giving those cells back to the same patient.

So, in part of our recommendations to the FDA, some of the benchmarks that we were alluding to are benchmarks for the overall consistency and quality of a production facility, rather an benchmarks to be assayed on every lot of cells, given to every patient.

CHAIRMAN RAO: So, to go back to what you'd said, then--so is it true, for the sense--for early studies, as Dwaine pointed out, that when you're looking at Phase III trials, and you're looking at a company, and you're releasing a product where you have a long history, there's a different set of requirements. But when you're doing this early, you want to have a definite cell type which you can then take reasonably to a Phase III trial if you were going to do it. What would be sort of a minimal criteria that people would consider as important in terms of how you look at product development?

And, to me, it still seems--and, again, I would have the committee weigh in on this, is that we still need a minimal definition of what's in that cell type. And we clearly still need how it was isolated--as, clearly, distinction, because

that's a different cell type. And we need to know the passage number and the karyotypic stability of the cells when they've been grown in culture, and that's irrespective of whether you're doing it early or late, because otherwise you won't be able to compare.

And you need a lot of the data and information so that if you have any of the small trials, that you can actually see if you can truly extrapolate--like you pointed out--from one trial to the other, so that you have that. And that in the readout you need some sort of potency-type assay where you can say--which is a maybe generic substitute, and it may be the best that one can have, given the limitations in the field on what can be there. And maybe for myoblasts it can diffuse and form myoblasts because that's the mechanism of action, and that's what you use each time; and that for the overall generic product that you have--so let's say it's myoblasts from different patients--you should have some kind of biomarkers and assays that have been defined in a more rigorous fashion.

Is that--

DR. SCHNEIDER: May I play the Devil's

advocate for a moment with respect to karyotyping?

I'm curious how one would use the data from karyotyping if an abnormality were to be found after three or four weeks of what I consider to be relatively short-term culture, if there were no objective evidence for tumor formation in animals following six to 12 months of follow-up in preclinical data? I mean, are you using karyotyping as a surrogate endpoint for tumor formation even in the absence of data that tumors would occur?

CHAIRMAN RAO: Hold that thought, and I think maybe Bruce is going to take about what we missed in saying this is the dose.

DR. BLAZAR: No, I wanted to follow up on your point as well. I think part of the issue as you go to define the products is if you're going to call something a skeletal myoblast, it has to have certain proportion of cells--which I haven't heard what that is--that are defined as skeletal myoblasts. It should have some limitations as to what the other cells are.

For karyotyping--which I think is important--we need to know whether there are unstable karyotypes, even if retrospectively to go

back and say "this culture was a different culture than another culture," regardless as to the tumorgenic risk.

And for the assays, I think if you're going to use in vivo assays as readouts, then they have to be able to reproduced from lab to lab with some sort of standardized ability to say that this cell has a certain potency. With islets, that can be shown; that many different labs can come up with the same sort of readouts.

But the difficulty for me in listening to this discussion as outside the field is I'm still walking away with saying I don't know what kind of product definitions are going to be required, other than recording the data. What is a reasonable composition of matter? And are there potency assays that are exportable and evaluable in multiple different laboratories for assessing some level of potency that can be reported in the literature to correlate with clinical outcomes?

DR. KURTZBERG: I agree with that, and I also don't think a panel of non-experts should be the people deciding the potency assay. I think that people who are experts in the field ought to decide that and come back and say this is what we

think is the best we can offer.

CHAIRMAN RAO: Dr. Epstein?

DR. EPSTEIN: Dr. Rao, I think you summarized the issues brilliantly. I'd just like to make two points.

I think a consensus panel of experts would be critical to define in vitro and in vivo assays. I think it's critically important to make certain we understand that myogenesis is different from angiogenesis, so that you have two consensus panels.

But then I would suggest--because the point just raised is excellent--not everybody has the ability--not every laboratory, not every facility has the ability to do a reliable in vivo assay. And I would suggest that the FDA consider the possibility--perhaps in collaboration with NIH--of developing a core laboratory so that products can be sent to that core laboratory and tested in an absolutely uniform way.

And Michael made a very important point. The in vivo assay is not going to really be helpful in the acute situation. But we can retrospectively analyze the results, and try to correlate an in vivo assay with a beneficial effect or a

non-beneficial effect. But I think for some of these assays, they're rather sophisticated. You do have to have experience with it, and I would think--and I don't know if it's financially feasible--but that development of a core laboratory where specimens can be sent would be a very important part and role for FDA to play in characterizing what we're giving these patients.

CHAIRMAN RAO: Dr. Mule, did you have a comment?

DR. MULE: I just wanted to get back to Dr. Rieves' point about the stages of product development as it relates to the complexity or the outgrowth of trials associated with cell-based therapies. And there is a history here from other cell-based therapies, not necessary, of course, in treatment of heart disease.

But the point, again, is that if one is running a Phase I trial and it's limited to a single institution, it's inconceivable to me that that individual should be held responsible for a transportable assay that other sites not affiliated with the single-site study should be given the stamp of approval, for instance. I think that comes later.

I think for these limited Phase I studies that are single institution, to me it would almost be a barrier to require that investigator to have a robust enough assay that's transportable. That's my point.

CHAIRMAN RAO: I want to ask the FDA: do you feel that you've heard enough about Question 1 and Question 2, in terms of a generic picture on these things, or just left too open in your mind in terms of what can be done?

Go ahead.

DR. AREMAN: Well, I just wanted to make one point that--people have been discussing potency assays. And we really do not require that there be a potency assay in place when you start doing a Phase I or a pilot study. You should be considering what you might use as a potency assay when you get to your Phase III trial. But that definitely is not--should not be a barrier to initiating a Phase I trial.

CHAIRMAN RAO: Yes, I think all the committee members, in one sense, were trying to say that if you have to take these cells and extrapolate them, you have to know some measure of what they're doing, and so you need that. You

don't necessarily have a direct dose-response or potency that you need, but you need to be able to say that when I take this lot, and I want to put them in, because I think that this is the mechanism, that these cells do fuse and form myotubes and at passage four, this is what they do. Or, you know, in passage one, this is what they do.

And so it's just one more characterization assay on what it's going to do, and that this lot has that kind of phenotype. When you have cells, you have to define them in some fashion as a phenotype, and we can't just do it with markers.

DR. ITESCU: I would just like to--the conclusion that was just drawn about a barrier; that increasing the data required to move into Phase I being a barrier to a single center initiating a trial being a bad thing. I think, in fact, it's exactly the opposite from my perspective: it's a good thing.

I think we want to raise the barrier to the level where you understand as much as you can about the biology of the product, about the potency of the product and about the safety of the product. I think we want to raise the barrier to prevent the conclusions that we're coming to that every cell

type works, that many small trials have been initiated. We can't conclude anything at this point in time because not enough product understanding has occurred.

And I think to increase the barrier is a good thing, not a bad thing.

CHAIRMAN RAO: I think the FDA always likes to hear that--

[Laughter.]

--people are asking for regulations.

DR. MURRAY: I mean, I view this through the prism of how we treat the human subjects in these trials. And if--to the extent that we can actually draw meaningful data from the trial, we just have a better justification for involving human subjects. And even in these Phase I trials.

To the extent that we have total non-standardization, and, you know, we're letting a thousand flowers bloom, I understand some might favor that, but I think, at minimum, we want to be able to have comparability, or at least to know the bases for comparability from trial to trial. And that's simply one way of showing respect for human subjects.

Now how do you do that? It's not simple.

I mean, I will return to this when we get to the clinical--discussion of the clinical issues. But that would be a reason I would advocate, you know, any sort of cooperation, standardization, etcetera, that we can ascertain at this time would be desirable from that perspective.

CHAIRMAN RAO: I'm going to ask Dr. Grant and Dr. Rieves--do you feel that you've got a sense of what the community feels, basically, on the whole manufacturing process and early stages?

DR. RIEVES: The information's been very useful. If we understand correctly--with my confederates here--the feedback that we are getting is largely consistent with what we have been trying to apply to cellular product development--not only in the cardiac field but in other fields in general. Your comments are very useful.

If we are understanding correctly, you are not objecting to some flexibility in early product characterization. You're encouraging exploration, but that has to be tempered by the need for attempts at the most consistency as possible, such that the data are interpretable. And, basically, we're not hearing objections to the procedures that we've been using in cellular product development,

in terms of manufacturing information.

CHAIRMAN RAO: I think one important point that came through, I think, as a caveat, at least to me, was that one can't simply consider a product at the level of "you've got it in a vial," because that really doesn't define it in any fashion. And so there has to be some information on what happens when you put it into any model that you do. And if there's going to be death, we need to know that that's consistent, because if you have too little death or too much, that will be a problem. If you've selected for some sub-population that grows, that's going to be a problem.

So that's going to be--and that the mode at which you deliver it can't be extrapolated. So you can't say, "Well, you know, today I used a 27-gauge needle, and that was how we defined this product in the manufacturing that you're going to use." It's got to be at least factored in in terms of what has to be done when you're comparing anything, or when you look at the sense.

But, other than that, you look at what's the best that can be done.

But, to me, it seemed that those were two additional things that people don't normally

consider in drug release maybe. But that needs to be factored in to the cells. At least that was my sense.

DR. SCHNEIDER: To paraphrase Dr. Murray: let a dozen flowers bloom.

[Laughter.]

I think that for many of us, the hazard, as I've said, is the impression created by the high visibility trials that this is easy; that this can be done by any cardiologist or cardiac surgeon with access to a blood bank. And that's adamantly to be discouraged.

CHAIRMAN RAO: Go ahead, Dr. Noguchi.

DR. NOGUCHI: Yes--I think this has been an excellent discussion, and we appreciate the rigor with which the committee and all the participants here want to move the field forward.

I will point out that, to a large extent, this is not FDA's field. It is our job to look and to evaluate independently what comes in. If, indeed, you're talking about a dozen flowers, if we get 4,000 applications I can guarantee you my staff will review every single one of those applications.

We would prefer--

[Laughter.]

--that we get some selectivity, but that is not our judgment. That is not our duty, and that is not our responsibility. The responsibility is clearly that of the community that is trying to develop these products. That is clearly determining what may be true North or North by Northwest, or even maybe giving you the first step on the journey. It's not for FDA to tell you, it's for you all, together, to come to consensus to develop the scientific knowledge to consider the subjects absolutely as the center of all your discussions, and bring that, not just to us, but to the public so that we can have a reasonable discourse about it.

