DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMMITTEE

MEETING #37

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GUEST SPEAKERS

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Robert J. Lederman, M.D.
Emerson C. Perin, M.D., V.A.C.C.
Silviu Itescu, M.D.
Phillipe Menasche, M.D.
Doris A. Taylor, Ph.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order

CHAIRMAN RAO: Welcome to the discussion part of the meeting today. As is usual with all of these meetings, we have to go around and re-introduce the people who are on the committee, and then open it up for public questions subsequently.

So I'm going to ask Dr. Neylan to start by introducing himself again, and then we'll just go around the table.

DR. NEYLAN: I'm John Neylan. I'm vice president of clinical research and development and Wyeth Research, and I sit on the committee as industry representative.

CHAIRMAN RAO: All right.

DR. SIMONS: Michael Simons of Dartmouth Medical School. I'm a vascular biologist and also a cardiologist.

DR. SCHNEIDER: Michael Schneider, Center for Cardiovascular Development, Baylor College of Medicine. I'm a cardiologist and molecular biologist with an interest in cardiac growth and cardiac progenitor cells.

DR. CUNNINGHAM: Susanna Cunningham from

the University of Washington School of Nursing in Seattle, and I am the consumer representative, usually with the Cardiovascular-Renal Advisory Committee.

DR. BORER: I'm Jeff Borer. I'm a cardiologist from New York. I am chief of the Cardiovascular Pathophysiology Division at Cornell, and the head of the Howard Gillman Institute at Cornell, and chair of the Cardio-Renal Advisory Committee of the FDA.

DR. HARLAN: I'm David Harlan. I'm chief of the Islet and Autoimmunity Branch at the NIDDR, within the NIH. My interests are immunotherapies for diabetes and islet transplantation.

DR. TSIATIS: I'm Butch Tsiatis. I'm a professor of statistics at North Carolina State University.

DR. MULE: Jim Mule, associate center director, H. Lee Moffitt Cancer Center in Tampa. I oversee cell-based therapies for the treatment of cancer.

DR. MURRAY: Tom Murray, resident of the Hastings Cents Center; a long interest in ethical issues in medicine and science. I write a lot about genetics and some of these new cellular and

gene-based therapies.

CHAIRMAN RAO: Dr. Ruskin, we missed you--can you--

DR. RUSKIN: Jeremy Ruskin--I'm a cardiologist and electrophysiologist, and I direct the Cardiac Arrhythmia Service at Massachusetts General Hospital.

CHAIRMAN RAO: I'm Mahendra Rao. I'm at the National Institute of Aging, and I'm a stem cell biologist.

MS. DAPOLITO: Gail Dapolito, Executive Secretary for the Committee. And I'd also like to introduce the Committee Management Specialist, Roseanna, Harvey.

Thank you.

DR. KURTZBERG: I'm Joanne Kurtzberg. I'm a pediatric hematologist-oncologist, and I run the pediatric bone marrow transplant program at Duke, and the Carolinas Cord-blood Bank, and I have an interest in cord-blood stem cells; transdifferentiation and plasticity.

DR. HIGH: My name is Kathy High. I'm a hematologist at the University of Pennsylvania, and my research interests are in gene transfer as a means of treating bleeding disorders.

DR. ALLAN: I'm John Allan. I'm a virologist at the Southwest Foundation in San Antonio. My area is non-human primate models for AIDS pathogenesis. I also sit on the HHS Secretary's Advisory Committee on Xenotransplantation.

DR. BLAZAR: My name is Bruce Blazar. I'm at the University of Minnesota in the Department of Pediatric Bone Marrow Transplantation. Our lab is focused on the immunobiology of bone marrow transplantation and its complications. In addition, we're using non-hematopoietic cell therapy to treat organ tissue injury after bone marrow transplantation.

DR. CANNON: I'm Richard Cannon. I'm clinical director of NHLBI. I'm a clinical cardiologist by training.

DR. AREMAN: I'm Ellen Areman. I'm a product reviewer with CBER, Office of Cellular, Tissue and Gene Therapy.

DR. McFARLAND: I'm Richard McFarland. I'm a pre-clinical reviewer in the Pharm-Tox Branch in the Office of Cellular, Tissue and Gene Therapy. And my training background is immunopathology and toxicology.

DR. RIEVES: Hi, there. My name is Dwaine. I'm a medical officer at the FDA.

DR. GRANT: Hi, I'm Steve Grant. I'm a medical office at the FDA. I'm a clinical reviewer, and I'm also a cardiologist.

DR. NOGUCHI: Phil Noguchi, acting director of the Office of Cellular, Tissue and Gene Therapies.

CHAIRMAN RAO: Thank you, Phil. I'll turn the mike over to you so you can make the opening remarks.

FDA Opening Remarks

DR. NOGUCHI: Thank you. This will be very short, because we have a lot to accomplish.

The first acknowledgment I'd like to do is we neglected yesterday to say that this is Dr. Rao's actual first meeting as the formal chair of the BRMAC committee, and we gave him an easy assignment, which is to make sure we leave on time today.

[Laughter.]

And to pick up with apologies to Gandhi, yesterday--I think we clearly are in a situation where no one is ignoring this entire field. We did have some laughs yesterday, but it was not laughs

about the absurdity of the approach but, really, about all the nuances that we see.

There was a quote today in the Washington Post about the success of CNN. And, actually, instead of fighting, I would say we are fulfilling that; and that is the public's business is best done in the public, which this is a very elegant example of. And I'm sure today will be even more of an example. And the goal, of course, is to make sure that when we leave that we do so with a better knowledge of how we can actually win in the end.

And, with that, I think Dr. Rao, it will be time for opening the Open Public Hearing.

Thank you.

CHAIRMAN RAO: We have a couple of people who wanted to make comments. And I want to emphasize right now that if anybody else from the audience needs to make a comment, this is a good time to make it. Sometimes making comments at the time when the committee is deliberating becomes much harder, and it's hard to recognize people, given the time constraints as well.

Open Public Hearing

CHAIRMAN RAO: The first speaker is going to be Dr. Neal Salomon, and he's going to speak for

about five minutes.

DR. SALOMON: Good morning. I'm Neal Salomon. I'm a cardiac surgeon, and for the last several years I've worked part-time as an associate medical director for Parexel, a large CRO based in Waltham, Massachusetts. During this time I"ve worked with GenVec, formerly known to us as Diacrin, as both a medical monitor and a consultant in the implementation of their clinical trials, using autologous myoblast transplantation.

I would like to very briefly summarize the currently updated results of the three Phase I pilot safety and feasibility studies--as I believe that GenVec currently has the largest clinical experience in the United States.

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[Slide.]

This is just a brief overview. And all subjects in these studies have received their multiple epicardial injections in the region of maximal transmural myocardial, epicardial scar.

The first study was just six patients, all of whom received 300 million myoblasts concurrent with LVAD replacement as a bridge to heart transplantation. I believe that HeartMate was used

in all of them.

The second concurrently running--run CABG study was a cohort of dose-escalation study; 12 patients. All of these patients had EF's less than 30 percent, and the injection of myoblasts was done concurrent with their bypass grafting.

The third--the most current study--was a cohort of 10 evaluable patients. All of these patients, however, had injection of 300 million myoblasts. However, this group had a much more extensive--and I should say expensive--preoperative evaluation and follow-up using core laboratories standardized protocols for Echo, MRI, PET and multiple, multiple 24-hour Holter examinations.

Next slide, please.

[Slide.]

In slightly more detail, this is the six patients--probably should call it "LVAD" instead of the CHF patients. Three of the patients received heart transplantations. Two died, and one is still awaiting transplant after over two years.

Histologic--as part of the informed consent, the explanted hearts were to be made available for histologic evaluation, and that has been completed in five evaluable patients. That

was recently published, last year, in JAC. You can see the reference there.

We couldn't identify any related SAEs.

Next slide, please.

[Slide.]

This is the dose-escalation study in four separate cohorts. You can see the number of cells was much smaller than was mentioned yesterday in the Paris study. The initial three only got 10 million, then 30 million, 100 million, and the final three got the 300 million myoblasts. Seven have completed 24-month follow-up. Five are still within that time period. And, again, we didn't really find any obviously related SAEs in this group.

Next slide, please.

[Slide.]

In the most recent and current study, which has just--I think the last patient is just being enrolled--all these patients received the 300 million myoblast cells. There was one early death--an elderly gentleman, bad re-do, bad targets. He died seven days post-op. He was already out of the hospital two days, and a question of primary arrhythmia versus an infarct.

And on autopsy, he had fresh thrombus in a right--and a sequential graft going to two branches of the right. We suspect that that fit his clinical pattern and he had a primary MI.

And, again, all these patients are getting thoroughly evaluated by serial MRIs, echo, PETs, multiple Holters, by standardized core labs.

Next slide, please.

[Slide.]

And in slightly closer focus--as obviously the AICD, and the arrhythmias is significant issue, both clinically and from a regulatory perspective--let me just tell you a little bit about all these folks.

The first--the first patient listed there had an AICD placed prophylactically at week two. He had non-sustained V-tach, and some new kind of chest pain within a week after being discharge. Urgently re-cathed; had significant kinks in his mammary graft; question of flow limitation. Placed on Amyoterone, resolved his arrhythmias, but he had an AICD placed prophylactically anyway.

The next two patients are very similar, both at month 10 and month 15. Both patients had AICDs placed, essentially due to progressive heart

failure. There was no improvement after the--cardiac function after their grafts. Neither patient ever had VT--and I don't believe any of these three have had a shock.

And then, the last group, one patient had an AICD week three, who had non-sustained V-tach, also severe LV dysfunction. His pre- and post-operative Holters, however, were not really different, but he had an AICD placed. And the very last one had it, again, placed prophylactically for a position T-wave alternans test, which some cardiologists feel has significant prognostic significance.

So my conclusion from evaluating this is that it's really patient-related variables, rather than specific procedure-related variables, and do reflect some expanding indications for the use of AICDs in this problematic patient group, over just the four years that these have been running.

