support might not buy that argument.

DR. LIPICKY: No. But in fact they do. One of the most recent development programs that we've been associated with with a small company -- the liability issue postmarketing was a big deal, and they were willing to put more into the development program thing than suffer the pangs of having postmarketing liability. They looked into it in great detail. So, if that's logically approached premarketing or during development, I think one would come to the same conclusion, and I know one that did.

DR. KONSTAM: But, Ray, that might not apply when you're talking about a 1,000-fold increase in the dose range.

DR. LIPICKY: It's only three times more than 300. So, that's only one more arm.

(Laughter.)

DR. KONSTAM: Okay. I suppose this is a question that Milton didn't ask, the "wouldn't" question. I still think that there is going to be a lot of resistance. I still think that your assurance that there would not be a penalty, in terms of approvability, will not sufficiently dissuade that concern.

DR. LIPICKY: All they have to do is look at all of the drugs that are on the market that have dose-related side effects. There are. We have approved drugs

that do that.

DR. KONSTAM: I actually would like to ask another question. Maybe this is a naive question, but an ethical question, regarding informed consent. Particularly as we're getting into the issue of exploration of adverse events at very wide dose ranges, perhaps at dose ranges that, despite we don't know adequate dose response, some people might construe as unlikely to yield significant additional benefit.

Maybe there are studies done this way, but I've never been involved in one, where a specific goal of the study was to identify the dose range of adverse events. Usually you say, well, we're exploring efficacy. We don't know everything about adverse events, so there's risk. Here are the adverse events we know about, and you should know there might be others that we don't know about. But we're really exploring efficacy.

This is now different. This is now saying, well, one of the purposes of this program is actually to find adverse events.

DR. LIPICKY: Right. I know and I shouldn't have said what I said. The purpose of the program is to find the greatest effect one can find. So, that requires increasing dose. One may not be able to increase dose sufficiently to find that greatest effect, in which case

adverse effects would be limiting. The only reason for my assertion of we ask people to hurt people is that the excuse that, as you are looking for the greatest effect you can get, might hurt somebody doesn't seem like a reasonable excuse to me. It's much better to know that, once again, in the premarketing circumstance than in postmarketing. But you're searching for the greatest benefit.

DR. KONSTAM: No. I understand that part. I guess I'm saying one of the constructs that I think that had floated around as a situation that would be acceptable, that you've adequately explored the dose range, despite absence of a maximal effect, is that you've identified dose-limiting adverse effects.

DR. LIPICKY: Well, no. I understand, but I think the notion is that if you have been able to identify a maximal effect -- and I would accept Emax with tight confidence limits as having demonstrated that -- and you haven't found adverse effects, that's fine. I wouldn't push for going to a higher dose.

DR. KONSTAM: So, you'd never be, despite some comments that have been said, proposing a program that specifically would be seeking --

DR. LIPICKY: That is correct. The purpose is to find the greatest effect, beneficial effect, and that is the purpose. The thing that bothers me, all told, is we

have this one ACE inhibitor over 1,000-fold dose range and it still couldn't show it had the found the maximum effect. Now, that's a bother to me. So, that means it probably should have gone higher.

Well, then up comes the business of side effects and you might hurt somebody. My response to that is, sure, you may. You may not too. And if you do hurt somebody, the best time to hurt them is in the development program. It should not occur postmarketing. So, if there are things that are dose-limiting, you ought to find that out as you're working the drug up. You should not find that out when it goes on the market.

DR. BAKRIS: Milton, let me just build into what Carl mentioned and what the discussion was right here because it occurred to me, as a former IRB member, that there may be a limiting factor and it will have nothing to do with the company. That is, the company may say fine and they may propose it, and the sites they go to and the IRBs that they use may not allow the maximum doses. So, I think that's something else to --

DR. PACKER: I don't understand that. When a sponsor proposes a dose, it does not know, so the IRB cannot know, what is in fact the appropriate dose-response relationship. So, it is impossible for me to understand how an IRB could object to what is almost always an

arbitrary selection of doses.

DR. BAKRIS: Right.

DR. LIPICKY: Well, I can see where some people might say if you're studying a 1,000 times something, that that's just too much. You don't have to know much to know 1,000 times is a big number. A priori, they will say that's too much.

DR. BAKRIS: We're not talking about physiology here. This is gut feeling of people.

DR. SHEINER: With respect to this, though, you have the tradition in oncology where they have now escalation studies not within an individual, not crossover type, but small numbers of people and you keep on increasing the dose. So, if it was really important, there are ways to design studies that put minimum number of people at risk, and you can do that if you think it's important enough. In oncology, they always have because they have wanted to be side effect-limiting in general.

DR. PACKER: From the sense that I've heard today, all we're encouraging sponsors to do is maximize their asset. What we're saying is that if you have a product that lowers blood pressure and you can only give it in a limited dose range because it produces side effects, then you've understood how that drug should be used. If you've given it in a range that lowers blood pressure but

is very well tolerated, you haven't explored its full potential. It may be the single best antihypertensive drug ever. In fact, it may be so good that it is the only antihypertensive drug a patient will ever need and would, in fact, fulfill that role in everyone in the world. You would never know that if you limited the potential to ask questions.

One would never, I think, willingly reduce the potential of an asset. Everything that's being talked about here is simply to say there are straightforward, non-expensive, non-burdensome ways of expediting the process of exploring the full potential of an asset, which up to now has been under-utilized, perhaps non-utilized, and that doing so is in the sponsor's interest. It's in the interest of regulatory clarity and, as Carl said, regulatory consistency over time, and it's in the interest of public health.