So I think, really, we've heard--for the manufacturing, we've heard a lot of very good suggestions. We've heard a lot of preliminary discussions. The refinement of this we will help. But it's up to all of you to provide the data so that we can make the evaluation.

CHAIRMAN RAO: So, as Joanne pointed out, somebody has to help formulate a committee of, you know, cardiologists to look at that.

DR. TAYLOR: Dr.--

CHAIRMAN RAO: Is it a big comment?

Because you're keeping everybody from a break now.

[Laughter.]

DR. TAYLOR: Dr. Rao, there is one issue that I didn't hear at all, and that's vehicle. And I think vehicle is an important issue that we can't ignore here: what the cells are injected in.

CHAIRMAN RAO: Yes--I think that's an important point, and I sort of--people raise this issue, and it was raised before in terms of whether serum is good or bad, and whether there's a serum-shock effect, depending on how much is there. Dr. Epstein, for example, pointed that out. And that excipients, just like in any drug, are also an important component that has to be fully defined in terms of doing this. And I think that's going to be important to do when you look at comparing anything, or look at when you're delivering cells.

And you're absolutely right; it's even the glucose, and the PBS that you put in when you deliver cells, it's going to be important. And I think that's an important thing that the committee would suggest to the FDA as well, is that when you define that product, that that information should also be collected.

DR. SCHNEIDER: Very quick response to Dr.

Noguchi's suggestion about a process for consensus development.

Betsy Knable and NHLBI have planned for this coming September what promises to be the most authoritative collection of investigators on the subject of cardiac cell repair. And it might be useful to communicate with them that, as one potential long-term outcome of that meeting, that process of consensus committees be engendered.

CHAIRMAN RAO: So we'll take a 10-minute break, and attack some of the next questions.

[Off the record.]

CHAIRMAN RAO: Back on the record.

It's time to get back to work, I guess.

[Pause.]

So this is going to be a little bit easier, though not doubt as contentious, I guess. And the only reason I think it's going to be a little bit easier to consider this issue is that we've discussed aspects of this already. And I'm going to try again to see if we can summarize a little bit of what people have already talked about.

So there seems to be some consensus in the field that if you're looking at physiology and

overall global function, and you're looking at certain of the tests which are non-invasive, it seems that you are quite critical in terms of needing some large animal models.

However there are some disadvantages to large animal models, and there are alternatives in terms of small animal models which may be useful because they have certain specific advantages.

And one contentious issue seemed to be that even though we have some advantages with small animal models, we have to worry about the immune-suppressed state, and that there are some disagreements on whether you can use an immuno-compromised model as a xeno-model, where you can transplant, say, human cells into a small animal model.

And, otherwise, the field seemed to think that one should be doing comparable cells. So you take, you know, bone marrow cells from the same animal and put it back in a syngenic field.

Does that seem to be a fair summary? And maybe I'll ask Doris that question--just as a yes, no.

[Laughter.]

DR. TAYLOR: I think that's accurate.

I think devices--obviously, you've got to do in large animals. And some of the other things--cells you can do in small animals.

CHAIRMAN RAO: Dr. Epstein? Or Dr. Itescu, can you--would you say yes or no to that summary?

DR. ITESCU: Yes.

CHAIRMAN RAO: So, keeping that as a background, maybe we can look at specifics in some of these models. And, again, that hopefully gives us a clear-cut breakdown into small and large animal models--right?

And maybe we can start off with Dr. Borer's point about: you have to integrate information--right? And that you have to collect data. So, maybe if you take a large animal model--maybe, Dr. Borer, would you like to say what one would like to collect, and what kind of animal model? Would there be any preference, or an absolute requirement for a particular model?

DR. BORER: Sure. I don't--well, yes, okay. I'll tell you what was an absolute requirement. An absolute requirement are hard natural history endpoint collection; death, major clinical events in the animal: myocardial infarction, stroke, what have you. I mean, we

could define a list--infection, whatever.

But can I just say one more thing? And maybe I'm going beyond what you're asking me, but a point that was raised yesterday--and I want to raise it again here--is that there are several different things that are happening in the myocardium. Putting in cells that differentiate in a way so that they can generate force is wonderful, but there has to be a remodeling process that goes on.

And the cellular remodeling--cellular remodeling--differs among species. So that while there are certain things that I think we can look for in small animals, over and above the generic stuff I just said, there are other issues that really probably cannot be judged in mice, for example, because the myocytes and the fibroblasts in mice do different things than the myocytes and fibroblasts in species closer to humans.

And I would just, again, bookmark the issue of cellular remodeling. We heard a little while ago from Dr. Taylor that the heterogeneity of the product that's injected probably is important. I think it probably is, too. I think it's very important. I think it's very important because of

the points that Dr. Epstein made yesterday; that is that the cells are secreting stuff. We don't know what they are, but they're probably crucial to the whole system working well. And, again, those processes differ among species.

So I think when you start to look at the global issue, and the remodeling issue, you really have to be closer to people than to mice.

CHAIRMAN RAO: Can I ask you one question just as an extension of this?

Is there a sense, then, that since animals are not like humans, for example, and that there are going to be species' differences and these are physiology differences which are critical, that you can't just do animal studies that will match? Or should you be doing both xeno- as well as syngenic studies? Or that's not something that the committee thinks is a good thing to do?

DR. BORER: Well, I mean, I'm not--I hope I'm answering the appropriate question here, and that I understood it properly--but, we can't answer all the preliminary questions that we need to answer to be able to go forward with clinical trials by doing clinical trials. There have to be--there has to be some information that is at

least intuitively reasonably predictive to suggest that you're going to do something good and you're not going to do something bad once you start working in people.

There are many examples of animal studies done in species closer to man than to mouse; you know, on dogs and in pigs and even rabbits--and primates, of course--which have been reasonably predictive of the general response that you see in people. Will that lead to a clinical benefit, or will it not? I don't know. That's what clinical trials are for.

But I think that you can and must do certain animal studies to at least suggest that it's reasonable to infer that there might be a benefit, and might not be excessive harm outweighing the benefit if you go to people. So I think that there are studies that should be done in animals. The assay for potency that Mike and others have talked about I think is key, and that probably can be done in small animals.

And I'm probably getting much more specific than you wanted me to. But I think that several animal models have a place here; that it's crucial to do preclinical studies before you do

clinical studies. My only argument was that in all species we look at, we have to look at deaths, infarctions, strokes and other major events, and that we shouldn't forget about the remodeling issues because, as Steve pointed out yesterday, these cells know better than we do what they're supposed to be doing, and they do it, and we don't know what they're doing.

CHAIRMAN RAO: Bruce? And then Dr. Schneider.

DR. BLAZAR: One question I haven't heard answered is the role and function of human cells in rodents. It's been implied that you could use human cells in rodents to assay biological function. We know for some cell types--core blood in non-SKD mice, you can get some assessments, whereas human t-cells put into rodents in general don't function well.

There are certainly non-cellular sources in rodents that don't receive the right inductive or survival signals, and I guess the question is whether the fraction of cells that survive, are they biologically functional if you put human cells in rodents?

I didn't hear a lot of discussion about

that. And given the heterogeneity of the population, between myoblasts, fibroblasts, macrophages, SP cells--to what extent, and where is the barrier drawn for being able to assess biological function in either small or large animals, of the actual human product?

CHAIRMAN RAO: Before I ask one of the cardiologists to answer, I'm just going to ask if--Dr. Schneider, is your question similar to Bruce's?

DR. SCHNEIDER: I was actually going to follow up on that.

CHAIRMAN RAO: So should we, then, have that question so that maybe the cardiologists can answer that together--other cardiologists.

[Laughter.]

The presentations can answer that. Maybe I should make that clear. So go ahead, Dr. Schneider.

DR. SCHNEIDER: I was going to say, in response to Jeff's point about the balance of large and small mammals, that I would probably draw the line of preference at a slightly different point.

I think there's clearly a need--and an

unambiguous need--for large-mammal models, where delivery systems are to be studied, such as catheters or, conceivably, specific complex surgical procedures beyond the kind that we heard about in yesterday's presentations; that, inherently, because of geometry could never be adequately tested in a smaller mammal.

If the question is: does the biology of the smaller mammal allow complete predictability of the human situation, the answer would be no. My point is that that also would be true for the large mammal. The large mammal studies are not done in aged animals. They're not done in animals with disseminated atherosclerosis. So there always will be a gap between what we can learn--even in the best of circumstances--from the large mammal and from the human.

CHAIRMAN RAO: Would you add to that about safety, as opposed to efficacy?

DR. SCHNEIDER: Safety issues as well.

What I would do is to try to emphasize the point that the job of the preclinical data is not to predict the outcome of a Phase III trial. The job of the preclinical data is to predict the safety of a Phase I trial. And from that point of

view, I think a preponderance of small-mammal data is more than sufficient, with the exceptions that I noted, where complex devices are concerned.

It's to show the reasonableness of a benefit, and the reasonableness of safety. Ultimately, those have to be judged in Phase I trials. And if Phase I trials work, the more complex larger trials later.

CHAIRMAN RAO: Joanne.

DR. KURTZBERG: I was just going to add that I think the allogeneic models are important. I don't think we know what direction this will ultimately take. And I think they're important to ask question about tolerance induction and whether the use of allogeneic cells will be feasible--because it may be that, in the long run, it will be technically more straightforward to have the cells ready when the patient needs them, and it may be timing is important to get it right away or, you know, shortly after the MI--or whatever. And with autologous cells, you may not have that option.

CHAIRMAN RAO: Dr. Cannon.

DR. CANNON: This is really a follow-up to

Dr. Borer's and Dr. Schneider's comment about the limitations of large animals, as far as safety and efficacy.

And a good example is estrogen therapy. Hormone replacement therapy was believed to be safe and efficacious in all animal models tested; virtually all tested, including primates. And yet it did not predict the response in individuals with diffuse atherosclerosis and its risk factors.

So I think there are major limitations to even large animals.

CHAIRMAN RAO: Dr. Ruskin, and then Dr. Epstein.

DR. RUSKIN: Just a comment about the safety question and animal models.

I thin, with regard to cardiac safety, and particularly this issue of arrhythmagenesis, the small animal models are not going to be useful. They may be--they're very useful from a biological perspective, and potency, and other elements that people have raised. But I think that given the relative infancy of this field, that having experience in some of the well established large-animal models--particularly dogs, but also in pigs; dog models have been around now for three

decades of acute and sub-acute and chronic infarction, for example and, more recently, some heart failure models--can be very useful. And I would never suggest that the information obtained from these studies would be dispositive, but they can be informative from a safety standpoint, particularly if safety issues arise; that is, they tend to be rather insensitive. But if you see a major safety question with regard to arrhythmagenic effects in a canine model, that should be a red flag for whether or not one moves forward, and how one moves forward into Phase I.

