evaluate in dose-response studies. In other words, instead of the range of doses being, as Ray said, 1.75X, or whatever it happens to be, or 2X, what Ray is putting forward is the proposition that maybe they should still do their dose-response studies but do it over a range of dosing which is more likely to yield useful dose-response information than the doses that they've been exploring to date. So, this should not necessarily be viewed as a major incremental imposition on the drug development process.

Second, another point is that the hesitancy they have in pursuing higher doses has been I think

motivated twofold. One is they're afraid that if they hit higher doses, they're going to get side effects, and the side effects at higher doses will appear in labeling. Ray has made it clear -- and Ray, you might need to say it one more time so everyone hears it -- that if side effects appear at a dosing range outside of that which is then recommended, it doesn't appear in labeling because there is a big perception in industry that if you hit doses that are going to be outside the recommended range, the labeling will suffer as a result of that because what you will see in labeling is placebo and active therapy and all of the side effects at the highest dose, which they evaluated because they believed in your proposition, would now be counted against them. So, maybe you could just reiterate your statement that that in fact won't happen.

DR. LIPICKY: That is correct. It will not. It's hard to say. I always hate to say it will not because under some circumstances it might. But given the current perceptions and the current practices and the current way in which people think, it will not.

DR. PACKER: The other advantage that comes to industry is that -- my sense is it's not sufficient for us here to say that we think this is a good idea. Industry has to think that this is in their interest as well. My sense is that if, in fact, they are able to show that their

drug has a broader range than they previously had expected of the agent -- remember what we're talking about today is a model where there are no AE-limiting side effects not the model where there are AE-limiting side effects. If, in fact, you can show that your drug is a lot more effective than you thought, then a whole host of superiority claims become possible that previously were not possible.

Ray has said, reluctantly, that he would be receptive to such claims, even when the database is less than adequate, if in fact one compared against an old model drug that had AE-limiting side effects. I didn't say you would be enthusiastic, but you would be receptive.

DR. LIPICKY: I need to make just one comment. There is no need to have a larger database. The problem is that an antihypertensive NDA will contain all dose-ranging studies, 2,000 patients, sometimes 3,500 involved in parallel group, fixed dose, placebo-controlled dose-ranging studies, poorly conceived, not analyzed properly, incompletely thought through. All the goals are wrong. If I present my seven slides and Don and Lew are listened to, 150 patients, you've got all you need for defining dose response. But people don't do it because they don't think anyone cares, and they don't know what they're looking for. So, we need to just enunciate what do we want to know.

DR. PACKER: Paul has been waiting patiently.

DR. ARMSTRONG: Milt, let me make three points that I think are controversial but hopefully will be useful. Ray started off this discussion by saying that blood pressure was very easy to measure and that's why he thought it was useful to talk about. On the one hand, I think he's right.

On the other hand, I think that's deceptive. The issue of whether systolic, diastolic, or pulse pressure is the right thing to measure -- and indeed, the technology about continuous blood pressure monitoring suggests that many of the blood pressures that have been measured in these trials bear little relationship to what we might hope to achieve. So, I think that's deceptive.

I guess it leads to the question, why do we want to lower blood pressure because we don't have phase III trials relative to this?

Which leads me to my second point, that a number of the agents that we know lower blood pressure have different effects on what we would like to achieve. So, the target that we should be looking at presumably, as we extend this discussion, might be things, perhaps regression of left ventricular hypertrophy. Maybe it's retinal arterial diameter. Maybe it's a neurohormone. I don't know. But I think the issue of the objective of the exercise of lowering blood pressure, as opposed to just

lowering blood pressure, needs clearly to embrace this conversation.

The third point is that, notwithstanding the beauty of classic dose-response curves from smooth muscle baths that many of us have worked in exploring vasodilators, the applicability of that to an intact human being or an intact human being who has disease is very difficult. Indeed, although I support the decision to move upwards, to get some degree of flatness or to acquire some confidence that we've achieved maximum in whatever population, the likelihood that we'll be able to model that in a classic DRC seems to me unlikely.

DR. PACKER: Paul, let me just say that the doability of this is what the discussion is about afterwards. Ray is saying that a lot of this information can be obtained very efficiently and hopefully in an interpretable fashion. The focus now should be whether we think that this is important, whether it's desirable. It could be that we're going to say it's important and then Lew is going to say, well, you can't do it. So, really sorry to disappoint you.