DR. SHEINER: That being said, I think the reality is that without regulatory pressure it won't happen. It won't happen for two reasons. One, because pharmaceutical companies tend to function that whatever we did in the past, we'll do in the future because we have a system for that.

The second is that despite the fact that you said it's straightforward -- as far as I'm concerned it's

straightforward -- it isn't. It's a little more complex. The design of the study is a little more complex. The interpretation of the study is a little bit more complex. And adding these two elements of fear and the fact that there will have to be an investment in a relatively unknown thing that they'd have to do because the guidance of exactly how to do it -- in fact, the knowledge of exactly how to do this -- in the most efficient way doesn't exist.

So, what I think we have to acknowledge that without regulatory pressure, we will not get the pharmaceutical companies to do this and begin the exploration on a larger scale that we in academics have started on a smaller scale, but the exploration is going to be required to find out what are the most efficient procedures for getting this knowledge.

DR. PACKER: Paul?

DR. ARMSTRONG: Milt, I'd like to pose a question in relationship to this discussion of dose. If we establish the minimally effective dose of a new compound, do we have a sense as a group of what a feasible or realistic range would be to approve marketing of that compound in this era of medical errors? Notwithstanding the wish to make the mistakes before it's marketed, we know for certain that there will be continuing problems after it's marketed based on inappropriate use. Do we have a

sense of feasibility and range that's realistic? A 1,000-fold, for example, would be very difficult for me to accept. Could we have some discussion on that point?

DR. PACKER: Paul, let me pose a way of thinking about it. That is that if a sponsor would normally look at a dose range from 2 milligrams to 10 milligrams, just making this up, and found that that was acceptable, but because of this discussion, was encouraged to look at a dose of 100 milligrams and found out that 100 milligrams was really very much more effective, based on whatever model one would think, and was still very well tolerated, what the sponsor might decide to do is, rather than instruct physicians that ranges of dose from 2 to 100 milligrams, which seems quite wide, are recommended, they might want to further explore maybe whether that recommended dosing range might be usefully confined perhaps to the upper range rather than the lower range. I'm just putting that out as a possibility. And they might be so confident in that range because it was so much more effective, they would be able to do comparative studies with other drugs showing it was better. Therefore, they would primarily develop the upper range, something they would have never done if they hadn't explored the full dose response.

Jeff?

DR. BORER: Paul raises I think a very important point that I would like to discuss a little further, that is, the need to define the minimally effective dose. I don't think we have to define the minimally effective dose. I don't think a sponsor has to define the minimally effective dose. Just to throw it out on the table, it seems to me like defining the ED50 and knowing that that's safe and knowing that another dose, either higher or lower, is safe, and having some idea of the dose-response curve would allow someone -- having enough information to define a good range of the dose-response curve, if not the entire dose-response curve to maximally effective dose -- to titrate, to allow a doctor with a label to titrate to the effect that he or she is trying to achieve in his or her patient.

If it's blood pressure we're talking about, you don't have to know the minimally effective dose for the population. You've got to know the effective dose to get to where you want to get in the patient. And if you know that the dose-response curve is X, and it's shaped this way, and you know that a dose that's up here is safe, you can titrate down from it and figure out where you want to be. Who needs to define the minimally effective dose for the population I would suggest.

So, I think it's a very important point, but I

don't think that that should be the goal of the sponsor, to define the minimally effective dose. I think the goal should be to define the dose-response curve and then to define safety at a couple of points, however many points seems appropriate along that curve, so that some reasonable directions for use can be given.

It may be that in phase IV more points along the curve, higher up, have to be defined -- the safety of them, that is -- but a titratable drug, if you know the slope of the dose-response curve, why do you have to spend a lot of money on defining minimally effective population dose?

DR. PACKER: As I understand it -- and I'm just looking at the equations used for calculating the Emax model -- a sponsor doesn't have to define the minimally effective dose. The sponsor simply has to define the full range of dose and describe the relationship. What might be a minimally effective dose emerges from knowing the shape of the curve. But the intent is not to identify the minimally effective dose.

DR. BORER: I didn't mean to suggest that the current rules indicated that one needs to do that. We know that they don't. But rather, just moving on from what Paul had suggested, that not only do you not have to do it, but it's not something that you would want to spend precious

resources on.

DR. PACKER: Jeff, I think you're emphasizing that's frequently misunderstood. There appears to be a considerable energy frequently expended by sponsors to define a minimum dose in the absence of defining the whole shape of the dose-response curve. I think what you're saying is no good purpose is served in that kind of energy expenditure unless one is going to do that as part of -- in other words, the motivation is to define the dose-response relationship, not to define the minimally effective dose. Defining the minimally effective dose without defining the dose-response relationship serves no purpose.

DR. BORER: That's right, although I would suggest that there is no such thing as a minimally effective dose for an individual except for 0. The dose-response curve is a continuum, and you got to titrate in your individual patient.

DR. PACKER: Any other comments, questions?

(No response.)

DR. PACKER: Ray, I think you have our strongest recommendation and encouragement to take measures to encourage the elucidation of the full dose-response relationship for antihypertensive drugs, both for the individual and for the public health.

DR. LIPICKY: Thank you.

DR. PACKER: And we are adjourned.

(Whereupon, at 2:54 p.m., the committee was adjourned.)