So I would make a plea for doing work in large-animal models fairly early on--certainly well before considering Phase I trials with an aspect of these new therapies.

CHAIRMAN RAO: I'll have Dr. Epstein and Doris make quick comments.

DR. EPSTEIN: Yes. Bruce, just in answer to your question: if you wanted to test either safety or efficacy of human cells in an animal model--immunosuppressed--I mean, I guess the bottom line is there's no--as everyone has said--there's no perfect animal model. Because the effect of the cells you're injecting may not be primarily a

direct effect of the cells, but their ability to orchestrate, for example, an inflammatory response.

So if there's no inflammatory--host inflammatory response, that could either be efficacious or it could be--lead to adverse effects. So it's not a perfect model but, nonetheless, it could provide some important information.

So the bottom line is, I think that large animals, small animals--none of them are perfect. All of them can provide some important information. What should be required is obviously going to depend on what the specific question being asked, and what the specific cells are that one is thinking of injecting.

DR. BLAZAR: So can I--just before you leave the microphone, just ask you: what--is there a different frequency--if you put human cells in rodents, dogs, pigs, what fraction of those cells have any biological function or survival in the different species? Because while it may not correlate directly in each individual species, if the fraction of cell survival and being able to function in vivo is extraordinarily low in rodents and increases as you go up the ladder--

DR. EPSTEIN: You mean in the absence of immunosuppression.

DR. BLAZAR: However. To me, it's still whether there are appropriate inductive and survival signals. Forget, necessarily, the host immune response, but are there just signals so the cells just don't sit there. Because I know you can engraft human MSCs and MAPCs etcetera in rodents, but the frequency is extraordinarily low in many cases, without the necessary inductive signals.

DR. BLAZAR: Well, I guess the bottom line is that studies have been done, and published in excellent journals, demonstrating that you get a biologic effect. And as Dr. Borer has been emphasizing, you know, that is what you're interested in.

Now, what percentage of cells survive, and which specific cells survive is an important question. But there is important biologic activity when you put in human cells in a rodent model.

CHAIRMAN RAO: Go ahead, Doris.

DR. TAYLOR: I'm sorry, I just wanted to say very quickly that one of the slides I showed yesterday, in terms of comparing myoblasts and myoblasts plus--angiogenic myoblasts were human

myoblasts transplanted into SCD mice. And we saw a biologic effect. So--and I didn't emphasize that.

But I think, in terms of injecting human cells in small-animal models to test function, I think that's fine. I think to test safety, you have to move up the tree.

You know, nobody wants this field to move forward more rapidly or more quickly than--or more safely and quickly than I, but I think we have to answer the safety questions. We didn't anticipate them all with myoblasts, and now we have the opportunity to do it differently.

CHAIRMAN RAO: So before we get to you, is there anybody who strongly disagrees with the statement that Doris made?

Just--Doris said that, you know, for safety studies it seems to be quite important that you might want to consider larger animal models as well. That was her point. She said that--I'm summarizing, but--

DR. SCHNEIDER: If the operative word is "consider" rather than "implement," I think--

CHAIRMAN RAO: Yes.

DR. SCHNEIDER: --I think that's the distinction.

I mean, Dr. Ruskin makes a very good point about the safety issue with respect to arrhythmias. But it's one point that needs to be balanced against other considerations. If I were asked to weigh the predictive power of dog cells re-injected into the dog, versus human cells injected into a mouse as indicative of what human cells would do when injected into a patient, I'd rather know what the human cells do.

In many cases, the markers don't exist to isolate the cells from some of these large mammals. And as Steve Epstein pointed out, if one wants to use an immuno-compromised dog, sheep or pig, one is obliged to use drugs that have many confounding effects. Cyclosporin is used routinely in the transplantation field, but in heart failure studies many of us have been looking, for the last six years, at complex molecular effects of calcinurine-dependent signals.

So, from an immunological point of view, a mutant mouse is cleaner and more predictive than a cyclosporin-treated pig.

DR. MULE: So I've been hearing almost a consensus of the--not necessity for animal models, but the preference for animal models, perhaps.

What I haven't been hearing is what are we asking these animal models to provide us with information? I've been hearing a lot about the weaknesses of small animal models, large animal models, xeno-transplants, human cells into immuno-compromised mice--and, again, layering the complexity of the disease, which has not been replicated in any of these animal models. I've heard that one cannot necessarily predict the toxicity of the cell-based therapy in perhaps large-animal models.

So I guess the issue is: if we have myoblasts as sort of the therapy to be considered here--as one of the therapies, and we can conceivably understand that if we put certain parameters on that population, that in vitro will produce myotubes, for instance.

What are we asking of these animal models? Are we asking that 90 percent of the cells will die when they're injected? I think we already know that. And so what I have not heard--other than weaknesses in all these models--is what precisely we're asking these animal models to provide us with information that will help us to go to the clinic.

CHAIRMAN RAO: Hold that thought, and I'll

maybe ask you to re-phrase it again in the next five minutes or so.

Go ahead, Dr. Murray.

DR. MURRAY: Well, actually, Jim asked, in a broad frame, the same kind of question I wanted to ask. And I've been trying to listen carefully to the various things that have been said, and the questions that we're being asked to help the FDA address.

So, I've been trying to create a conceptual map to help myself understand what's at issue here. So let me just--what some elements are: we want to know something about the basic biology; what happens to these cells; what are these cells; what happens to them if you stick them in a heart--by various routes, by various means--you know, with all the various different ways people prepare these.

And you want to know about autologous cells, you want to know about--and you want to know how human cells behave in, you know, in an animal model, so you've got to have an immuno-compromised animal model. And there are all kinds of disadvantages there.

The hearts differ in these different

animal models, and their anatomy, the cell type functions; the geometry, physiology and electrophysiology. The disease--the disease models differ. You've mostly got fresh experimental lesions, rather than a good model of chronic congestive heart failure. Plus, in humans, you've got this background of long-term disease, with all the stuff that's happened, plus the drugs and other treatments and other interventions that have gone on--all of which make it difficult.

The hearts differ in these animal models and what you can measure. You know, a mouse heart beats--what?--600 times a minute? Is that what I learned yesterday? And it's probably a little hard to catch what's going on in those 600 beats per minute. Larger animals beat more slowly, or more like humans--allow more measurements.

So this is the sort of map I've been putting on this. And it's pretty clear that no single model is right. There are a lot of different questions you ask in different ways.

We're going to learn about the--ultimately, you want to learn about the safety issues involved with doing the sort of interventions that people are proposing to do, and

almost certainly that will involve some use of larger animals that are closer to the human.

CHAIRMAN RAO: Deborah?

AUDIENCE: I run a large primate program involving hematopoietic stem-cell biology, and I've also worked quite a bit in xenograft with mice.

I would stress that, like Bruce said, I don't think, if you have no efficacy in a xenograft you necessarily know if that is going to predict no efficacy in a large animal or human. The homing and engraftment of cells, if we're going to give them intravenously, or look at cytokine mobilization in a xenograft is, I think, completely useless.

Mouse spleens behave extremely differently from human and large animal spleens. The cells all go there. For most of the hematopoiesis studies, you have to splenectomize mice to get any information out that's going to apply to humans.

Non-human primates--we have lots of reagents like cytokines and cell service molecules, and the ability to culture cells that are very analogous to humans. What we don't have is cardiologists and cardiac surgeons who've worked in these models.

So as we tried at the NIH to bring some of these cell therapies into the non-human primate to test them, there just isn't very much known, and there's not a lot of comfort with the surgeons and the cardiologists in knowing how these animals react, in terms of arrhythmias and everything else. On the other hand, dogs, where you do know a lot, and pigs where you know a lot, you can't have any idea if the cell populations are correct. So, I either would try to put resources at an extramural level into better defining reagents, antibodies and cytokines for dogs and pigs, or get some cardiologists and cardiac surgeons more comfortable with working in non-human primates. Because for highly manipulated products, like MSCs, you're going to over-express AKTN, or MAPCs, I really don't think that you would want to put those into humans without having some long-term safety studies in a large animal saying where the cells go, how long they last, do they form tumors? You know, labeling them with iron or other moieties to try to figure out exactly what's happening to them, both acutely and sub-acutely I think would be pretty important.

With non-manipulated cells, and

mononuclear cells from the bone marrow that you're shooting into coronaries and things that have already been done, maybe that's not necessary, and maybe you can do it in dogs. But for the manipulated populations, I think you need to try to improve the primate models--potentially.

CHAIRMAN RAO: Go ahead. Just introduce yourself.

DR. KELLY: Ralph Kelly. I'm from Genzyme Corporation. And I wanted to follow up with Dr. Ruskin about the comment regarding arrhythmias.

For the MAGIC trial that Phillipe Menaasche is currently running, the protocol specifies that the skeletal myoblasts--autologous skeletal myoblasts--be placed not only in the center of the scar, but also in the border zone surrounding the scar, which obviously brings in issues such as reentry. And you discussed the canine model, for example, but then just sticking them in a dog and then doing Holter monitor studies and so forth may not be practical, or at least efficient way to do it.

Can you comment on optical mapping techniques, for example? Other measurements that might give us an idea how pro-arrhythmic these

cells might be?

DR. RUSKIN: That's a good question, and a difficult one to answer.

The technique of optical mapping is very useful for mechanism and for characterizing the electrophysiologic properties of the tissues, but doesn't tell you very much about arrhythmagenic potential. So I think you would probably end up doing continuous monitoring with implanted devices, and also electrophysiologic studies.

And I suspect that the yield would probably be quite low. And the concern, obviously, in these models always is that they are insensitive. So if one sees nothing, you can't take much away from it.

If you say a signal--for example, a high sudden-death rate among the animals--that would be a red flag, obviously, for a major concern. And that was my only point.

I don't think that ;there's a highly specific probe that we can use that's going to answer the question in an animal model as to what's going to happen in the human situation.

CHAIRMAN RAO: Dr. Harlan?

DR. HARLAN: You started the session with

the question: are animal models required before we move to the clinic, or should we do both concurrently. And then Dr. Mule asked about what question are we asking from the animal models.