DR. LIPICKY: Paul, I guess it doesn't have to be blood pressure. If you want to look at the dose-response relationship for left ventricular hypertrophy regression, that's perfectly fine. But the question is,

you don't think there is one? You don't think you can define a dose-response relationship for whatever it is you're interested in? This is really generally applicable. It turns out it's easy to measure blood pressure. That's why it was chosen. We have lots of data. But we can do it for mortality if you want. It doesn't matter.

The question is, do you want to know? And if you want to know, what do you want to know about that relationship? Then you may decide, well, look, in this setting, I just can't have what I want to know, so I'll be satisfied in something less. But in the hypertension arena, whether you care about blood pressure or not, you can know anything you want. What do you want to know? That's the question. We're not talking in hypertension about death or anything else.

DR. PACKER: Ileana?

DR. PINA: I have two comments. I want to follow up on Jeff's statement that maybe we can approve a drug because of a broad range of safety with adequate blood pressure and then demand more studies that open up the range of dosing to higher dosages. I think that's a problem because, the majority of times, the clinicians will never get the higher dosages relayed to them, or they will never develop comfort with them if they don't come out at the outset of the drug.

I share what was being said on this side, that the clinicians will only use smaller doses and will be very afraid to push beyond the original dosing that was given. So, I would rather see it all done before the drug gets approved rather than later.

The second comment is that I think we're being naive if we're thinking that blood pressure now is what blood pressure was before. It's analogous to saying if you give digoxin and diuretics to a heart failure, that's plenty and you really don't want to know what happens to neurohormones because they're not important. I think we've even learned that blood pressure lowering enough may not be enough either, and I think the ALLHAT trial has proven to us that the lowering of the numbers may not necessarily affect the outcome.

So, I am very interested in harder endpoints. It may be left ventricular hypertrophy. It may be neurohormones. If you look at JNC-6 -- and I'm imagining that JNC-7 even more so is being targeted to specific disease entities within the hypertensive population so that you target therapy depending upon what the underlying clinical position is. So, I don't think we can just sit here and say let's approve drugs now the way we used to before when we're dealing with hypertension. I think we've grown up quite a bit.

DR. PACKER: Again, let me just focus on the issue of just blood pressure. Blood pressure lowering is an acceptable surrogate, and we are not going to get into issues whether it is in fact or not an acceptable surrogate. We can't go there. We just can't.

One thing, I would like to make an observation. There is an enthusiasm on the part of clinicians and I think enthusiasm on the part of sponsors to develop combination products for the treatment of hypertension in the hopes that if you add two drugs in the same tablet, you'll get a greater antihypertensive effect. Maybe it's additive. Maybe it's synergistic. Maybe it's less than additive. Who knows. The hopes are by putting the two drugs in the same tablet -- the patient would normally be prescribed these two drugs separately, but they can be put into the same tablet to enhance convenience.

The same argument could be made for dose-response relationship for a single drug. You can think of a higher dose of a single drug as being a fixed combination of a low dose plus a low dose of the same drug. As long as there's no dose-limiting adverse reaction, then the same convenience issue pertains to a high dose of a single drug in a tablet versus a low dose of a single drug in a tablet.

DR. LIPICKY: But why are you asking that question?

DR. PACKER: No. It's just an example of the fact that convenience issues sometimes drive physician practices and therefore the use of a higher dose, which is better, which doesn't produce side effects, would enhance compliance.

DR. LIPICKY: I guess I just want to say that the same concepts to developing a combination drug apply and that currently people do dose-range both drugs. In fact, they would be able to do it better, cheaper, faster, if they did it differently.

DR. PACKER: My sense is that a lot of our responses are being influenced by perceptions, maybe accurate and maybe inaccurate, of how hard or easy this would be to do.

DR. LIPICKY: Oh, duck soup.

DR. PACKER: Before going forward, therefore, and asking the committee to formally consider the questions before us, maybe we need to have a better sense as to what this would entail.

DR. LIPICKY: Seven slides, about 30 seconds each.

DR. PACKER: Who's going to deliver it?

DR. LIPICKY: I will. I didn't show them.

DR. PACKER: I thought Lew was going to deliver it.

DR. LIPICKY: No. I had seven slides that address the issue, and then Lew is going to address the broader issues.

DR. PACKER: Is the sequence you first, Lew second?

DR. LIPICKY: I had them in my first presentation. I decided, when I got to them, that I should stop.

DR. PACKER: Okay. Then let's pause here for a moment. Let's find out what this would entail from a conceptual framework, and why don't we hear Ray's 2-and-a-half minutes. Then we'll pause for some questions and, Lew, we'll go directly to you for your presentation.