And the last slide, please.

[Slide.]

Thus, the total enrollment is 28 patients over four years. The average follow-up, as you can see, for the CABG patients is a year-and-a-half; for the LVAD patients it's been three months. We

could not identify any specific procedure, rejection-related complications; really no definitive SAEs--that one possibility, but probably not.

Histologic evidence for cell survival is currently available. And the standardized core lab assessment for all the things mentioned, including Holters, are ongoing. So both I, independently, and GenVec thank you for the opportunity to present this data to the committee and the FDA.

Thank you very much.

[Applause.]

CHAIRMAN RAO: There's just one question for you from the committee, Dr. Salomon.

DR. BORER: Borer. I guess when you say the results are pending from the core labs, there really aren't any results yet available. But, let me ask anyway.

If I understood properly, one of your studies--I guess it's CABG 002--was a dose-response study--

DR. SALOMON: Dose escalation, yes.

DR. BORER: Well--escalation, but you had one dose given to four different groups; one dose to each group. That's right?

Okay. So you can define a dose-response curve from those data, albeit the numbers are small, you could.

Do I understand correctly we don't know if cell survival varied among the doses used in any dose-related way, and we don't know if there was any functional parameter that was altered by the treatment in a dose-related way?

And the reason I ask, obviously, is that this is the only study that has, in essence, a control. I mean, it's a dose-response study, which could provide a great deal of information, you know, if the information become available. So that's why I'm asking specifically about that study.

The others are, you know, observational studies with millions of confounds. This one has confounds, too. But, you know, in addition to the surgery that everybody had, there was a dose-response design--a parallel group, differing dose design.

Can you tell us anything about results in that group? Or they're just not available.

DR. SALOMON: You know, this was really confined--with no allusion to efficacy whatsoever,

of course, in terms of functional alterations. I haven't addressed that whatsoever. So--

DR. BORER: But you made measurements. You have echo, you have PET, you have--

DR. SALOMON: Oh, sure.

DR. BORER: You have stuff.

DR. SALOMON: Sure. Sure.

DR. BORER: And I wasn't suggesting you could look at efficacy. I was just asking about functional concomitants of treatment.

DR. SALOMON: Right. No--I understand.

No--the answer is no obvious correlation; no dose-related correlation. Correct. Too many variables.

DR. EPSTEIN: I'd like to ask a question--Steve Epstein. I'd like to ask a question of the FDA.

I don't mean to be critical of this study, but in light of what Dr. Manasche said yesterday, if you have concomitant CABG, and you're putting cells in, there is no way you're going to get any information. None.

So here are patients who are being exposed to some risk, with the expectation of having no information, because there's a CABG.

What is the FDA policy on something like this.

CHAIRMAN RAO: Let's leave that question for later, then, Dr. Epstein.

Yes?

DR. SCHNEIDER: I have a question for you about patient recruitment for the Diagran GenVex study.

How many recruiting centers were involved? What was the average number of patients recruited in each? And what was the range in the number of patients recruited by each?

DR. SALOMON: By each center?

DR. SCHNEIDER: By each center. Because one of the issue in a trial like this is reproducibility, hands-on experience. I'm trying to get a feeling for what the range was in the level of participation and recruitment by the centers.

DR. SALOMON: Yes--excellent question.

There was a predominance of--I guess I shouldn't say names of centers, so I won't. But there was a predominance in both of the--well, actually, all the trials, with just maybe--we had a total, I believe, in opportunities for eight to 10

centers, but virtually 80 percent of the patients came from three to four of the centers.

DR. SCHNEIDER: And the other 20 percent came from centers that were doing one or two patients each?

DR. SALOMON: Had fewer patients each--correct. Correct.

CHAIRMAN RAO: Thank you, Dr. Salomon.

DR. CUNNINGHAM: What were the genders of the patients?

DR. SALOMON: Only--of all these--of the 28 patients, only two female.

DR. CUNNINGHAM: Thank you.

CHAIRMAN RAO: Thank you.

Dr. Reiss?

DR. REISS: My name is Russ Reiss. I don't have any slides prepared. I've just been sitting at this meeting for the last day and am somewhat frustrated.

I'm a clinical heart surgeon at the University of Utah who--we also have a very active basic science laboratory, and we are also planning to do cardiac trials will cellular therapy.

But what I wanted to say--actually, I'm glad that Dr. Salomon did just give a little bit of

information from the cardiac surgeon side--and a little bit of rebuttal to Dr. Epstein.

I do not believe that just because we can put these in with catheters that that is the actual safest way to do this; and that maybe in the operating room, with the heart under diastolic arrest, completely in a controlled setting that is probably the most controlled, most sterile setting we have from clinicians today is the cardiac operating room. And just some of the quick points I just wanted to let the FDA know, that in response to putting a CABG graft on a heart and saying that you can't tell any difference, I don't agree with that at all. Because we've all revascularized a heart and seen no difference in wall motion, because that area is not graftable, or there's an area there that's thin but not dead. And you may not see anything at all.

If you put cells in that area that you did not put a graft on, you can follow that. And we've seen some very nice images--Dr. Lederman yesterday showed beautiful cardiac MRI images with very specific areas of the heart and the walls that can be followed with high definition. We can see what happens to the area that is not revasculizable with

a CABG graft.

And I would say that all the concerns that have been raised with catheters--we heard yesterday that the catheter was very safe, and nothing ever happens in the cath lab. We'll that's not true. Cardiac surgeons repair valves, we repair aortas. That thin transverses the groin, the aortic arch. There's all kinds of misadventures that happen with catheters that cardiac surgeons have to fix.

So I would just say to the FDA that, you know, it's going to be done with a catheter one day. It's already being done outside this country. I think that is going to be eventually how the majority of cellular therapy is going to be delivered. But, as far as safety, some of these trials probably should be also considered in the cardiac setting, in the operating room, where much of the pre-clinical data has been done with direct injection, under arrested heart.

And the last thing, about safety: all our patients also go to the ICU, and they're under the most monitoring on a daily basis that you can have. And we can also apply what other types of safety monitoring the FDA would like to see us do. But often the catheter patients do not get the same

level of post-operative monitoring.

So, just a plug for the cardiac surgery side, since it seems that we're a little bit under-represented.

CHAIRMAN RAO: Thank you, Dr. Reiss.

Dr. O'Callaghan?

DR. O'CALLAGHAN: My name is Michael O'Callaghan, and I"m the vice president of pre-clinical biology at Genzyme. I'm responsible for many of the pre-clinical studies that are to look after safety and efficacy for the cell products and many other products at Genzyme.

I'd like to thank the FDA for, first, allowing us to speak and, secondly, for putting on this two-day series of seminars, because I think it's critical to the way we move forward.

I would remind people of this document called "Innovation and Stagnation," which is a document that just recently came out from the FDA. And if you look at the graph which is on Figure 2, you will see that in 1993, there were 17 BLAs submitted to the FDA, and progressively over the next 10 years to 2003, there was virtually a straight line downward plunge to 14 last year. If

you continue that, that's 5 BLA losses per year. So by 2007, there won't be any.

So, I think what we're talking about today--and some of the things that we're talking about today--is how do we get to a better process or procedure or strategy that will allow industry and the FDA to come to a more transparent, perhaps, and faster or more efficient approach to this.

If you think about some of the issues that have been discussed and the complexity of what we're dealing with, you may recall from much of yesterday's conversation that many of the procedures that we are using to deliver cells--in fact all of them--invoke some sort of pathology of themselves. So if you think about the emboli that were produced in the intra-coronary delivery, or you think about needle tracks or catheter delivery systems that ago through the wall or travel through the heart, there is a primary pathology created by that.

On top of that, there is the pathology that is behind the infarct itself; whether it's a recent infarct or an old infarct, which complicates interpretation, and complicates the safety and efficacy issues we're trying to deal with.

A third variable, of course, is the cell death that we all heard about, obviously invokes some sort of pathology. And, on top of that, we have our understanding of the pathological, or physiological processes that we have in great abundance in the literature, and that's our sort of background in trying to understand how to provide studies that answer the safety questions or the efficacy questions.

And then on top of this background, we're attempting--with the few surviving cells that are there, and presumably the ones that are going t o give benefit to the patient--out of that morass, try to find out whether there is a safety issue, or efficacy, on top of many of the other things, like CABG.

So, how does that translate to dealing with the regulatory authorities in trying to demonstrate that there is safety and that there is efficacy? The difficulty, of course, is that background. I think the other difficulty is outlined, in part, in this document: and that is that the process as it is at the moment is an iterative one, where it's almost like a five-year poker game, where each one is holding the cards

against their own chest and only giving out the card that matters. And that goes on for several years, and as you play your card, or pick up a new card to try and strengthen your hand, you end up spending a lot of money in the process and, in the end, many of these products shown on this graph die very slowly.

So my plea at the moment, or to this body, is that we need to think about how we are going to make the process more transparent so that quicker decisions can be made. And I think it has to be translated at two levels: one is at the level of policy and strategy--how the FDA is going to interact with industry. And, secondly, what was pointed out yesterday by Dr. Noguchi and McFarland, how to translate that down to the individual case, where the sponsor and the FDA are having to work out, between them, on that one individual case, how to get to a satisfactory solution as quickly as possible.

Thank you.

CHAIRMAN RAO: Thank you, Dr. O'Callaghan. I think the FDA shares the frustration--and all the stem-cell biologists also, in how can one translate some of these things into an appropriate

methodology that can be used.

I'm going to ask Dr. Noguchi to maybe say a couple of words on what a BLA is so that people who may not be familiar with it are aware of what a BLA application is.

DR. NOGUCHI: Okay. Yes--BLA stands for "Biologics License Application." It's given under the authority of a section of the Public Health Service Act that we call "Section 351," and it is in a parallel situation to the Food, Drug and Cosmetic Act. The main distinction, from the legal point of view, is that if you have an approved NDA--new drug application--you don't need a simultaneous BLA, and vice versa.