I think the answer to the latter question, and then to your question, is that we're--in all cases, we're gathering data; that we don't know what we don't know. And, to me, I don't think there is any ideal animal model. We learn something from each one. And I think we learn stuff in the clinic that we can't possibly learn from any animal model, and so that you need to do both, and that then the question is: how do you do the clinical trial in the way that is least likely to do harm. And that will be, I think, the major topic of discussion.

CHAIRMAN RAO: I guess it's you, me and Rumsfeld--right? There are known knowns and known unknowns, I guess.

DR. ITESCU: I'd just like to add a little bit about the small animal models, and disagree with one of the earlier speakers--that, in fact, we've done a lot of work looking at homing and cytokines and chemokines in mice and rats--those immuno-compromised animals. And, in fact, it looks

like they're excellent models for being able to predict the ability of human cells to home and target the myocardium; that many of the chemokines and cytokines produced in these rodent models do, in fact, interact with the receptors on human cells.

So I think, in fact, they're very adequate models to study many of these processes. And perhaps the biggest difference between these models and the primate models, obviously, are the immune responses. And we just need to keep that in mind.

But, otherwise, many biological questions can be addressed pretty adequately.

DR. BLAZAR: I wasn't saying that the models were inadequate. I was not clear as to what ;you all had as a consensus as to the relative use of these xenogeneic system to get where you wanted to go--the way Jim phrased.

So if the consensus is that this does provide you the necessary readouts, despite the limitations of a xenogeneic environment, I think that's fine. But it did not come out in the presentations as to whether that was necessarily the case.

DR. ITESCU: Yes, I didn't show yesterday,

but we've got some pretty convincing data on a variety of cytokines and chemokines made by rodents, and how they interact with the human cells in a similar way to what happens in man.

DR. HARLAN: I just want to quickly comment that when you look at your cells and they do home appropriately, what you don't know is what other cells might not work in that model, but would work in a different model. So it's just the same point: we don't know what we don't know.

And so I think it's important to not rule out the possibility that a cell that doesn't work in a non-SKD mouse might work in a different species.

DR. ALLAN: Yes, I just wanted to come back to what animal model is appropriate. Because, I mean, I'm not in this field. So I sit here and I go, "Gee, you know, I don't hear that much about non-human primates." You know, because to me it's a no-brainer. You want to be using non-human primates.

And then--so it was interesting to hear what some of the reasons are why people aren't using non-human primates. It's a comfort zone: cardiologists never used--haven't used non-human

primates very often for this. Maybe it's also a question of cost, and numbers of animals--things like that--which I can understand.

And in this particular case it seems to me that what you're dealing with is basically cost-benefit--or risk-benefit, and that is, well, if you're shooting cells into humans, you probably aren't going to kill them, and therefore you don't have to use non-human primates because you're not sweating as much. Because in xenotransplantation, they have a bar, and you've got to do pig-to-primate transplants and show that the organ survives for more than, you know, five days or 10 days before, you know, they let you go into humans. Whereas here, you know, you shoot a few cells, and you probably are not going to kill the patient. And so therefore maybe you don't need to use non-human primates.

But to me, I mean, it's like--I mean, the non-human primates, it's not a perfect model--obviously it's not a perfect model, but it's a better model than any of the other models, in terms of you've got cytokines that you can use. I mean, this GCSF study, you know, they probably could have done some of that work in non-human

primates and would have got some ideas.

And it doesn't mean that that wouldn't happen anyway because, I mean, you look at gene therapy trials. Some of the studies in macaques show that if you give them too much virus you kill them, and yet, you know, they still went into humans with the same dosage and there were some adverse reactions there.

So I'm just--I'm not trying to promote the use of non-human primates, but I was just sort of like curious as to why people aren't using that more often.

DR. BORER: I'd like to get back to the issues raised by Dr. Mule and Dr. Murray, because I think they're very important issues. And let me try and take a crack at an answer.

CHAIRMAN RAO: Dr. Borer, can we hold off, then, on that--

DR. BORER: Sure.

CHAIRMAN RAO: --because I want to try and complete this--it's part of the question we want to address which is Question 4, but I want to try and get this whole idea of do we absolutely need models, and which kinds of models, and is there any absolute criteria that we should use first.

DR. BORER: That is what I was going to respond to, actually. I think that's the crux of what the question was: do we really need animals if we don't know how to interpret the results?

CHAIRMAN RAO: I think Dr. Murray's point was what kind of readouts, and what are you really using the models for? And I want to wait on that just for a couple more minutes if we can.

DR. BORER: Okay. Maybe I wasn't responding to Dr. Murray's question.

CHAIRMAN RAO: Okay, then.

DR. SCHNEIDER: So you don't want a response to Dr. Mule's question: why do we use the animal models?

CHAIRMAN RAO: Yes--not just yet.

DR. SCHNEIDER: Okay. Let me respond to why cardiologists--

[Laughter.]

--don't use non-human primates.

Apart from the fact of expense, lack of experience in most of the university medical centers, we are also cognizant of the fact that the non-human primate models are, to the public, an abomination.

CHAIRMAN RAO: Kathy?

DR. HIGH: So--maybe I have to wait, too, because I wanted to respond to Dr. Mule's question.

[Laughter.]

CHAIRMAN RAO: So maybe we can really list these as comments that can be made--give me a minute, then, to try and see if we have some sense of consensus on this minimal first part.

From what I heard from everyone here was that nobody thinks you should rush to go and do human trials without doing some sorts of animal studies--right? That seemed to be pretty clear.

And what also seemed to be pretty clear to me from listening to everyone was that there's no perfect animal model for the disease. So we're not trying to mimic a particular disease, but you're really trying to look at sort of some kind of critical issues on the cell type that you will use, and the choice really depends on the cell type that you're going to use, and that's why you have to vary between choices of models.

And there seems to be clear-cut consensus that for certain things you have to use a large-animal model. So, for physiology, sort of geometry, imaging issues and so on, it doesn't seem that you can answer those questions with a small

model.

But there are other issues where, maybe because of speed, maybe because the behavior has already been demonstrated, or there's a whole history in terms of sort of bone marrow studies which can be addressed in small-animal models--and there's no reason why they shouldn't be addressed in small-animal models.

So, ultimately, you may have to choose which model you use, depending on the type of cell you choose, and what type of readout you're looking at. And such models exist for doing that. But clearly there's no perfect model which will clearly answer all of these studies.

There still seemed to me a little bit of dissension--and I want to make sure that I haven't missed that--is there seemed to be some argument that safety studies could only be done in a large-animal model. And I wasn't absolutely sure--maybe some types of safety issues are really critical and can only be done in a large-animal model such as, you know, tachycardia perhaps, geometry and reentries phenomenon. But other studies may be simply more important in small-animal models--right? You know, where we

have--if you're looking at immuno-compromised animals and so on.

The last piece that seemed to come through from everybody was that animal cells are animal cells, and there are many, many reasons why they will be different. And we already know that they're different, so that though you can do syngenic, they're not going to be absolutely predictive of what will happen when you take human cells and put them into human patients, and you have to keep that view in mind. And if that's the case, then there might be certain times--or depending, at certain stages--where doing either xeno-models, or correlating it with--as Dr. Harlan pointed out--with clinical trials which are happening at the same time might be quite critical.

Is that--at least for part of choosing--we've not yet talked about what the Hell are you going to learn from a model--and I apologize for my language, I guess--

[Laughter.]

--but at least it sets up the fact that we need some kind of model. That seems to be irrespective--that we need something, and we nee to

get some information, and we need to collect a large amount of data from it.

And, Dwaine--

DR. RIEVES: But, Dr. Rao, those are excellent points, and it's very difficult to talk in generalities.

But if in the discussion the committee members could also consider something Dr. Dunbar touched on, is whether, as witnesses, or reviewers or production of development programs, we should consider flexibility with respect to the nature of the cellular product itself, as to how it's manufactured--these heavily manipulated products, the cultured products.

Should the preclinical testing for those type products be different from the many academic investigators across the country who say, "I'm harvesting bone marrow in the operating room suite, and I'm filtering it to get the specules out, and I'm administering it." When those sponsor-investigators come to us, they're going to ask is there some need for pre-clinical study. Or is it inherently safe because it's autologous and minimally manipulated.

If you could consider those type issues in

the discussion, too.

CHAIRMAN RAO: As soon as we start talking now, and hopefully, just next is what do we want to learn from an animal model, and why do you want to put cells in.

DR. TAYLOR: [Off mike] When I said the word "safety" I meant arrhythmia. I didn't mean--so there's really not dissension. When I said "safety" I meant electrical safety.

CHAIRMAN RAO: So maybe we can go with Dr. Borer, who was trying to summarize or respond, and then go with Kathy, and then Dr. Schneider, since you wanted to respond, too, sir.

DR. BORER: First let me say I agree with everything you said.

[Laughter.]

I think that where we may be going here, and what seems like a little dissension that I don't think really is dissension, is that what everybody wants is a preclinical construct that would be perfectly predictive so that you really knew what the problems are, and you really knew what the potential benefits were, or what the functional changes in the heart might be so that you could then give your therapy in patients and be

concerned, really, only about clinical outcome; you know, is there a clinical benefit, is there not, or does the benefit outweigh the risk.

There is no such preclinical construct for any disease--in cardiology. I mean, in other disease there may be. I don't know. But certainly there isn't in cardiology.

So I think what we want from the animal studies is two types of information. First of all, one would like to have some confidence that there isn't an overwhelming show-stopper lurking out there, safety-wise. Jeremy made the point: animal studies are not highly sensitive, in general, for cardiac events, but when cardiac events of certain types occur, one should take note of that and be cognizant of that in designing clinical studies if, indeed, it even seems reasonable to do that after you know about the major potential risks that one might have picked up in animals.

With regard to the minimally manipulated cells that are taken out of the bone marrow, filtered and put into a person--into the same person from which they came--is there any need for preclinical studies? Well, I would argue that you would at least want to test the implements that

you're going to use to take and do, to make sure you haven't changed the cells that you've taken out in such a way that they clump, form emboli and, you know, block arteries, for example.

I mean, so some kind of preclinical testing relevant to the specific situation would be appropriate, but here we're talking more about mechanical, I think, than biological problems--although there may be biological problems, too, with the minimal manipulation--I don't know.

But, anyway, that's one type of information one seeks from preclinical studies.