DR. LIPICKY: So, these are two designs, fixed dose, parallel, one drug versus placebo. Clearly this is easier to do because there are only two arms.

I apologize for the fact that IBM computers don't know how to make electrons flow right.

But if you have a placebo arm here, and for the first 2 weeks you're at 1X, and then you up it and you go to 3X, then you up it, and you go to 10X, and you up it and go to 30X, and you up it to go 100X, you've covered a 100-fold dosing range in 10 weeks, with sufficient time to get into steady state. Lew is going to tell you how you analyze this data because it's complicated. But, indeed,

for the first 2 weeks, you have the standard stuff you could do.

If you are afraid of that, you could go back to the other design. It's just that you have this fixed dose titration in the high-dose arm and then you haven't lost this. Then if you buy into all that, you can actually go over 1,000-fold with three arms, placebo-controlled. You have to be able to analyze this. Here you, in fact, have at the end of the first 2 weeks a shot at standard, pair-wise comparisons over a dose range of 100-fold.

If this still bothers you, we've looked at ABPM data, and I'm not going to talk about it much, but basically I don't care what you want named, 24-hour average, a.m., p.m., nighttime, before breakfast, after breakfast, during eating, the coefficients of a Fourier curve, the coefficients of a polynomial, the mean of this, the mean of that, or anything you want named. There ain't no placebo effect in short-term antihypertensive trials. There's a nice drug effect. So, you can get rid of the placebo arm.

In these same trials, no placebo effect in the placebo group, but in the -- I'm sorry. This is the placebo group. This is the treated group who had ABPM measurements, but there is a clear placebo effect for the office cuff, the same population. So, the ABPM short term

offers one the opportunity to perhaps use baseline blood pressure, no parallel placebo group. Then you see you can do this, three arms, and you cover a 1,000-fold dosing range. No big deal.

DR. PACKER: Ray, what you're saying is that in order to elucidate the dose-response relationships, if one used ambulatory blood pressure monitoring, because of the absence of a placebo effect --

DR. LIPICKY: And a very different way of analyzing data.

DR. PACKER: Which we'll hear about.

DR. LIPICKY: Right.

DR. PACKER: One can elucidate the entire dose-response relationship using this kind of study design.

DR. LIPICKY: 150 patients, 9 weeks.

DR. PACKER: Let me ask a question because I'm sure it's in more than one person's mind. How do you know you got steady state? There are some drugs that don't reach steady state in 3 weeks.

DR. LIPICKY: You don't.

DR. PACKER: Does it matter?

DR. LIPICKY: Well, it does and it doesn't because, you see, you're going to have to study a couple thousand patients for a new chemical entity. Right? Now you got your dose range pretty well figured out. Now you

can figure out what you really want to know. If you want to look at how long it really takes to come to steady state, fine.

DR. PACKER: If you found it took 4 to 8 weeks to come to steady state, is this adequate?

DR. LIPICKY: Then this dose response would be a little bit wrong. Right?

DR. PACKER: Right.

DR. LIPICKY: But you would have a 1,000-fold dose range covered safely without any problem, and if it all worked out okay, 2 weeks would be enough. For most of the drugs we see, 2 weeks is enough. You're to about 80 percent, 90 percent of the final steady state effect-wise.

DR. PACKER: And your sense is this would provide information that would replace a lot of the dose --

DR. LIPICKY: Everything that people do now.

DR. PACKER: Would replace what they do now.

DR. LIPICKY: Right. So, now you have another 2,000 patients --

DR. PACKER: That you can do something useful with.

DR. LIPICKY: -- that you can do something useful with. Get rid of the dose response easy unless there are other things you want to know.

DR. PACKER: But people spend millions of

dollars and years doing dose-response curves.

DR. LIPICKY: It's stupid. I don't understand why they do that.

DR. PACKER: This is enough?

DR. LIPICKY: Yes.

DR. PACKER: Oh.

(Laughter.)

DR. KONSTAM: What about adverse events?

DR. LIPICKY: A different problem. Again, you're back to the 2,500 patients more you have to study. You're talking about rare adverse events. You'll pick up dose-related adverse events here pretty well. You're talking about the 1 percent incidence of torsade.

DR. KONSTAM: Yes, but can't rare events be also dose-related?

DR. LIPICKY: Well, they might be, but then they will be in the category of angioedema in ACE inhibitors.

DR. KONSTAM: Right, but you said you wanted to know about that.

DR. LIPICKY: No. You said you did.

(Laughter.)

DR. KONSTAM: Okay, we agree.

DR. LIPICKY: Yes, that is a problem. There are still problems. I'm just trying to get rid of the