The basic requirements for a license application is that you have a product--let's give a hypothetical example of a cellular product for future cardiac repair--that can be made in a manner that is consistent; that is, for many biologics, we do not need to have an ultimately precise definition and specification for a pure entity, however we want you to be able to make it the same, time after time after time, within certain limits.

If we go back to the original law--1902 law--the legislative history is basically states:

what we want is something that's safe relative to the indication; that's pure as possible; and that is potent, so that the practicing physician, in his or her capacity, will have some confidence that when this product is given that their patient will have some expectation of therapy; that is, they'll be better after than before.

So I think--that's sort of more of a philosophical thing, but the end game is really: if you have something that we know works, and can be--works in a manner that it can be convincing, which is usually based on planned clinical trials--occasionally we may have historical data that can be used in terms of an approval. But, clearly, for experimental products such this--we heard yesterday, eloquently--that without a placebo how do you know that this is actually working, since all the non-controlled trials say they all work.

So if it's effective in a reproducible way, and you can make the product the same again and again and again, so that, again, the practicing physician gets a vial of cells, says, "Okay, I know this is pretty potent. This is the dating period. I can give it. Or, if it's past the dating period,

maybe I'll give a little bit more." It's to give the physician the maximum flexibility in prescription, as well as to validate and provide that assurance that the product actually works and can be made consistently. That's what the BLA is all about.

It can be done by a major pharmaceutical company. It has actually been done, in a few cases, by universities and by state public health entities. So it's a very flexible approach. It can go all the way from the very largest multi-center, multi-national, hundreds of thousand patient trials down to even those with about five to 10.

So it's a flexible mechanism. But, again, the end game is: does it work? If it does, we'll approve it.

CHAIRMAN RAO: Thank you.

I think a couple of people have questions for you, sir.

DR. MURRAY: Phil, what's your response to Dr. O'Callaghan's claim that we've gone from having rather a large number of these BLA applications in a year, to a declining trend? Is that--if that's the data--I have no reason to doubt the data, but

the interpretation of it was what is not clear to me.

DR. NOGUCHI: Yes, myself not having all the primary data at hand--but it is--like anything else, it depends on what is put into the publication. We do, for example, license blood banks, and those, literally, will be coming in at a much higher rate. We do not necessarily count those as new molecular entities.

It is true, but it's not just for biologics applications, but also for molecular entities--for drug molecular entities--that in a very real sense there has been a tremendous set of developments and follow-through of things that are known. And we have entered, somewhat asynchronously, a time where there a lot of things that have been solved, in a somewhat prosaic way. All the easier diseases really have been done, and now we're dealing with the ones that are very hard. Cancer, as an entity, sounds like it's not just one, it's a very hard disease in order to make progress above and beyond extension of live for several months, or--and so forth.

So a lot of what we're seeing is: what's known has been done for those diseases for which we

know how to treat. But what we are now seeing is all the rest of them here: cardiovascular disease, congestive heart failure. We saw how the cascade is just a very long one, and we're trying to intervene at perhaps a point where it's a little bit hard to reverse years of damage. Likely it car be done, but how we get there is very dependent, tc a great degree, on what the science and knowledge of disease is.

So, I think what we are seeing is that we are seeing fewer applications in the whole drugs and biologics arena. And part of that is that our scientific knowledge, on the one hand, for making products is expanding rapidly, but our understanding of the--quote--"simplicity" of disease is proving to be--well, it may be very simple, but, boy, that's pretty darn hard compared to what we already know.

There are no easy solutions to any of these diseases that we see right at the moment. And that's part of the lag we're seeing.

Dr. McClellan's emphasis on the critical-path initiative is really to try to help everyone to come back and focus as to what are those things that will make a difference, and then

what are those things that are simply going to be increments and improvements that may only give us a little bit of extension of life, a little bit longer acting drug, but may not be actually altering the fundamental disease.

CHAIRMAN RAO: Joanne?

DR. KURTZBERG: I have a question that goes back to the cardiac transplantation issue at hand--or the cellular therapy issue at hand.

In the current proposed tissue regs, minimally manipulated or non-manipulated products are not really candidates for BLA or licenses. So, for example, if you take bone marrow from a sibling and you transplant it directly into the patient, there's no license involved with doing that.

And some of the therapies that both are being done now and are being proposed involve what we've done with bone marrow for years; taking it and putting it somewhere else--in this case, usually autologous, or mobilized blood, or even CD34 AC133-- selected products for which there already are devices that are either under IND or licensed.

So how would the FDA--you know, so this therapy crosses a bridge between using things that

we use already, but just putting them in a different place; and then, also, modifying those--some things, ex vivo, with culturing and other technology.

You could interpret the regs as they are proposed as saying the minimally manipulated product doesn't need a license or a BLA, and only the ex vivo manipulated or culture, transfected, etcetera and so forth products do.

What's the FDA's view of that.

DR. NOGUCHI: Well, we really did not have this meeting to try to focus on the question of whether we need this approach versus that approach. However, I'll just quickly say a couple of things.

First, the tissue regulations are still in the process of being finalized. However, the point--one part of the regulations does say that if you use something that would otherwise be considered to be not manipulated beyond its normal biological characteristics, if it's used in a manner that inherently does not seem that it logically follows--which is what happens in this case--we've already heard yesterday, and we see throughout the past year, in terms of the active literature, if bone marrow cells of whatever never,

however purified, are put into the heart by means of devices, or by direct injection, or by surgical procedures, that, in fact, either you get regeneration of heart, you get vascularization, you get transdifferentiation--none of which have been proven by any means, in any clinical trial, let alone in any animal studies that have been done--we term that a "non-homologous use," because it has not been shown, and the current science does not show that any of those possibilities are actually, in fact, what happens.

And so, for that reason, we are saying these are highly experimental procedures they're using in addition to the product itself, which is experimental. We're using products--other products such as catheters in an experimental way--and, all put together, clearly merit the justification and the overview of FDA regulation at the IND level.

DR. KURTZBERG: I'm not questioning that. But--

CHAIRMAN RAO: I'm going to cut this here, because this is not part of the whole mandate for the committee. And these questions--this whole idea of--I just wanted people to know about the BLA.

DR. KURTZBERG: But it is important. Because if it works, do you then have to go have a BLA, or a license to use bone marrow for this, when you wouldn't have a license to use bone marrow for the other indication therapy.

CHAIRMAN RAO: And that's certainly an important issue, but I don't think we want to address it in this committee because it's not part of our mandate for the question.

[Pause.]

Are there any additional comments from the audience? Anyone?

Go ahead. Just make sure you identify yourself, and if you have any financial--

DR. GRANT: My name is Stephan Grant. I'm working with Viacel in Boston, and I'm running the European branch of Viacel--a small company named, Curion.

I would like to make a comment to the issue of immunosuppression in animal studies. There has been a position by Dr. Itescu yesterday saying, well, it doesn't make sense to use immuno-compromised animals treated with cyclosporin or rapomycin, or whatever, in order to do our studies.

I would like to challenge that position a little bit, because I think we also heard that stem cells are quite heterogeneous, and we see the problem that how can we make sure that an animal stem cell preparation is really very homologous to the human stem cell preparation, which may carry the same name but could be different, in terms of the cell composition or other factors. And we don't have the tools in our hands to discriminate, or to decide whether the animal stem cells are really the same--have the same quality, the same properties, the same purities as the human product.

So we had made a conscious decision to work with immunosuppressed animals, immuno-compromised porcine--pigs, treated with cyclosporin, and tested our stem cells, human stem cells in that setting, with good results so far.

And I think taking that strategy, we are on the safe side with respect to testing our products in terms of efficacy and safety, because we don't have to make this transition or translation of the animal that, say, the animal data generated with animal stem cells then into the human setting.

And somehow, I--I mean, I think it's fine

if the authorities accept the, let's say known xenograft, or xenograft-avoiding strategy, but it would be--I think it would be a pity if we would now have a dogma that studies with immuno-suppressed animals would make sense in this context.

CHAIRMAN RAO: Thank you.

DR. ITESCU: I accept that point. That's a valid point.

The point that I was making simply is if you're going to use immuno-suppression in an animal model with human cells, you've got to take into account the potential effects of the drugs on the cells you're studying. And as long as you've got appropriate controls, as long as you've taken that into account, it's reasonable to look at those sort of models.

CHAIRMAN RAO: We're going to move on.

Briefly? Is this relevant.

AUDIENCE MEMBER: I'm very sorry to re-comment, but Dr. Epstein's query didn't really get a response--at least from me.

And the other issue is the clinical trial design, with human subject protection. And these pilot studies weren't designed--efficacy as a

stand-alone procedure, because clearly you have to get safety and feasibility first.

So, it's really difficult to do cell implantation studies, I think, as a stand-alone procedure, and they had to be done concomitantly with bypass grafting. I think that was really the rational; not to prove efficacy.

Thank you.

CHAIRMAN RAO: Thank you.

I'm going to ask the FDA to pose the questions.

Dr. Grant?

FDA Charge to Committee

DR. GRANT: Hi--I'm Steve Grant. I'm one of the clinical reviewers here at FDA. I'm also a cardiologist.

I wanted to start out today by thanking the members of the committee and the invited speaker--as well as the speakers who were kind enough to join us during the open public hearing--for coming here and sharing their time. We know they all have very busy and very productive professional lives, and we thank you for joining us today to discuss these very important issues.

I'm going to briefly review why we've

asked you to come here yesterday and today. And I'll then review the questions that we've asked you to discuss.

Next slide, please.

[Slide.]

We have asked you to discuss certain safety concerns that need to be addressed to initiate human trials of cellular therapies for cardiovascular diseases. These concerns are part of our mission to promote and protect public health. We are, however, also responsible for facilitating the development of safe and effective therapies--and I've put up here an addition that was made to the FDA Mission Statement in August 2003.

This revision explicitly states that "the FDA is responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer and more affordable."