The second is some evidence that it's reasonably likely that a benefit might occur if used as therapy. You know, we can't test animals for clinical benefit, per se. I mean--or at least it would be very difficult to do it--unless we learned how to talk to the monkeys or, you know, followed the animals for a longer period of time than we usually do to look at outcomes of other sorts. But at least one can look at surrogates that seem, from a tremendous amount of prior experience, to be at least reasonably predictive of the likelihood that something good clinically may

result.

And for that purpose, I would say you would want to see some consistency among different types of models, properly selected for functional markers of one sort or another. And I don't want to get very much more specific.

Now, at the end of the day you've done all that, and you still may be wrong--as Richard pointed out. I mean, you know, all the animal studies can look great and you put the product into people and it doesn't work, or it does bad things that you didn't expect. That can happen.

But I think it would be wrong to expose human beings to a putative therapy without at least having done some reasonable screening so that you could--so that a bunch of reasonable people sitting around a table who had experience could say it seems as if we are unlikely to cause great harm, and it seems reasonable to infer that we may cause good.

Yu know, I think that's the basis of doing these studies. There's no perfect predictor, but without the kinds of evidence that I've been talking about, I don't think we could reasonably go to humans.

CHAIRMAN RAO: Kathy?

DR. HIGH: So, I just want to make two points, and I think I can be fairly brief because I want to agree with some of the points that Dr. Borer has made.

But just that, to me, the point of the preclinical studies--part of the critical goals of those is to define a safe starting dose and at least get a bracket around what would be an efficacious starting dose. And from everything I heard yesterday, that means work in large animals.

And the same point can be made about the deliver system. So that's one point.

The second point I want to make is to respond to Dr. Rieves' point about need for preclinical studies for single-site investigators who are doing small trials. As far as I'm concerned, they need to be held to the same standard. They need to show that the way they process the cells, and the way that they deliver the cells has some reasonable expectation in their preclinical studies. And I don't think that they should be able to avoid that responsibility.

CHAIRMAN RAO: Did you have a point, Dr.--

DR. CUNNINGHAM: Yes, I just wanted to

comment that there is a subset of the population who do not like primate studies, but the large segment of the population expects the FDA to ascertain safety. And so there's a large segment of the population who would also expect everything that was reasonable to be done to ascertain safety be done.

CHAIRMAN RAO: We're still trying to focus on the point that: what do we want in the readouts, and it is specific to specific cell types, so that Dr.--you know, that we address some of these issues. So if you can try and--

DR. SCHNEIDER: Yes. With respect to skeletal myoblasts, I think the goal in the preclinical data, along with the safety issues, is more straightforward than for some of the other cell types that we've talked about. The goal in skeletal muscle therapy is to replace cardiac myocytes with another contractile cell type which, regardless of the presence or absence of electrical coupling, does have strong animal data--as Doris and Phillipe showed yesterday--suggesting that they improve pump function in the regions of the ventricular wall that receive the cells, and also global pump function.

So, to your point and Jeff's I would say: the skeletal myoblast trials are very simple. What they're trying to treat is heart failure, and it's functional correlates as measured by MVO2, or ejection fraction, or pressure volume loops; and in patients--but not in the animals--symptomatology, and whether or not they also have the other kind of clinical correlates--reduction of hospitalizations, reduction of the need for transplantation, reduction of mortality. That's one of the things that the animal models just won't answer.

For me, the goals in the angiogenesis--or in the pleuripotent cells is more complex. And maybe Steve or Silviu could comment. Many of those are also being done with pump function as a major endpoint. These studies are done in a different setting clinically, typically, with treatment within the first days of myocardial infarction, and it's likely that the mechanisms of efficacy include at least some cytoprotective effect on jeopardized myocardium, plus angiogenesis, plus--and this point is highly controversial in the field--the conversion of the bone marrow or circulating cells into cardiac myocytes.

Steve, I'm not aware of any cell therapy

trial that's been aimed at intractable angina as the--

VOICE: I think there have been several.

DR. EPSTEIN: Yeah.

DR. SCHNEIDER: Okay. So I think what one is asking of the animal models in those cases is different, and not the same as for skeletal myoblasts and chronic heart failure.

CHAIRMAN RAO: Dr. Epstein?

DR. EPSTEIN: Yes, and I would agree with you--

CHAIRMAN RAO: Before you answer, Dr. Epstein--

DR. EPSTEIN: Yes--sorry.

CHAIRMAN RAO: Dr. Harlan, did you have--

DR. HARLAN: Oh, I was just going to respond to Dr. Rieves' question that he asked about should there be different standards of safety and product release for cellular products that just come out of the patient, versus those that get manipulated.

And I would simply endorse what the FDA does; that the further you get from what is taken out of the patient, the more rigorous the testing. I think what you guys do is right.

CHAIRMAN RAO: Dr. Epstein?

DR. EPSTEIN: Yes, there have been, I think, four studies published, including our own--and Dr. Perin's, really--which are not an acute myocardial infarction studies. They really are angiogenesis trials. Even Dr. Perin looked at patients with reduced ejection fraction.

But I think the goal there was to improve perfusion of that ischemic myocardium. And our study was in chronic stable angina.

So I think there are two approaches for angiogenesis. One is in the acute myocardial infarction setting, which may be part myogenesis, part angiogenesis. But then there are many--several centers that are involved in sort of chronic refractory angina.

And I completely agree with you. The endpoints that one looks for in the animal models for efficacy would be very different than for myogenesis.

DR. KURTZBERG: I have two comments.

One, I want to really endorse what Kathy said and just also say that I think if you define all these things going forward, you will save time. You will make progress more quickly. I think we

learned that in the bone marrow world after we didn't do that. And it took us 15 years to get together and agree what engraftment meant.

But if you have those common definitions ahead of time, you can talk between your studies, and you can compare things. And so I don't think it matters whether it's a Phase I study at a single institution, or it's a multi-institutional study. I think having those agreements makes you be able to talk and make progress much more quickly.

And I also think, you know, you may be doing skeletal myoblasts now, but who knows what other kind of myoblasts you'll do in a few years. And if you don't agree to have the same common terms and endpoints--even though you'll modify them--you won't be able to compare one to the other.

So I think that's really important.

And then the second thing I wanted to say was just to clarify my comments about autologous, unmanipulated cells. I think they should be studied under IND for delivery, but I don't think they should become a product. I don't think that we should have to pay--the patient should have to pay extra for their own cells that are not

manipulated in any non-classical sort of standard of care fashion.

So once they're proved to be efficacious, and the delivery systems are defined, etcetera, then I just don't want to see them turned into a commercial product.

CHAIRMAN RAO: So, you know, there are a couple of things that are still a little bit confusing to me, and I'm going to try and see if we can focus on those as well.

So--you know, to me, it's pretty clear that one needs animal models to do some sort of safety study. But, to me, what's not clear is what kind of safety studies are absolutely critical, in terms of when you put the cells into an animal model?

For example, if I were to deliver cells by IV, you know, I don't just want to look at the heart and look at safety studies and look at V-tach. You know, I really would like to know, for example, what's happened to the cells where we didn't want them to know. You know, probably a lot of them go to the kidney and the spleen and the lung. And should we be, in animal studies, be worrying about where they are if that's the method

of delivery?

If we put cells in, you know, with a catheter, and then that's the animal model that you're studying in terms of safety, should we be saying that, you know, you always want to have to look at a leak--right?--because that happens with a certain frequency. Is that a really specific thing that we need to worry about? And are there certain, sort of simple, obvious things like this which need to be considered, or should be required in an animal model?

I mean, Kathy pointed out one thing and, you know, it came up with Dr. Murray and with several people, is that we need something about dose--right? It doesn't matter whether they're minimally manipulated or not, or whether they've been grown in culture. We really need to know what's a safe dose when you deliver them, and we need to know that in that animal model, and we need to know where they are. And that came up when we talked about it.

So are there any such other things that one might want to consider, specifically with taking a particular cell type which has been manipulated in culture, you know, and that has been

put in by a certain methodology, that you would absolutely want to highlight and say, you know, "If you do this, and you put in an animal model, we really want to worry about this?"

For example, in the nervous system, you know, epogen cells which have maintained in culture, I mean we really, really want to know whether they continue dividing for up to six months, and whether they form a proliferating mass. I mean, we consider that a requirement when you put the cells in--right?-- in terms of doing it.

Maybe there are some things like this that should be clear to the whole cardiac community. And maybe there's a consensus. And maybe the cardiologists can tell us.

Who wants to take a first shot at that?

[Laughter.]

DR. SIMONS: You know, I find it very difficult to speak about these models in such general terms. I think we haven't gotten into any amount of detail you need to sort of talk about it.

And I'm not sure we have enough people around the table, or in the room, who are extensively familiar with these models--of course, we will get into the use of devices, the use of

cells. And if that's an important issue--and I believe it is--maybe it should be a subject of a separate discussion by a separate panel. I would really like to suggest that that could be an important step forward.

And we're talking about the cells sort of transformed as if this was a single disease. It's not. There are at least two different circumstances in which this is going to be used clinically, and each of the circumstances will actually dictate a very different model and a very different delivery strategy.

And we either have to get into a very profound amount of detail to sort of go over it, or we should maybe sort of postpone this.

CHAIRMAN RAO: That's an important perspective and I think, unfortunately, the FDA doesn't have that luxury. And so--

[Laughter.]

--we have to see whether--that the conclusion can be that this is all we know, that there's some even generic sort of advice that one can offer.

DR. TAYLOR: I'm not a cardiologist, but I've been thinking about this for a long time.

And, obviously, moving into clinical trials is an important step.

I think we're in a very early stage here. When the first myoblast trial was designed, for example, MRI was the surrogate marker that was used as an efficacy endpoint. Partially through the trials, people discovered that, in fact, ventricular tachycardias were emerging, and that people had to have AICDs implanted. And all of a sudden the endpoint was no longer useable.

And I think it illustrates how dynamic this field is right now, and how flexible we have to be in terms of changing as more knowledge comes forward. And I think that's what the FDA has to keep in mind; that many of us who have been thinking about this for 15 years haven't yet gotten together and defined all the terms. We're doing that now, but we don't know.

CHAIRMAN RAO: You're right. It's important. You're echoing what Dr. Simons just said.

But let me ask one specific question before we get to Dr. Harlan.

Do you think that one could say that, well, we really, really, absolutely, for safety,

need to know about cells, so they have to all be labeled so that we can follow them--in a reasonable study.

Is that something that should be like a de rigeur requirement--you know, an observation. We don't--

DR. TAYLOR: In a clinical study? Or in a preclinical study?

CHAIRMAN RAO: In a preclinical--since we're talking about animal models, and--

DR. TAYLOR: I think right now it probably depends, to some degree, on the cell type. The short answer would be: I think we need to do bio-distribution studies that we haven't done.

There are data that, you know--we know some of these cells track to bone marrow. We know they then get recruited to other places that we don't know anything about yet.

On the other hand--and a lack of a label has been a real issue, and that's one of the reason small animals--mice--where you can use genetically labeled cells are an incredibly important model to be able to track these cells in vivo. That's a situation where safety studies could very easily be done in small-animal models and be important.

Do I think clinically we need to be able to label and track these cells? No.

CHAIRMAN RAO: Dr. Harland?

DR. HARLAN: Well, I just want to respond to your specific question about other potential safety tests to consider, and to follow up on a comment you asked about this morning about karyotype.

I wonder if anybody is looking at, say, cells that have been propagated in culture, transplanted into a non-SKD mouse two years later? You know, I think that may be--it may be something that's not being looked at right now: the tumorgenicity of these cells. And I would suggest that would be a good way to look for that. Karyotype's one way, but an in vivo test would be better.

CHAIRMAN RAO: But would you agree--I think it's a very valid point. But say, for example, that that can't be generalized to all cell types because there might be a lot of data on, say, minimally manipulated bone marrow cells, for which there's long history of operative reporting, but may not be true for other cell types that are put in.

I want to ask: do you feel that this sort of addresses some of the issues that you had raised, in terms of the kind of things that one needs in an animal model?

DR. MULE: It does.

DR. TAYLOR: I slightly disagree with regard to minimally manipulated bone marrow cells, because of some rodent data that haven't fully been explained yet, which are that GFP transplanted--animals were ablated and green fluorescent protein cells were used to replenish their bone marrow. Tumors were implanted in those animals, Several weeks later the tumors were explanted and the vessels were green in those tumors.

I think we don't know exactly where these--we know these cells go where we want them. We also suspect they go places we don't want them. And until we started--we do need to begin to address that preclinically, I think.

At the same time, that's no different than is already being required. I think people are doing tumorgenicity studies with most of these cell types before they have the ability to implant them.

CHAIRMAN RAO: On this note--and I know

that there still is sort of sense that there's no perfect model, and that we don't have a single model that we can look at, and everything depends; and that "everything depends" is sort of anathema to, you know, the FDA--I guess.

But let's add to that just one more issue here so that we can see whether this sort of uncertainty also extends to specific models of ischemia.

So--a lot of things that we've looked at--there has been--the data that we've heard has been about transplanting cells in the animal trials and the human trials has been in some sort of either ischemic infarct, or with low ejection fraction where there has been damage.

Are there any merits to any specific model, that you would say one is better than the other, in terms of either the cryo model or the banding model, or it's any species? And, again, maybe I can ask one of the cardiologists who has experience with this to make some general statement and see.

DR. RUSKIN: There are a number of canine models that are relevant to the human situation with regard to ischemic left ventricular injury.

So, certainly, if I were given a choice, I would choose one of those over a cryo model, which is really not a physiologic model. Cryo produces very uniform scarring, very discrete margins. It doesn't bear any relationship to the architecture of myocardial infarcts.

So I think if I had to pick a model--

CHAIRMAN RAO: Dr. Ruskin, when you make this, would you also sort of consider this in the light of "predominantly safety" versus efficacy studies, as well, in terms of a bias?

DR. RUSKIN: I think that it's relevant with regard to both safety and efficacy.

The model that we developed in the late 70s, and continue to use, are the transmural myocardial infarction in dogs. It is highly analogous to some of the questions that are being raised here in humans, in terms of wanting to treat areas of myocardium that are truly dead. This is a model of LAD occlusion with ligation of all the collaterals, from the right and the left circumflex coronary arteries to produce an aneurism at the left ventricular apex. It produces a thin transmural scar, with very little in the way of islands of viable myocardium--which would seem to

me to be an ideal substrate in which to test this kind of question.

So, if you asked me to pick a model, that's certainly one of them that I would pick. And, generically, I would certainly pick a true ischemic-induced injury over a cryo or some other synthetic kind of injury, if you will.

CHAIRMAN RAO: Dr. Simons?

DR. SIMONS: I certainly agree with Dr. Ruskin that the cryo injury model is probably not the way to go, for a number of different reasons.

There are two standard ischemia models that's been used as a basis for a lot of the growth-factor trials. One is an amyloid model, which is the most--which, over the last 10 years became the most common cause of coronary artery disease in pigs. And we know a lot about this model. We knowhow it works.

We also know that the drugs or devices or cells or genes that work in that model don't work in people--which raises an issue of how useful that is. It certainly can be useful for safety testing, and a lot of other natural history. But it's clear that if--a pig, and if you have coronary disease, we're going to fix you. And unfortunately that

doesn't happen in people. And this could be the fact that these are young pigs, that are going to grow. They don't have any lipid disease, and they are not taking drugs. So, it's a hard one to study.

As the other model that I think is getting a lot of play now is the hind-limb ischemia in an APE knockout, or an LD with a septal knockout mice, because here you can mimic age, which you cannot do in pigs and dogs. And here you can mimic a lot of human disease.

And it's interesting that the data is sort of emerging now is that none of the growth factors actually work in that model, and that could well explain why they actually don't work in people.

So I think you can use pigs or dogs with a chronic ischemia model such as an anaberoid to study how effective your devices are in getting the desired cells in place, and you can use the diseased-mice models to get more of a functional readout of whether the desired therapies will work in the setting of age and disease.

CHAIRMAN RAO: Can I ask one more question here, is that even in terms of safety, is it really important to study the effect of these cells in an

animal model--in some kind of ischemia model? Because the environment has changed; you know, the cytokines have changed, the milieu has changed. So when you look at safety studies, should you be really doing it in some kind of model of ischemia or not?

DR. SIMONS: I think the safety study in animals should sort of mimic as close as possible the clinical trial design. So, if this is going to be a trial of cells injected in-- that's how the testing should be in animals, because of ischemic milieu, and actually it has to work in ischemic milieu, will have a different effect than if you're doing it in healthy animals without it.

CHAIRMAN RAO: Dr. Schneider, then Dr. Borer.

DR. SCHNEIDER: To follow up on Dr. Simons' comment about using ischemic models to mimic ischemia, the harder part, I think, will be using heart failure models to model heart failure.

And if one considers the heart failure population that Dr. Perin was speaking of yesterday, and which is nominally the substrate for many of the skeletal myoblast trials and some of the other therapies, many patients have heart

failure as the result of prior coronary artery disease and infarction; not all of them do. Many of them have longstanding hypertension as a contributing cause, but not all of them do.

And what I would say is that a number of animal models--rather than seeing a limitation of the field being that no one can agree on an animal model which is perfect--specifically, no one can agree on an animal model which is perfect for all clinical situations. I would also say no one can agree on an animal model which is perfect for either of the clinical situations.

You know, you've heard convincing allusions by Dr. Ruskin and Dr. Simons to one of the best ischemic models, in the dog, and one of the ischemic models, in the pig. And I personally don't think that someone who comes to the FDA with preclinical data should be precluded from using one of those rather than the other. You know, a number of alternatives are possible, as well.

The situation becomes more complex in heart failure, where there is far less agreement on what an adequate large mammal is. Some investigators used rapid ventricular pacing in a dog or some other species. I would say that the

smaller mammal models, or the rodent model--Syrian hamster model of cardiomyopathy, which one speaker alluded to yesterday--in fact mimic human heart failure better than the pig or dog models that currently exist.

CHAIRMAN RAO: Dr. Borer.

DR. BORER: Yes, unless Richard is going to disagree, I think we're all in unanimity here--those who are cardiologists around the table--because I think the point is well made that if the therapy is going to be given to people with ischemic heart disease, then a physical injury model is not appropriate, because the myocardial milieu--the response of the extracellular matrix, etcetera, etcetera--is going to be very different in that setting than in an ischemia setting.

Having said that, of course, the animals don't perfectly mimic people. So what one would like to do would be to look at several models. The dog model is the one that we used to use at the NIH regularly, because it was easy to manipulate and seemed to be predictive. And there's a god deal of information about the predictive value of the dog and the pig in certain situations.

The point I would make here, though, is

the one that Steve Epstein has mentioned again and again: the selection is going--the selection of model is going to depend, in part, on whether you're thinking about myocardial function alone, or angiogenesis--or arteriogenesis, to be politically correct--because the different species differ, for example, in their collateral development response to coronary occlusion, etcetera, etcetera.

So one would like to select the animal depending upon what it is you want to look at.

Having said that, the point that mike made is very important. There is no really--you know, there's no perfect model for heart failure. All of them are deficient in one or another. And earlier today Dr. Grant said that heart failure is the only cardiac disease that's increasing in incidence over time.

There's a subset of that: valvular diseases are also increasing over time. And the valvular--the valve manipulation models produce heart failure that mimics human disease as well.

The point is, there are several types of models one could use. As Mike said, I think you want to use several, and try to find some degree of consistency of the effect of the therapy in the

different models, none of which is absolutely perfect.

The only thing I think that I would avoid is the physical injury model, which I don't think has much relevance.

CHAIRMAN RAO: Would it be fair to say that if you were looking at the behavior of cells which are being transplanted, that it's far better to look at them in an ischemia model--preferably as close to a human disease as possible--and that that would be better than looking at it in a wild-type or a non-injured model?

DR. BORER: Absolutely.

CHAIRMAN RAO: Because the behavior would be--

DR. SCHNEIDER: Absolutely--not only for the reason that you cite--that the milieu in which those cells are required to function would be different, but also for the reason--going back to Dr. Mule's more general question, "What are we looking for in the animal models?"--we're looking for evidence of efficacy.

And so to rescue ischemic dysfunction, one needs ischemia.

CHAIRMAN RAO: Can I ask one more question

before--

DR. EPSTEIN: Just--directly--just to support what you've said, there was a very recent and very interesting paper in Circulation, where they were looking at adverse events of cells, namely a pro-atherosclerotic effect. And they were using the ischemic mouse hind-limb model.

Cells derived from APLE knockout mouse increased atherosclerosis, but only in the presence of hind-limb ischemia. So that's another point that substantiates what you and the others have been saying.

CHAIRMAN RAO: Did you have a comment?

DR. WEISS: Yes, I'd like to make a comment. My name is Judy Weissinger, of Weissinger Solutions.

I wanted to make more of a philosophical comment in the concept of agreeing on an animal model, or requiring large animals for certain things; requiring small animals for certain areas.