Although this was made explicit in the 2003 revision, facilitating the development of safe and effective therapies does promote the public health, so I would argue that this was always implicit in our mission statement.

We have convened the committee to solicit advice about certain issues that have delayed the development of potential therapies for cardiovascular disease.

Next slide, please.

[Slide.]

Here's one of the clinical challenges that exists in cardiology--I think you've heard about it from several speakers yesterday. There's--very simply stated--there's over a million people in the United States who acute myocardial infarction every year.

For those of us who have a bit of gray hair, they can remember when taking care of MIs consisted essentially of putting people to bed. The mortality rate for MI has been declining fairly rapidly. It's gone down 30 percent over the last two decades. And this has been due, at least in large part, to the advent of reperfusion therapy; both thrombolysis and percutaneous coronary intervention. However, these therapies are not entirely effective. Most patients who will suffer acute myocardial infarction will be left with a variable amount of left ventricular dysfunction.

Because increasing numbers of these

patients are surviving, there are many, many more patients each year that have diminished cardiac reserve. It fact, congestive heart failure is the only cardiovascular diagnosis whose absolute incidence is increasing year by year. And it's partially due to the aging of the population, but it's also, in large part, due to this phenomenon.

And therefore we are very interested in facilitating cellular therapies because they may benefit these growing numbers of patients with congestive heart failure.

Now, I don't want to suggest that this is the only indication for which I think these products might be used, or that even for sure, that this is an appropriate indication. Conceptually, there are many, many other types of cardiac disease that could be benefitted by cellular therapy.

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[Slide.]

I'm going to talk a bit about the regulatory requirements. Before a new product is administered to humans, FDA is required to conduct an independent and detailed assessment of the risk to human subjects. The regulations provide the mechanism by which we conduct this assessment.

They provide the framework wherein we can answer this question--which is never trivial, I don't think, for any trial, but most certainly is not trivial for novel therapies such as these--and that is: how do we balance individual subject safety against the potential public health benefits of new therapy?

The risks are borne by the few, and the benefits go to the many. And our society has designed a mechanism, and provide a framework, and charged us to make this assessment. And the regulations are how we do that.

This risk assessment must be sufficiently--must include sufficiently detailed information regarding the following: product characterization and safety testing. And I think it's fairly obvious--safety testing, that we wouldn't transmit, for example, infectious agents in a product.

Product characterization--as Dr. Noguchi has already discussed--is a bit more difficult for cellular therapies than it is for a drug. A drug, you know the--you can characterize the reagents that go into it. You know and understand precisely the manufacturing processes. You can chemically

characterize what comes out. You understand--you manufacture the pill.

We talk about manufacturing with cellular therapies as well, although even to my ear it still always sounds a little strange to talk about "manufacturing." I mean, we're really--it's a process that we use to produce these cells, and that process, in some ways, is the way we characterize them. But, still, there are certain concerns that we have to be able to characterize that end product in some way that's meaningful--because you can't run a clinical trial if you don't understand what you're giving to the patients. I think it's kind of self-evident that if you don't understand, or don't have a way of characterizing what you've done, you don't have a trial you have a case series of a group of people who are given something you don't understand.

You have to provide supportive pre-clinical or clinical data. You have to provide data that allows us to independently assess the risk to the subjects as best as can be done. I mean, we've heard already about the difficulties of finding appropriate pre-clinical models. That doesn't--because they're difficult doesn't excuse

you from not having any.

And you need to be able to identify a safe starting dose. And then you need to have a monitoring plan that suggests that you're going to be able to detect the adverse events in a timely fashion, so that any subject that suffers those adverse events can be identified and treated quickly, and so that subsequent subjects will not be exposed to the same adverse events.

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[Slide.]

And with that as the background, I want to go through the common issues that have delayed initiation of clinical trials in this area--and I've probably seen most of the submissions to the FDA, And these are the four things that we have identified as being problems.

One: the cellular product that is administered--or the cellular product that's proposed for the clinical trial is different from that that's used in pre-clinical studies. You know, we--some people, I think, would advocate--we certainly heard yesterday people who would say once you've seen one bone-marrow mononuclear cell you may have seen them all. But there may be

differences within these preparations.

Secondly: insufficiently detailed safety data--and particularly, we will sometimes get, as a safety data base, just published reports. It's very difficult to get, from a publication, the kind of detail. We have to be able to do an independent analysis and, generally, publications will not include a detailed protocol, which will include all the protocol-specified assessments, and it won't include either the case report forms for a clinical study, the line item of raw data for a pre-clinical or non-clinical study.

Three: limited information about the compatibility of the cellular product and the delivery device.

Four: an inadequate plan for monitoring of subjects during and after product administration.

And I think you'll see that the questions that we've asked you, with the exception of the seventh, which is just a bit different--but the first six clearly all are derived from these issues. We'd like to get advice about these issues so that we can help understand how to resolve these, and so the investigator community can help understand, so that we can get submissions that

will go forward.

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[Slide.]

So the advice that we seek from you are general comments and recommendations about certain manufacturing issues, certain preclinical testing issues, and about pilot clinical design, with respect to certain issues that need to be addressed to permit safe initiation of clinical development--which we are quite anxious to see happen.

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[Slide.]

Question 1--well, these first two questions are going to relate to safety in characterization of the cellular product.

Question 1: we know that because the specific cells, mechanism of action and cell-device interactions are still in very early stages of investigation, the appropriate and adequate safety testing and characterization have not yet been defined, and may conceptually vary, based on the cell source and type of manipulation.

We would like you to discuss the intrinsic safety concerns for cellular products for the

treatment of cardiovascular diseases, and the testing that should be performed to ensure administration of a safe product. Among the factors that you might consider are tissue source, manufacturing process, formulation, storage, route and site of administration.

In your printed version, in the briefing document, these came out as "a, b, c, d." We by no means think that you have to discuss each of those as a separate subpoint, but consider them, instead, in your discussion of the overall question. And I would caution the committee to try to remember that we're talking here about treatments of cardiac diseases. The larger field of cell therapy is quite a broad one, and we would like to stay to the specifics of cardiac therapy today.

Question 2--

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[Slide.]

--these products are all heterogeneous, in terms of cell types contained and, in some of them, the biomarkers also are different on different cell types; the degree of heterogeneity present in administered cellular products may be an important variable in characterization or in determining

their safety or efficacy.

Therefore, please comment on the elements of product identity and characterization necessary to generate meaningful data about safety and efficacy. And, conceptually, we think that these may include comments about specific biomarkers--that would be most particularly with the bone marrow-derived products--and the types and percentages of cell types that would apply to both the products derived from muscle biopsies, as well as those derived from bone marrow or from peripheral blood.

And there may be other parameters that you would identify as being important. And we would ask for your comments.

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[Slide.]

Question No. 3--the next couple of questions, 3 and 4, concern the kinds of pre-clinical data needed to assess safety, and identify a safe starting dose prior to initiating human clinical trials.

Various--we've already had part of a discussion of this. Various animal models have been proposed to support the safety of cellular

products used in the treatment of cardiac disease. These include studies of both small and large species; studies utilizing either immune-competent or immuno-compromised animals.

Each model has some advantages and limitations, which have been reviewed by the speakers and previously discussed. For instance, human cellular products can be tested in genetically immuno-compromised rodents, but these animals provide limited clinical monitoring of cardiac function, and cannot be used to assess the safety of devices. Large animals allow for more extensive monitoring of cardiac function and the use of the same delivery device intended for clinical use.

Please discuss the merits and limitations of various large and small animal species for providing pharmacologic, physiologic and toxicologic support for cellular products used in the treatment of cardiac disease, and please consider the following: the intended human clinical cellular product; the delivery system that's proposed in the clinical trial; and extrapolation of study results from animals to humans.

Question No. 4: Please discuss the merits

of animal models of ischemic disease with respect to ability to generate proof of concept data, and generate toxicologic data of relevance to the clinical disease. And, conceptually, animal models of ischemic disease could include normal animals--or no ischemic disease--as Dr. Vouye presented a very interesting study with essentially normal dogs.

The models--again, the models of ischemia that are available are many; cryoablation, ligation, ligation-reperfusion, ameroids.

Question No. 5, please

[Slide.]

The next question concerns the types of evacuations needed to assess the compatibility of the cellular product with the delivery device. Please discuss evaluation of potential interactions between cellular products and cardiac catheters; adverse effects of catheters on the viability and functionality of a specific cellular product; factors other than cell concentration and simple viscosity that might contribute to clogging or other adverse events; injection of cells into system circulation, the pericardial space, thoracic space via needle catheter; effects of depth or

spread of injection into they myocardium on either the safety or, potentially, the efficacy.

Question No. 6--these last two questions are about two design elements of early-phase clinical trials. The theoretical risk of these products include the generation of non-cardiac tissues, abnormal cardiac tissue and/or local inflammation. These outcomes potentially could lead to myocardial dysfunction, arrhythmias, or conduction abnormalities.

Also, these products are administered because some of the cells contained are self-renewing and possess developmental plasticity; that is, they can differentiate into cells not found in the tissue from which they were obtained. Since uncontrolled cellular proliferation may result in tumor genesis, these products could theoretically result in subjects' developing neoplasia.

So, please discuss the appropriate frequency and duration of follow-up. In addition to any other events, please consider the following potential adverse pathological and clinical events in your discussion items: scar formation, left ventricular dysfunction, ventricular arrhythmias,

and neoplasia.

Next question, please.

[Slide.]

Some adverse--this is the question that's not--that is a little bit different than the previous six, but I think it's important to discuss. Some adverse events potentially due to administration of these products, such as ventricular arrhythmia, worsening left ventricular contractility and death may be identical to events that occur during the natural history of the underlying disease. The subjects in these trials--in many of these trials--have been quite sick. So a high proportion may suffer one or more of these adverse events.

Consequently, adverse events related to the cellular product or its administration might not be discernible without concomitant controls. However, invasive procedures are frequently utilized to deliver these cellular products.