I think what I'm hearing today is a lot of people are identifying the question we need to answer, and the considerations that we need to address in developing these products, along with the potential models, the studies, the methods that

we need to address.

And these questions and considerations are really important for the sponsor to propose a plan based on the product--the uniqueness of the product they're developing, and the clinical design of the study.

And so I just want to caution again--and go along with the traditional biologics approach of identifying the criteria that are needed to evaluate a new therapy, as opposed to specifying and requiring the exact studies that are needed.

Thank you.

CHAIRMAN RAO: That's a good point.

On that same--I just want some sort of general feeling from people is that, you know, almost all the viral studies we think about, or any other study, we also always have some sort of sense of how long you want to follow--right? Even in a safety thing--like we talked about tumors.

I mean, is there any sense in the cardiology field, for example, that, you know, if we do this animal study and, you know, you want to look at an animal, and we have to look at this--should it be six months? Should it be one year? Should it be--you know, "Well, three weeks

is enough?"

DR. BORER: Let me try to answer that in two ways.

First of all, you asked a question before that's relevant to this point. And I don't think it received a specific response.

You said given the fact that with some forms of delivery cells will be distributed systemically, leads to questions about whether you should look at other issues besides cardiac issues. And I think the answer is absolutely yes, but there must be--and I don't know what it is--must be a rich experience from hematology studies over the years to tell us about how and what one should be looking for. In that situation, I think one would want to do that, in cardiac studies as well. And that would drive the duration of follow-up in some animal studies in a certain way.

In terms of the duration of follow-up for, specifically, cardiac problems, that depends upon the outcome you're interested in, and it depends upon the model; and, specifically, it depends upon the expected outcome of the animal naturally. You know, mice don't live very long. I'm not sure what the duration of follow-up of a mouse would be that

would be meaningfully extrapolatable to people.

But, you know, the average life span of a dog or a rabbit is known, and one would like to follow the animal for a substantial period of that life span that might be relevant to the natural history of the disease, I think. That doesn't mean that every study has to be done that way, but one might like, for example, in a rabbit to be able to follow it for two years, if you're looking at heart failure issues.

I mean, I don't want to give a specific number. But the principle is that the follow-up, at least in some studies, should be relevant to what you expect the outcome to be in people, I would think.

CHAIRMAN RAO: So that seems to be the consensus from a lot of other stem cell fields, where you expect cells to persist for a long period.

I mean, for example, when you think about the nervous system, that seems to be the case; where you say, well, we do it in mice, we want to look at least 50 percent of the life span. They live about two years, so you're going to follow at least--not "at least" in every study, but for

particular studies, at least follow for a period of a year--but not in every study.

DR. TAYLOR: Talk about a hurdle! I mean, we know that in most of our preclinical studies, the function gets better in a month to two months, and it doesn't get better after that. It stays pretty level.

In patients, the data seem to suggest there's an improvement at three months. It seems to be maximal about six months, and it stays stable after that.

I think requiring two-year follow-up in these animal studies, in light of that, doesn't make a lot of sense--at least from what I can see.

CHAIRMAN RAO: Dr. Ruskin.

DR. RUSKIN: I was going to agree with that. I'm not sure--I would say that it doesn't make sense. I think that it's very difficult to do, and part of this has to be tempered by the patient populations that are going to be addressed by the studies. And if it's going to be Class IV heart failure, with ejection fractions less than 20 percent, I don't think you need, you know, five-year follow-up unless we're talking about a miracle here--

[Laughter.]

--which would be wonderful.

So I suspect that the preclinical requirements will evolve as the therapies evolve, and as we begin to use them in earlier phases of heart failure, if this pans out, then clearly the preclinical requirements will become much more rigid and demanding with regard to longevity of follow-up.

CHAIRMAN RAO: Dr. Borer.

DR. BORER: Yes, I mean, I agree with what Jeremy said, and I agree with what Dr. Taylor said--but, to me, the issue isn't whether continuing improvement occurs, but whether deterioration occurs. And you can't know that unless you study--at least at some point, in some model, and in some way--the natural history of the treatment effect; you know, which may not persist. And I think we ought to know that somehow before we start giving it to people.

Jeremy is, of course, quite right. If somebody is expected to live six months and they live two years because of the therapy, that may be a clinically acceptable benefit and you don't have to know any more. But still, at the outset, I

think you'd like to know the natural history of the effect of the treatment.

DR. ITESCU: I think that the barrier should be set exactly the same as you would set it for any other pharmaceutical product or biological compound that the FDA requires for testing at the present time.

And an example--it depends on which cell you're using, and what type of outcome you're looking for. Some of the cells--as Dr. Epstein presented yesterday--simply are agents that release preformed effect, and you're looking for an immediate cytoprotective effect that may be fairly short-lived, and the cells themselves may not engraft, may not survive beyond the first couple of days.

So I think you've got to keep those things in mind, and not expect a more rigorous approach here than you would with any other type of an approach.

DR. BORER: I think that may be correct, but I'd like to point out that the approach to testing with pharmaceuticals is aimed primarily at other issues--at least in cardiac diseases--because we give the drugs every day. So the issue there is

development of tolerance, or tactiphylaxis, and there are--you know, we know from trial and error that if an anti-anginal drug continues to work for three months, the patients will continue to benefit, you know, for a long time--who knows how long?--but for a long time.

Same thing with drugs for heart failure, etcetera, etcetera, where the follow-up has been even longer. But the drug is given every day.

Here we're giving one treatment, once. And we don't know about its persistence.

So I would say that while what Dr. Itescu says is absolutely right, I do think that there is a slightly different standard here because of the differences in administration, and expectations of the administration regimen.

CHAIRMAN RAO: I'm going to ask the FDA--go head--

DR. McFARLAND: I was just going to--from a practical standpoint--I mean, I've really enjoyed the discussion, the way you've been managing it, and the scientific points that have come out.

From a practical perspective, what I'm getting--and I want to see if this is the correct consensus--let's say next week when I have a

pre-IND meeting and they ask what preclinical trials should we do? What preclinical studies?--it would be reasonable--a degree of flexibility, I mean, on what particular model people choose; that it should be a model that if you're looking at an ischemic disease, it should be a model that clinically monitors ischemia; that there isn't really a consensus on versus cell types, versus a myoblast product versus a hematopoietically-derived product, in terms of what kind of preclinical models people should suggest.

And there's not definitive consensus on chronicity of the study, except that it should be long enough to cover the period where we would expect maximal time of safety readouts; and that, you know, given the fact that none of the animal models--particularly double-sided models--a point Dr. Ruskin's made and others have made, is that a positive signal is very important, but a lack of a positive safety signal shouldn't give us over assurance.

And--is this sort of the consensus of--

CHAIRMAN RAO: I would add two more points, which I thought were emphasized. And one is that bio-distribution, at least to some extent, in a

particular model is really quite critical, and that a dose escalation of any kind is really quite important in terms of being able to do it. And that's irrespective of cell type--that's important.

DR. McFARLAND: And one specific question that I don't have an idea of a consensus on: the point was made that large models are important for monitoring delivery systems, and you would expect to see animal models when you're doing innovative catheter delivery systems.

There was no comment on, you know, chronicity of the model with respect to that. I mean, we've heard various viewpoints outside of the room about--well, from an hour to six weeks to--and I would like some discussion on that particular specific point related to the catheter delivery systems.

CHAIRMAN RAO: How long to follow?

DR. McFARLAND: What sort of a length of time in an animal study of a catheter, in a large model. Is it any different--I mean--there are problems with acute toxicity with the procedure itself--potentially. And then, you know, problems with somewhat of chronicity, and I haven't heard discussion about that.

CHAIRMAN RAO: Should we be considering that point when we talk about devices and delivery in the next question?

DR. McFARLAND: Oh, right. Okay.

CHAIRMAN RAO: Does the committee feel we've captured some of this discussion in a reasonable summary? That we really can't be specific, but we need more than one kind of model. It's important that we have models that are run in parallel when we're doing this, and that they are important for safety, even if you're using minimally manipulated cells--what you require.

DR. SCHNEIDER: I wanted to reiterate Dr. Borer's point that a reasonable duration of follow-up is advisable, even for interventions like angiogenic cells, where the expected mechanism of action might be over a short period of time.

I think it's logical to insist, before going into a clinical trial, to ascertain, in a relevant animal, that the benefit of induced angiogenesis is persistent rather than transient.

CHAIRMAN RAO: Did you have a comment?

DR. SERABIAN: My name is Mercedes Serabian. I'm the branch chief for the Pharm-Tox Branch, and also Soft Tissue and Gene Therapy.

I just have a couple of comments, real quick. I mean, the more I'm hearing with respect to all the animal models that are potentially possible is I stress early communication with FDA--pre-IND; what we call "pre-pre-IND" even; connect with us early. You're deciding you're going into preclinical studies, because these are very resource intensive studies, and we want to make sure that we're in agreement with what you're planning on doing. I think that's really, really important, the more I hear the conversation.

And just one more general comment. Again, with all these models that we're talking about--these disease models, specifically. I always question the potential validity of the model. I mean, whose--is it a lab that's doing it? Is it a--you know, a model that's been used before? Is it published in the literature?

Even more important than the number of animals that are used, the controls that are used; the potential blinding for the study. Again, just because if this is your efficacy as well as your safety study, that's really, really important for us.

CHAIRMAN RAO: On that note, I think we can

break for lunch. And the committee has some lunch for it already ready.

[Off the record.]

CHAIRMAN RAO: Back on the record.

So now that everybody's well fed, I think we're going to have a much shorter discussion.

[Laughter.]

We'll see. No, I think it will be shorter just because many of the points have been discussed throughout--from yesterday and today.

Before we start, Dr. Cunningham wanted to make a statement, and I think this might be a good time to make it.

DR. CUNNINGHAM: Thank you.

I just wanted to make a comment that doesn't fit any of the questions that we've been asked today, and yet I think it's important to include. And that is the importance of looking at both genders when we study this issue; that I think that Dr. Taylor has indicated--her data indicated that there's a signal that there may be a significant difference between the genders.

There may be more differences than that, and I think that, overall, in the long term, we want the populations to be studied to be

representative of the populations that we wanted to treat. But if we're talking even just a Phase I, I think at least we should begin with being sure that the safety data includes both men and women, and then from there on we'd like to have more diversity as possible.

CHAIRMAN RAO: So, I'm going to set up two extreme positions for this next question, and that's in terms of devices.

And you heard one relatively extreme position, I guess, which was that if you've got a device and it's already approved, and it's been approved for use, and there's a lot of studies and data on the safety of that particular device, then you don't need to worry, as long as you have some simple tests on saying that you can use those--give cells, and that the cells are viable, then that's fine.

And then the other extreme is that, you know, there are many, many things we don't know, and we'll never know about how they interact, and so we can't really make sure that we understand this in any simplistic way, and so we need lots of detailed studies; and that lots of detailed studies often is a red flag.

And perhaps there is a happy medium. But let's maybe sort of think about it, and try and set this up and whether it all makes sense to the committee as well.

To me it seems that catheters can be used to deliver in a variety of ways. And whether you're doing it through the venous end, or you're doing it through the arterial end, there are going to be differences. And so can't generalize from one site of delivery to another.

There's another thing that I felt that one can't generalize at all--and which, I think, Doris Taylor raised in her talk, too--is that a lot of the data in delivering cells has been using a needle which is at right-angles to the orientation of the fibers. And that's important. Orientation is really important. While a lot of catheters, when they deliver it with a needle, may be delivering it at right-angles to the epicardium, or delivering at a different angle than what we have studies on.

So, keeping those sort of thoughts in mind, maybe we can have people think about what should be studied, if somebody came to the FDA and said, you know, here is a device. It's already

approved, or we know how to use it and we've used it for hundreds of years. And, you know, here are cells. And we've already got a lot of data on cells.

What would be sort of really important in consideration that we'd have to worry about?

And one obvious thing has already been talked about, and that's pressure effects, and size and gauge of the needle; and, you know, how you're going to give it; and issues of vessel wall and pressure on the catheter.

So those are all straightforward things which are obvious. But there are also particular interactions between cells and reagents, and the FDA already raised them when they talked about things like the lubricants which coat, and so on.

So there are probably things that we who are not familiar with the field don't understand. And maybe some of the cardiologists can enlighten us, or raise red flags on this as well.

DR. KURTZBERG: I have a real simplistic question for the interventional cardiologists.

As I think about it, you're in there with a catheter, in a beating heart, trying to be precise about delivering whatever many cells in a

very small volume to an exact perimeter. I mean, how realistic is that, to think that you really can do that?

DR. SIMONS: I actually think that's the easiest part. There are lots of systems for doing this with any degree of sort of precision that you want. And I'm not sure that you want an extreme degree of, you know, precision. You can do it with, you know, a millimeter accuracy. If that's not good enough with a biosense system, you can do it with 100 micron accuracy. If that's not good enough, with--you can probably do it even better than that.

I think that really is the easy part.

DR. KURTZBERG: Even if you're moving a needle--

DR. SIMONS: Oh, yes. Absolutely.

DR. KURTZBERG: --through, that's causing trauma as it's going--

DR. SIMONS: Yes. Mm-hmm.

[Laughter.]

CHAIRMAN RAO: Dr. Borer?

DR. BORER: I think there are two sets of questions--maybe--

CHAIRMAN RAO: Will you hit the button?

DR. BORER: --or maybe six sets of questions here. But let me dispense with one that I think is important, first, and then move on to the second.

The issue of the safety of the catheter does depend, obviously, on the prior--the issue of how much testing you have to do about safety, placement, etcetera, depends upon prior experience. And I think, you know, there's a lot that can be done with catheters. And I should tell you I speak from the point of view of someone who did several thousand, first at the NIH, and then when I was running the cath lab at Cornell. There are a lot of things you can do with catheters.

The issue I would think, however, with a device that's already been approved for something else is, first, where are you going to put it? Are you going to put it in the same place that you've put it in for a hundred years, or are you putting it someplace new?

Manipulating the catheter can be relatively simple, but if you're putting it into a new location, you have to be reasonably certain you can do that safely; and not nine times out of 10. It probably has to be 99 times out of 100, or maybe

better than that. I don't know. And so some experience might be necessary there.

And then I would say, too, for the applications we're talking about, there probably will be multiple new devices with potential and putative advantages developed as better delivery systems than the already available delivery systems. And there, I would say that it is not--I don't think it's actually right to believe--and you said this yesterday, Dr. Rao--to believe that testing at the bench a few mechanical parameters is quite enough. You actually have to feel the implement, and to know how easily it turns, and torques, and da-da-da-da-da. And in gaining that experience, you have to keep count of the serious and non-serious adverse events.

So I think one has to have some experience with a new product, just in terms of the mechanical viability and ease of handling, and safety of putting a device into a body--as opposed to an old device that's being dealt with with new use. And there, I think the issue is a little simpler, but you do have to be sure that putting it in the new place is viable.

Now, once you get past that set of issues,

there is the major issue, it seems to me, of the viability of the product after it's extruded through the catheter. I was surprised--I tell you, honestly, I was surprised to hear about the 27-gauge needle. And you already made the point, Dr. Kurtzberg. You know, you do have to know that the product, once it's extruded through the delivery system, is not fragmented; that it is viable; that there are cells there, and not, you know, junk.

And, of course, there's the whole issue of the interaction of the--chemical, as well as physical interaction, of the product with the substance from which the device is made. You know, I mean, you've said it already. I don't want to belabor the point. But, you know, there are so many examples--not just with biological materials, but with simple drugs--where the drug is adsorbed to catheter materials. If some key component of the diluent, or the excipient, or something was adsorbed to the catheter, who knows what would happen when the product is delivered into the myocardium?

So, there are several different levels of questions, beginning with the safety of the device

mechanically, through the effectiveness of mechanically delivering a viable product, through the issue of chemically or biologically delivering a viable product.

And I separate the mechanical and the biological or chemical--or biochemical, or whatever--because the fragmentation of the product can raise safety issues by itself. And it would be naive to believe, in this latter context--that is, the interaction of the product with the device--again, that bench testing can tell you about safety issues beyond the viability of the product. I'm thinking specifically of thrombogenesis, for example. I mean, there are two different heart valves that, you know, meet the mechanical--valve prostheses that meet all the specifications. Both are approved, made by different companies. And it wasn't know until multiple years of experience that one of them turned out to be more thrombogenic than the other--importantly so, changing the recommendations for anticoagulation of one versus the other. It wasn't known until clinical testing.

Now, how much clinical testing you need so that you can be reasonably safe in a population as

sick as the population we're talking about is a different set of issues, and we can't solve that here. But that some information is necessary from direct testing--to some extent in animals, to some extent in patients--about the mechanical safety, the safety of manipulating the device in the heart and in the patient; the mechanical--the physical viability of the product, and the chemical and biological viability of the product, I think must be defined before you can approve the device.

CHAIRMAN RAO: Before Dr. Ruskin, I just want o make a statement and ask you to comment on it as well.

So, from what you said--or what I heard from this--was that it almost seemed that you would want to test this in an animal model. Is that what it seemed like?

DR. BORER: Absolutely. And before approval, I would think you'd want a certain amount of patient experience. But--sure.

CHAIRMAN RAO: Dr. Ruskin.

DR. RUSKIN: First, I'd like to just second Dr. Borer's comments about the need for getting hands on experience with any catheter design. Bench testing tells you a great deal, but it

doesn't tell you how it's going to perform in the body. And that can only be answered in large animal models, and in early clinical trials.

I want to come back to Dr. Kurtzberg's first question, though--or previous question--and expand a little bit on the answer that Jeff gave, and also Mike Simons. I think he was kidding, by the way, when he told you we could do this with 100 micron accuracy.

[Laughter.]

I think there are couple of components to the question as I heard it. One is mapping substrate, which we can do pretty well. We can delineate, by voltage mapping and other criteria the presence of what we believe to be scar, and we can do it with a reasonable precision, and we can do it reproducibly.

Getting the catheter where you want it to go is also achievable with current mapping systems, but I must emphasize something that Nick Jensen brought up yesterday, which is that catheters are inherently unstable in terms of holding a position in the left ventricle, and that problem has not been overcome yet. The mapping systems do help you mark spots and get back to them, but it doesn't

ensure that your catheter will stay there.

The other is the deliver, which is a needle of some sort. And I think that is a huge challenge, and one which is not yet solved. And I don't think we know where we're putting materials when we inject through needles via catheters. And we've done some of this with gene delivery, and I'm not at all convinced that much of the time we get anything into the tissue; or, if we do, I suspect it's a small amount.

So I view that, right now, as an area of enormous challenge, and not a problem that is solved, from a technological standpoint.

CHAIRMAN RAO: Dr. Lederman, you had a statement?

DR. LEDERMAN: I think I agree with most of the points made, except in the execution. So, sure, we'd probably need to know most of the information mentioned before deploying drug-delivery devices in early clinical studies.

But let's take the example of cells. Let's say than in animal models we have proof of principle for a given cell preparation that we'd like to deliver by direct myocardial injection. And let's say that those data come from small

mammals, and that there's no satisfactory large-mammal model of that cell.

What is it that we need to know about the catheter device before we can declare it adequate to deliver cells into humans? Would it not be satisfactory to measure a simple index, like tripan blue exclusion after passage, or after some dwell time? Do we really need to push cells through and then show preserved biological activity by some more complex in vivo measure? Doesn't that seem excessive?

CHAIRMAN RAO: So--before Dr. Simons--I think that's a point we want to try and really get to here is that are there certain minimum things? Is there a consensus on what's excessive or not?

And I think from the earlier part of what we looked at, we said that cells themselves need to be characterized in quite a lot of detail, and that we need to characterize them when they get there, in the heart. And that's why you needed to do them in animal studies.

So we have to keep that in mind and say: that's absolutely true, that what we need to study about catheters in general is true, and that those are simple things, and maybe we can look at them

and you can also get an answer to how you deliver. But then subsequently we really need to know, once they've been delivered from the catheter, what are the characteristics of the cell.

And--Dr. Simons?

DR. SIMONS: Well, you just said what I was going to say. Because you can damage cells at several different points when you use a catheter to put them in. One is in a physical contact with the catheter polymers; second when it goes through the 27-gauge needle. And, actually, most cell types will not get damaged by passage through the 27-gauge needle.

But a lot of damage occurs when the cells contact tissue at high sort of pressure, and you are not going to model that in vitro. You really have to model this in vivo, and you need to know what happened to the cells once they're in the tissues.

CHAIRMAN RAO: Perhaps even that could be modeled, say, in an animal prep, you know, where you--you have a heart prep, and you can look at those sorts of pressure--maybe.

So, I'm not arguing that we have to absolutely make it specific. I just want people to