Please discuss the pros and cons of using control groups in these early clinical studies, including any need for randomization or masking. Within your discussion, please also comment on the use of placebos in these studies; for example,

transendocardial injection of saline into the heart.

I would like to make a couple of points that aren't on my slide--one specifically about this. I want to make absolutely crystal clear that there is no--nothing in the regulations that prevent the use of controls in Phase I studies, and there have been many Phase I studies that did have controls. So there is no regulatory prohibition of this, nor is there any unstated policy of the agency that we don't allow controls in Phase I. I've heard that stated many places. I just want to make that absolutely clear.

Secondly, I would--these questions, any one of them, would allow for several hours, I think, of very useful and intelligent discussion. To get through them is going to be a challenge. I would encourage the committee to remember that these are issues that need to be dealt with so that we can resolve certain safety issues to allow initiation of early-phase clinical trials. I would discourage you--the discussion yesterday was quite interesting, but I would discourage you from discussion of issues that are dealt with in later-phase clinical trial: appropriate end-points,

eventual populations for therapy. These are things about which we haven't presented any data.

And I will note that--as you will note in the agenda--that FDA is always asked the questions, after all the FDA speakers, we never leave any time for us to be asked question--for good reason.

[Laughter.]

Committee Discussion of Questions

CHAIRMAN RAO: Thank you, Dr. Grant.

So, I guess now we come to the hard part. Many questions, very little time. And we're going to try and get through all of them so that we give the last few questions also fair discussion.

I'm going to try and see if we can try and focus the discussion a little bit, and focus on the manufacturing question, and try and get that addressed before the break.

So I'm going to make some blanket statements and ask the committee to see whether they agree or disagree with them, and then sort of go from there.

The first statement I'm going to make is that: a cell is a cell is a cell is not true. Even though in the heart you can put them in and they all seem to have the same effect, it's still not

true, in terms of how they have an effect and what you need to do in terms of the numbers that you put in and so on. So cells have to be treated differently.

That's one statement.

The second statement I'm going to make is that it seems the FDA and pharmaceutical companies know about how to manufacture cells to some extent. That's generic in terms of cells. I mean, Genzyme presented data on what their GMP facilities look like. They aren't the only company--and I'm sure there will be many other companies who will be willing to tell us how they are much better at doing it.

[Laughter.]

So it does seem to me that the general issues about cells, in terms of, you know, "Well, we have to look at viral testing, and we have to look at micoplasma, and we have to see that, you know, when we look at cells that the supplies are okay." And that's not something that we need to worry about in terms of the discussion today. Right?

So, we know how to make cells--or some people know how to make cells. And we know that

each cell is different, so we can broadly divide this and say that: are there specific issues to a particular cell type in a particular disease, or as it's applied to the transplanting into the heart, irrespective of the mechanism that you use.

And I'm going to further subdivide this into two broad categories. And I think we should focus on allogenic, because there's very little--we shouldn't focus on allogenic, because there's very little data on it, and we've not heard any data on whether that's going to be the same, except to make a statement that allogenic is different from using autologous cells.

And, broadly, I think for cells--at least in my experience with growing cells in cultures--there's a very big difference between cells which are freshly harvested over a short time period and put back, versus cells which have been grown in culture, have been manipulated in culture. So there will be criteria which will be uniquely different between those two cell types. And we'd keep those sort of generic points in mind, unless people specifically disagree with any one of those statements.

[Pause.]

So--great. It's amazing that we could start with a common basis, then.

[Laughter.]

So let's--

DR. MULE: I just have one comment, which relates not necessarily to the use of fresh cells. I think many of us would argue that there are less regulatory hurdles involved with using fresh cells as opposed to using cultured cells--with the proviso, of course, that with fresh cells it's a well-defined population that is being introduced into patients.

With cultured cells, what I heard yesterday, I think, is the issue of using fetal calf serum, which raises the point: if we can avoid fetal calf serum, that is a good thing.

CHAIRMAN RAO: If you could talk about some of these specifics--can we just hold that thought for a second. I can come back to that.

DR. MULE: Okay.

CHAIRMAN RAO: It's the second point, also, on some edition-specific--

DR. MULE: It just relates to the product characterization of using in vitro cultured cells.

CHAIRMAN RAO: Hold that thought, and we'll

come back to it.

Joanne, do you have something on--

DR. KURTZBERG: Yes, I had just one general addition. I mean, I agree with everything you said.

I think it would be a sad comment if we came out of here with anything that recommended or facilitated a company making a product as an autologous non-manipulated bone marrow or peripheral blood-derived cell--much as you would with an organ. And I think that's important.

CHAIRMAN RAO: So, given that viewpoint-and it's clearly going to be a contentious one--let's start at the other end--and look at cells which have been cultured for a long time period.

Does anybody here feel specifically--like you made the point about serum--are there specific things that you need to worry about that are unique to cultures which have been in culture for a long time period, and which are going to be transplanted in the heart. And, you know, some of them were raised in issues before. There was this idea of not differentiating, and there was this idea of cells changing, in terms of the different satienability, and only using the third and fourth

batches. You heard all of that, right?

So anybody--specifically on those comments, on sort of long-term culture?

Dr. Schneider?

DR. SCHNEIDER: Well, we heard about that from a useful from limited point of view. We heard that part of the efficacy monitoring in the process of manufacturing--the skeletal myoblasts, and propagating them to a quantity sufficient for human trials--was to make sure that over time they did not get overgrown by a sub-population that was differentiation-defective. That's clearly important.

What we did not hear as part of that presentation was that in vivo efficacy also is tested over time, or is tested for consistency between patient subgroups. There are good clinical data now, at least from the trials in Frankfurt, that heart failure patients, or diabetic patients have bone marrow-derived and circulating progenitor cells which are less functional in human grafting than other patients do. And there are some cell culture and in vitro correlates of that. The cell-culture correlates of that are decreased cell mobility and invasiveness. The in vivo correlate

of that is that if those human cells are put into an immuno-compromised rodent model of hind-limb ischemia, with patient cells that don't work, don't rescue hind-limb ischemia in a rodent. So there are predictive models, both for clinical heterogeneity, or for potential heterogeneities introduced in the manufacturing process.

So I would say that what we heard, in terms of the characterization of culture not introducing a distortion to the potential biological properties of the cells was nicely raised yesterday, but there are other elements to that, including cell heterogeneity over time, and cell function by other measures, that we'll need to talk about this morning.

CHAIRMAN RAO: So, clearly, one issue is that if you grow cells for some time in culture, you should be testing them at the stage that you would use them, to figure out whether they have the appropriate characteristics and properties that you want to use them for; and that these methodologies exist--right? You said mobility assays, some other assay.

And there was one other sort of issue on this long-term thing--Dr. Borer, go ahead.

DR. BORER: I'd like to--this is Borer. I'd like to follow on to what Mike said, because it's appropriate to separate out the different categories of the process as these questions have done. But I think it would be unfortunate to completely separate them and forget that they overlap in many important ways.

Steve Epstein suggested this in his comment about conditioned medium yesterday, and I want to restate it in another way.

We track and we study what we know about. We don't track and study what we don't know about. And it's easy to become fixated on your theory of pathophysiology, or my theory of pathophysiology, and study those things and miss other, or even more important, characteristics and factors.

So what we need to do is to combine the characterization of the product with the parameters that we know to look at with some integrator further down the road; that is, injecting these items into animals, or ultimately into people, and look at outcomes. And I don't mean just whether the cells survive or not, I mean it's important to track meaningful endpoints, even in small studies, so that you can pick up a's, so you can pick up

signals about survival--if they're there.

You'll never find those in small studies. Therefore, that statement--that concept--argues in favor of the FDA--maybe not in this committee today--but ultimately defining standards for data collection so that small data sets can be pooled in some way, so that signals can be amplified. Because, ultimately, if we try to define a list of characteristics that ought to be looked at to characterize a product, it will be a lovely list, but it may not be the right list. And the only way we're going to know that is by looking at the outcomes.

So I would just make that point: that we have to be thinking about data collection strategies to allow us to pool the small data sets into large data sets that allow one to pick up signals that will tells us there's something else we should have looked at.

CHAIRMAN RAO: I completely agree with you, Dr. Borer, and I think it's really important that--it's this general idea of what is required is much more important than any specific list that's developed.

Doris?

DR. TAYLOR: Have a question that I don't want to see get ignored in this process, which is definition of the cells, and definition of any given product, when a group claims that they're injecting--and the heterogeneity of that product. How do you define potency of a given cell population? Is it permissible for it to be less than half of what you're delivering? Or does it have to be the majority of what you're giving.

If you say, "Okay, we're going to give CD34 cells," does it have to be a hundred percent CD34? Can it be 50 percent CD34, with a mixture you don't know about? And that may change in culture.

And so I'd like to--

CHAIRMAN RAO: So, the important point is that we need a better defined product, and that's what is going to be some of the issues that we discuss in this Question 2, as well. Would that be a fair way of stating it?

DR. TAYLOR: Yes--and what's an acceptable range.

DR. HIGH: I have a question about skeletal myoblast processing. For material derived from humans, is expansion to a set number ever a

limiting factor, or can every subject, no matter what his age, be expanded to 10^9 cells, and our cell numbers are lot release criteria.

CHAIRMAN RAO: Doris, do you want to answer that?

DR. TAYLOR: Yes, I'll be glad--Doris Taylor. I'll be glad to answer that.

There are a limited number of patients from whom you cannot grow cells--for reasons we don't understand. Philippe has published data, and other groups have published data, looking at age. And there doesn't seem to be a direct correlation with age and an inability to grow cells. Occasionally we end up with a patient where we can't grow the cells and we don't know why. They're just not there.

Now, can you grow 10^9 cells? Generally the question is how long it will take to do that.

CHAIRMAN RAO: Go ahead, Joanne.

DR. KURTZBERG: I think whenever you work with biologic products there is always an element of unpredictability, and that you can never count on every patient growing the same number of cells, every patient biologically acting the same way. And if you try to design a trial that assumes that,

you'll never finish your trial.

So there has to be some understanding that biology is variable.

DR. HIGH: But should there be some minimum number that goes into--on injecting?

DR. KURTZBERG: I don't--I think that a lot of these questions are very premature. I just--we can't define the cell type today--we, you--anybody. I mean, I think what we have to do is do the studies to get some more data, to have some more general idea of some of this. And maybe the answer will be that--you know, if a certain kind of cell is beneficial, and you've done a collection from a patient and only collected 80 percent, are you going to deny that patient that 80 percent? Probably not. I don't know.

CHAIRMAN RAO: Again, I want to emphasize--and this is maybe just general, for information: this is historically a problem for all cell therapies--right? And you have to worry about cellular therapy when it's a single lot--right?--it's a one-unit dose that you're making, and it's from one patient, and you can't really do it for each patient. And as you all pointed out, it's going to be different from each

case.

And so what Dr. Borer pointed out is that we can't come up with a really absolute, specific list--as you said--that you can't.

So what--how do people do this in any of these systems? And from my limited experience has been that you either say that they're the same, because you have some definition of markers, or sets of things that you put together for cells, or you say they're the same in terms of some substitute assay in culture.

So, for example, if you're looking at pancreatic islets, you say they all release this much in terms of the number of cells that you give in terms of insulin release. Or, you know, in Parkinson's patients you say, well, this is how much dopamine is released by this particular number of cells, and you say that's an equivalency sort of measure.

And what, to me, from looking at--or hearing conversations seems to be that it's pretty clear that there's going to be that same sort of variability, and that there must be some kind of equivalency measure that must be looked at if you want to collect any kind of data.

Go ahead.

DR. BLAZAR: That was the point I was also going to make is it's--listening to the data yesterday, it looks like multiple cell types may, in fact, be additive or synergistic, so these preparations that are not 100 percent pure may, in fact, have some advantageous--potentially advantageous aspects to it.

So I think if it's well characterized, it doesn't necessarily have to be 100 percent pure. The dilemma is that if the in vivo readout is the critical final denominator, then the in vitro assays might simply just characterize the product, provide the information to the literature, which is then correlated with the clinical outcomes, and then in retrospect then define, potentially, product limitations.

I just don't know if you'd be able to, up front, say that "this is a desired product," so much as "this is the characterization of that product," to the best that we can characterize it, and then try to retrospectively do the clinical outcomes measurement, and then have that define the field of a useful product.

CHAIRMAN RAO: Go ahead.

DR. BORER: This may be a little premature, because I think it will be covered in another question. But the discussion that Dr. High and Dr. Kurtzberg just had I think is important, and I just want to put a bookmark in here.

What's being raised here is the issue of dose-response. And I would point out--and you all know this--that the shelves and the libraries are filled with expired patents of wonderful drugs that were never used, because the dose-response wasn't adequately characterized, and the drugs were developed at the wrong dose.

Now, I think we're--not with unprocessed bone marrow, but with cultured cells, there is incumbent upon investigators the need to define the dose-response in a broad, and as complete as possible way, because ultimately the application of at least that type of therapy will depend on the adequacy of dose.

So I just put that bookmark in. We'll be taking about it later.

CHAIRMAN RAO: I was actually kind of surprised--one issue that didn't come up with cultured cells was nobody seems to worry about looking at karyotypic stability of cells. And even

when people talked about this, nobody presented data where they said, well, you know, when we put in 100 million cells, that these cells were all--you know, we tested an aliquot, or we looked at it.

What does the committee feel about karyotypic assessment?

DR. BORER: Yes, I must say I had that written down here, but I thought since nobody mentioned it, it was probably silly.

The fact is, with multiple passages, I would have thought one would like to know how the error rate increases; that is the replication errors increase, because that's going to characterize the population, as well, and one could easily wind up with cells that have all the surface markers that we look for, and the antigenic markers we look for, and, you know, they look like what we're interested in, and yet you inject them and you come up with a cell rest in the myocardium that doesn't do what you think it should have done.

So I would think that it would be very important to assess the karyotype in the final product, as well as in the initial set of cells that you put in.

CHAIRMAN RAO: Joanne?

DR. KURTZBERG: I agree with you, but I have an unrelated point about administration--and it wasn't mentioned yesterday. But there were--during the talks about the devices, the needle gauge size came up a couple of times, and I heard numbers like 27-gauge, 29-gauge thrown around.

And, as a transplanter of hematopoietic cells, we would never put those cells through that small a needle, because they lyse, get crushed, get smashed, break apart. And then you're talking about doing it under high pressure, which only increases the probably of cell damage.

I understand there are other technical issues related to the heart and getting catheters in there, but I think it's really important to talk about that, and at least require some kind of bench testing that would demonstrate that cells can be--you know, aren't damaged when they go through that small a hole under high pressure.

CHAIRMAN RAO: Dr. Murray?

DR. MURRAY: If we're going to worry about dose response--that's if we need a numerator and a denominator--right?--the denominator's going to be

response. We're not talking about that right now, we're talking about the numerator, which--what do we count as being part of the dose? Is it how many hundreds of millions of cells? Is it how many millions of myoblasts in a set-up preparation? Is it how millions of cells with the normal karyotype of a particular cell type?

I feel very uncomfortable with the tremendous uncertainty of what it is we think we're looking at, and what subsets of that--the collections of cells we're looking at, etcetera. Some clarity on that I think would be helpful.

CHAIRMAN RAO: Doris?

DR. TAYLOR: Specifically, with regard to myoblasts, I think one of the issues is the assays you design for your cells. And with myoblasts--I can't say that we've looked at the karyotype of our cells over time. What I can say is that we've looked at the ability of our cells to fuse and terminally differentiate and form myotubes; and that that's used as a potency measurement of these cells.

And I think that is the kind of assay that makes a lot of sense in this particular setting, because once they're terminally differentiated,

they're not going to continue to divide in the myocardium.

I will say that--I didn't present these data yesterday, but we have preclinical data over a number of years showing that if we purify the cells to too great a degree of homogeneity they are less effective than if there is a mixture of cells present. And that doesn't surprise me, given the mitogens that, I think, are delivered by the fibroblasts and other cells that are there.

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

DR. BLAZAR: Yes. I think the issue of passage numbers and serum requirements is really critical, and as these studies go forward, even with characterizations, if the products look the same at three passages, and you're using them at five or six passages, the cells may well differentiate in a way that can't be well monitored in vitro.

And I don't know necessarily that there's an optimal passage number, but I think as the studies report their results, it will be very important to discuss those two issues which may affect in vivo survival and differentiation, as

well as karyotype stability.

CHAIRMAN RAO: That's a really important point, and maybe I can try and summarize what I felt was the sense of just this specific point: that when you keep cells in long-term culture, it's really critical to look at passage number. And that's more an absolute rather than just saying, "Well, you know, I used passage eight and it has the same apparent phenotype as an early passage," but that you really want to keep track of the passage number. And you can't just automatically assume one will be the other.

DR. BLAZAR: I think even added to that is cell density. We know that cell density is a critical influencer of differentiation potential, and minor changes in cell density can have significant abilities, not only to look at the growth rate, but can differentiate cells in ways that may be picked up in later passages because of the cell contact and growth-factor issues that--where one population influences another.

So I think, again, as we go forward, as much information in the reports as possible, to try to look at these effects, and if they are going to vary in even individual patients, so that there can

be a net body of information in the literature, it would be helpful retrospectively in evaluating the outcomes.

CHAIRMAN RAO: It's a good time to sort of consider also what you raised as an issue of the growth-factors in serum, and cytokines, which should be used in the manufacturing process perhaps. And if you have a specific comment--

AUDIENCE: Actually, it was back on the unmanipulated cells--I just wanted to make a comment on those.

CHAIRMAN RAO: We're going to come back. Hold it and see if you need to make that comment at that time.

Go ahead.

DR. SCHNEIDER: Michael Schneider.

I wanted to state that with respect to heterogeneity, skeletal muscle-derived cells over time in culture, in addition to the issue that Doris mentioned about the variable percentage of fibroblasts, there are two other specific populations to be vigilant about in the skeletal muscle preparations.

One of them is the so-called side population, or SP cells, which are very small in

number, but--as many members of this panel know--in bone marrow account for much, if not all, of the long-term self-renewal potential. And so it would be important to know whether the manipulation of the skeletal muscle cells in culture over time might be depleting that from the starting population; or, alternatively, enriching for that relative to the starting population.

There also has been described in rodents, by several labs, a SCA positive population, similar to the progenitor cells that we see in adult rodent hearts. SCA-1 is an allelic variant in rodents that doesn't have a precise equivalent in humans. But as Dr. Itescu alluded to yesterday, markers such as STOW-1, indicative of the pericyte might well be good indicators of the SCA-1 equivalent in the skeletal muscle preparations.

And so my point is that, in terms of the drift in time over culture, it's important to know in a consistent and reliable way what is happening to these other sub-populations that may be contributing to the in vivo efficacy.

CHAIRMAN RAO: So that's really--it seems to be a really quite important point, is that since we don't know what is the--and it's the point you

made, as well--is that we may not know the effective cell, and we need to know both about the concentration of the effective cell, in terms of whatever you think its mechanism is, as well as the other cells that are going to present in the media, because we may or may not know how useful or how bad they may be-- whatever may be the case.

DR. SCHNEIDER: It's not that these would be necessarily contributing to the skeletal muscle formation in large number, but they may be producing cytokines, growth factors, acting on the other injecting cells or, as several speakers alluded to yesterday, having some other kind of favorable effect on the host.

DR. MULE: If it's true that 90 percent of the injected cells are dying, it's hard for me to imagine, first of all, how one can do an appropriate dose-response. And secondly, we may spend an enormous amount of time trying to understand the makeup of the culture before it goes into a patient. But not having an understanding of whether certain subsets of cells within that heterogeneous population are dying off in vivo--with a 90 percent overall die-off, it's a struggle to understand--and it gets back to Dr.

Borer's concern about having appropriate endpoints in the trial that will allow you to get some biologic information about the cells that not only go in, but those that survive.

DR. MURRAY: This is Tom Murray.

My friend Carol Greider was once trying to teach me about Belgian beers. And the lesson didn't particularly take. But apparently--they go through multiple fermentations, and they utterly change their character, depending upon whether it's the first, second, third, fourth--I don't know how many times they do it.

And I heard yesterday--and maybe a little bit even today--the possibility that in different passages the cells' properties change. And it seems to me there are just--crudely, three possibilities. One is it doesn't matter how many passages, at least up to a certain limit, but the cells are the same all the way through. And that does not seem to be the case. I don't hear anybody saying that that's the case.

The second possibility is: they change, but in a continuous fashion. That is, whatever changes there are, they simply--they're additive, so the changes in each passage, they become more

extreme.

A third is--and this is what I thought I heard yesterday--was that, in fact, they change in interesting ways, such that three and five may be more alike than four. I may have the specific numbers wrong.

It would be very helpful for the FDA, I think, to ascertain what the best scientific evidence is as to which of those three models is the correct one, and then that will have implications for whatever you decide.

CHAIRMAN RAO: So--I want to get back to the point that Dr. Murray made, and that is that all of this assessment that one considers, you need to consider not just at the time that you've got the cells into a wire, but really have to have some assessment of what that means when you get them into the heart. Is that the emphasis that you've been making?

So if you're going to have deaths, then you need to know that you're going to have 90 percent die each time, because that's going to significantly change your dose, if you do something with it. Is that a fair--

DR. TAYLOR: I think one of the issues that

you need to think about in considering that is that the geometry of the injections, and the number of injections is really going to probably change the number of cells that die. If you inject a giant bolus of cells, it doesn't take a rocket scientist to figure out the fact that more are likely to die than if you inject 10 smaller populations throughout the scar, based on the nutrients they receive.

So I think you have to factor into trial design the injection patterns for these cells as well.

CHAIRMAN RAO: Dr. Borer?

DR. BORER: I thought that the issue I'm about to raise really would be subsumed under the preclinical studies area, but I looked at the question, and it's really not only.

And that is--and that follows from some points Dr. Itescu raised yesterday which broadly involve drug-biologic interaction. These products will be given to patients who have--who will have multiple drugs in their bodies at the time the products are given. And I don't think we know--I mean, I don't know the research in the field, but I didn't hear much about it yesterday--I don't think

we know how the drugs that routinely are given to patients who have the target diseases affect the growth and development of the cell products.

And I think this needs to be characterized. I don't know what we'll learn, but one could just, for example, learn that maybe you have to stop beta blockers for a few weeks in people with heart failure who are being given cells, because the cells won't grow properly--or optimally.

And I think that characterization has to begin before one gets to the in vivo experimental model studies, that it really does require some benchwork to look at the effect of drugs on the cell population.

So, again, just to bookmark--but we haven't talked about drug-biologic interactions, and I think that's an important area that we need to consider throughout these discussions.

CHAIRMAN RAO: Bruce?

DR. BLAZAR: I wanted to come back to the cell death rate. I think one possibility is, of course, mechanical, and the cells don't survive when they've been removed from an in vitro culture, and they're undergoing cytokine withdrawal,

etcetera. Another possibility is that they're just not receiving the proper inductive signals in vivo.

If it was the latter case, then a dose-response curve would actually help, because it's still going to be the same fraction of cells that is not receiving the appropriate inductive signals. And I think there is ample data in animals, with a variety of cell types, to say that if there is not a stimulus for proliferation the cells will either sit there or they will undergo cytokine withdrawal, or other apoptotic cell death pathways.

So I think despite the death rate, it's critical to evaluate the dose response because we do not know, as you remove these cells from the in vitro environment, what proportion of cells would survive in any location, given under any conditions. And while it's important to evaluate the cell death rate, I believe that several of these may relate to just inappropriate environment to be induced to proliferate the way that they are in vitro.

DR. MULE: I agree with you, Bruce.

My concern is that it will not allow you to achieve the highest dose

response--conceivably--limited by practicality, for instance. I mean, if you go up to 10^{10} cells, and you're losing 90 percent of those cells, realistically, how many cells can you generate over a given period of time, given the injections that are needed. Those type of issues--

DR. BLAZAR: We don't know how many is necessary--what fraction of surviving cells is necessary for a clinical benefit.

If you look at bone marrow infusions, most of those cells die. The vast majority of them are terminally differentiated myeloid cells, and, you know, we're injecting products where the cell survival rate is extraordinarily low. And, again, I think it's the inductive signals that are required.

Once it is known how best to manufacture cells to receive the appropriate inductive signals and to put them in the appropriate inductive environment, then we'll realize more of the clinical benefit. But even for now, I think, that as the dose response curves are done, since we don't know the fraction of cells surviving necessary for clinical benefit, those studies just have to be done and looked at the data

retrospectively.

CHAIRMAN RAO: Dr. Allan?

DR. ALLAN: The comment I'd like to make is when I read Question 1 what I see is safety. And most of the discussion here seems to be on efficacy; what's the right formulation in order to get the right response, or dose response. And to me, what I see the question is is mostly safety. And so therefore it's like the preparations, that if it's 80 percent fibroblasts maybe you don't want to give it, but if it's, you know, 80 percent myoblasts, then--what are the safety considerations? And so for a lot of this, it's really--because we're going to be stuck on Question 1 for the rest of the morning if we keep introducing efficacy into the discussion.

And I would say we just want to stick to safety.

CHAIRMAN RAO: Yes--I, in fact, would even say that we want to stick to manufacturing right now--you know. So--meaning, at the product. So all we're looking at is that can we define a product in light of what it will be, with some reasonable criteria, in terms of--

DR. ITESCU: Yes, and I think that was

really my point to Dr. Borer. Whilst I agree that there are many scientifically valid questions to be asked, I think the cell product that's being defined by whatever is being addressed needs to be viewed no differently than a pharmaceutical composition. And I think that's really the job of the FDA, to ask questions about, obviously, safety, but also dose-response questions, about efficacy, about production, manufacturing--scientifically valid questions then follow on from that.

But the definition of the product is the key, I think. And that can be based on surface phenotype or function.

CHAIRMAN RAO: Go ahead.

DR. WENTWORTH: Yes, my name is Bruce Wentworth from Genzyme Corporation. I just want to make a small observation.

There's been a number of suggestions of tests and assays that might be performed on cells. Some of those are, in fact, done in the normal and routine monitoring of cells in production. Every production facility will set limits on the number of passages that are used. I would point out that it is actually population doubling is perhaps the more relevant figure, rather than passage number;

and the conditions under which cells are passaged.

However, in cell therapy, really, it can never be quite like pharmaceuticals. Cells are inherently variable. There's no way around that. And I would ask you, in a moment of quiet reflection, to look at the back of your hand. You will see warts, cells that are dark, skin that's light, hair, no hair--it's all the product of karotynocites. Every one of them works. All of them are different.

You can make a useful product from that that actually saves the lives of burn patients. So if we spend a great deal of time analyzing the karyotypic difference, which is inherent to the back of your hand, we'll get nowhere and you'll have no new product.

Thank you.

CHAIRMAN RAO: Dr. Borer, and then Dr. Harlan.

DR. BORER: Just a philosophical point. As Dr. Allan points out, we're talking primarily here about preserving safety, but first of all, there are dose responses for safety endpoints as well as for efficacy endpoints. And so you have to know these things. And, in addition, I think it's very

artificial to talk about "safety," and not consider other effects--other effects of the product--that might contribute to clinical effectiveness because, at the end of the day, the issue isn't absolute safety, it's safety that's acceptable for the intended use.

So, one really has to keep the equation in mind always between effectiveness and toxicity. So I think it's reasonable to characterize the product in all these ways, even though it sounds like "effectiveness," in fact the safety characterization and the efficacy characterization are really different ways of looking at exactly the same characteristics.

CHAIRMAN RAO: And I'm going to try and ask everyone that let's try and focus on this first two sets of questions, which is: we've got cells--some kind of cell--and right now we''ve only focused on the cells that you've got in long-term passage, and that we've got some specific issues that we might want to consider when they're there, and one of the issues was that passage number is important, and the second issue was that you really should look at karyotypic stability as well, and that you should have some readout on what that composition of the

cell type is, and that none of these can be done just in culture. You really need to do them after you've implanted the cell in some fashion so that you have some readout of what you're actually delivering in terms of a product.

And Joanne made the really important point, I felt, was that what that means is that you have to include in this whole process is how you're going to deliver--right? That gauge of the needle that you deliver through; the method of delivery is going to be as important in that whole process as anything else, because 27-gauge for somebody is going to lyse their cell type, and if you use a 30-gauge, it's certainly going to give you based, and maybe that will be effective, but the mechanism will be different, you know.

And so those points seem to be pretty clear from what needs to be done. And I thought that another point that came up was that when you think about composition you're not just thinking about the effective composition of the cells, but you're really thinking about the total composition of a cell, because heterogeneity may be important in its function, but also what the other cells are doing may be equally important in what they might

not do--right?--or what they might worsen.

And we need to have that information. And the points you made about collecting that data is really critical in terms of having that sort of data in terms of defining a product.

So let's see if we can add to that, specifically in terms of these cells, because I'd like to try and extend this to also the non-passage cells as well and see if there's anything, really, that's specifically different in those as well.

DR. KURTZBERG: Well, I think you can learn lessons from cell therapy that's already in progress. And there are some simple things that are always done, like viability, sterility--and those--especially for the long-term passage cells, there has to be a protocol for determining sterility that doesn't involve setting up a culture the day you deliver the cells, because that's not going to be useful information.

I think in most settings you would characterize the population by phenotype or whatever other method you have, and maybe the potency assay would be a colony-forming assay, or a cytokine-production assay, or whatever. But whatever is decided would be done on all products.

I think, also--

CHAIRMAN RAO: Joanne, let me add just one point what you made--just make sure that I've got that appropriate.

Whatever surrogate assay you use has to match, or you have to have some data that it's a representative assay for what function you're going to use. Is that--

DR. KURTZBERG: To the best of your ability.

CHAIRMAN RAO: To the best of your ability.

DR. KURTZBERG: I mean, again, what Bruce said is that it may just characterize the cell, rather than directly correlate with your efficacy. But it's the best you can do at the time.

And then, finally--and this may have more relevance in the future--but there will be other contaminating cells in some of these populations, like t-cells, or macrophages. And while it may or may not have relevance, I think that at least knowing what immune-mediating kinds of cells are there could be important, and they should be characterized as well.

CHAIRMAN RAO: Dr. Simons.

DR. SIMONS: I would like to raise the

issue that the effects observed in all of the studies may have nothing to do with the cells that have been actually injected--at least with the live cells--and it's the dead cells that are having this effect.

With 90 percent of the cells dying, I find it hard to believe that whatever is left is really responsible for most of the biological effects observed. And that could be different in a setting of an acute myocardial ischemia, versus the setting of sort of chronic CHF patients. But I think, in talking about what this material is, it is important to consider that it could be t he dying cells, or the dead cells, that are the active sort of ingredients here, which I think sets a very different set of issues than if the active material is what's going to be left of the dividing cells.

And I would like to hear what people think about that.

CHAIRMAN RAO: I thought before we go into discussion--comments from some of the other people.

DR. HARLAN: I think you were making this point, Dr. Rao, but I believe that we don't know if any of these surrogate characterization tests that we wish to do are true North. I think we need a

"true-North" assay. For bone marrow transplantation we've had a lethally irradiated mouse, where we can test the various assays to see where they're predicative of anything.

What I heard yesterday is that we don't necessarily have a true-North assay in the clinic, or even in animal models, to say that this cell population is doing what want it to do. And without that, all of the characterization is difficult to judge.

CHAIRMAN RAO: A really important point, and let's keep that in mind. And I think it's good that you brought it on the table.

Go ahead.

DR. SCHNEIDER: I would disagree with Dr. Harlan's point because I think that the true North is there. We don't know why the true North is working.

The true North would be to inject the human cells proposed for use in human patients into an immuno-compromised rodent and show efficacy, as Dr. Itescu did. That could be done most directly by intra-cardiac injections or, as a surrogate for their angiogenic capacity in vivo, as rescue of hind-limb ischemia. And I think both of those are

perfectly appropriate assays to test for the angiogenic potential, or the myogenic potential of the proposed populations.

What I wanted to comment on, prompted by Bruce Wentworth's remarks, is to point out that the FDA, I think, has to anticipate some very different kinds of protocols in terms of manufacturing coming down the pike. Some of those will be large, very centralized studies using GMP facilities such as what we heard about from Genzyme, and as Dr. Rao alluded to--other companies with large, long-term experience in cell production of many kinds.

What I as an academic investigator see as one of the potential risks to the field is the illusion among academic investigators that cell therapy is easy, because of the proliferation of clinical trials that have been reported with high visibility. And as trials move or propose to move from a single, highly experienced center into half a dozen, or a dozen, or two dozen centers with variable degrees of experience, both in cell production and in cell administration, that's, in my mind, one of the principal issues for defining the criteria in terms of purity of cells and in vitro surrogates, and even in vivo surrogates

before a given trial be given a green light.

CHAIRMAN RAO: Can I expand on that statement before we get the comments.

I think what you've said is somehow also representative of what Dr. Grant started with, in terms of the frustration for the FDA; or, how can you really use data from one trial or the other to pool it when you have large numbers of small samples?

And I think what's coming through here is that you can't pool that data unless you really have very clear-cut description of what you really have put in--right?--in terms of the quality of the cells, or the number, or--you know, the markers that they exist, or some clear-cut surrogate marker. You know, it may be--as you pointed out--that it has to be done in an animal model, or it has to be done--but unless you have a common set of readouts which are all consistent, you won't be able to pull the data across many of the clinical trials, and you won't be able to extrapolate from one trial to the other.

And I think that was true, even when Dr. Menasche, when he presented the data that they had shown that, you know, when--even if you take

skeletal muscle and you look at different labs, if they do it slightly differently, you get different results. And so you really have to be very critical, in terms of how you can compare and not compare and it won't be okay.

DR. SCHNEIDER: It's the second of those aspects that I was trying to emphasize; the risk of extreme variability, even with a single trial, between different production sites.

CHAIRMAN RAO: Go ahead--you've been waiting for a long time, and then Dr. Itescu.

DR. GRANT: Thank you. Stephan Grant from Viacel.

My question relates to the testing of the finished products. Do you think--would the committee support a position saying that in vitro or in vivo differentiation studies would not be part of the final specification of the finished products, because certainly, I think, if we just transfer what we are doing with the small-molecule drugs, or even with recombinant proteins, we are normally not testing, for example, the receptor binding or a biological assay for potency or for efficacy for the batch release.

So the question is basically: would the

committee support a position saying, well, differentiation assays, in vitro, in vivo, are good for profiling of the product, but not mandatory for the release of the finished goods?

CHAIRMAN RAO: I'm going to try and take the liberty of answering for the committee, and if people disagree--

I think that that's not--the sense from the committee that I got was that, you know, it's really important. It's important that you know. And from what Dr. Murray has said, and what other people said, that you really need to have some potency equivalent--right?--that has to be--

DR. GRANT: May I just add a comment?

I was not--I'm not saying that we don't need such assays to be performed, but the question is if we have to test batches of finished products, batches to be released for clinical trials, or later for the market? The question is whether a differentiation assay should be part of every batch-release specification?

CHAIRMAN RAO: I don't want to be too specific, so we'll leave that topic on the table right now.

Go ahead, Dr. Itescu, and then--

DR. ITESCU: I just wanted to add to what Dr. Schneider said. I agree with him entirely--that I think that we do have good immunosuppressive models--small models--where you can test whatever human cell type you want. And I think that could easily be a surrogate outcome for potency for any given product that you're interested in.

I think, in addition to that, we would be able to put together some sort of consensus on what constitutes cardiac improvement. We really barely touched on that, really, yesterday, but I think, as a group, you'd find some sort of consensus about, maybe, systolic improvement. And I think if you had those two combinations, in terms of differentiation in vivo plus functional improvement, you've got potency.

CHAIRMAN RAO: Dr. Cannon, and Dr. Kurtzberg.

DR. CANNON: I wanted to follow up on Dr. Kurtzberg's comment about immuno-reactive cells.

I think it's also important for us to consider how the cells are obtained. I think there is interest in cytokine mobilization of cells, and certainly the experience in giving GCSF by our

transplanter colleagues has been very favorable. They really haven't seen much in the way of complications--a few.

But it may be very different in our patient populations that we want to treat. And the point I want to make is I think it will be important for us to characterize these cells as to whether they contain activated immuno-competent cells that might destabilize plaque.

CHAIRMAN RAO: Hold the thought, I'm going to try and summarize that and just make sure that I've captured it, if it turns out I haven't.

DR. KURTZBERG: I'd just like to propose--I think you need a cardiac therapy study group. I think the people who are interested need to come together, build a consensus, decide on how you're going to monitor your products and characterize your products; decide on what your endpoints are going to be for your clinical trials.

Because you have several products, and several endpoints, and several diseases--and there's models to do this in cancer therapy, in transplant therapy. And I think that's what has to happen now in order to pull this all together.

CHAIRMAN RAO: Can I try and extend--if you

have a comment, is it specific to this?

DR. TAYLOR: It is--it's specific to actually two things: one, to Dr. Schneider's comment about different groups coming forward.

One of the things that frightens me most about he field--and that I hope the FDA is going to be the regulatory body on--is the number of phone calls I get from physicians saying, "I can take cells out of the bone marrow," or "I can grow cells in a dish." "I can do a study, and here's the study I'm going to do." And it concerns--with no experience, necessarily, preclinically, in terms of understanding the vagaries of cell therapy, or the vagaries of growing cells, or measuring cells.

And so I really am concerned about that.

In terms of pulling together a cardiac study group, one of the commitments that I and a couple of other people in the field have made is to get all the thought leaders, in terms of academic investigators who are doing this work internationally, together to try to come to a consensus this year about what endpoints we need to be measuring, preclinically and clinically.

DR. RIEVES: Dr. Rao, we appreciate all the comments. They're very useful.

But in your summary, could you also incorporate the perspective of overall product development? Characterization, for example, is usually regarded as a continuum. As you've heard, we need some details in early clinical development, but our regulations, our acting procedures, allow a great deal of flexibility, such that flexibility for initiating a Phase I clinical study may be considerable with respect to manufacturing, compared to the flexibility that might be reasonable prior to initiating a Phase III study.

So, in your summary and discussion could you also incorporate the stages of product development? And specifically, we're interested in early stages.

CHAIRMAN RAO: Before we get to that, can I try and also--in the interest of time--try and extrapolate from all this discussion?

You know, we looked at long-term passage cells, and I want to say that many of these issues apply, but to a lesser extent if you've directly harvested the cells. And you can't extrapolate from one cell type to the other if the mode of selection is different.

And as has been already pointed out from

the data that's available, that if you mobilize bone marrow cells it's not that one mononuclear cell population is the same as another mononuclear population, because we don't know the mechanism of action, and we don't know the cell type. So that each cell type used in cardiac therapy, in some sense, irrespective of whether operatively you call it the same, is different because you have to define that particular product in terms of how it was isolated, and from what patient population it was done. So even though it's a one-shot dose, you can only compare it with a single one-shot dose from another patient where it was made and harvested much the same way.

So many of the issues that we raised here for passage cells apply to these cells in a generic way, but there will be specific concerns which are specific to each of those modalities.

Does that seem like a fair statement?

DR. HARLAN: If it's true--and one thing--I agree with what you said, but one thing that was stated, and if it's true I think it's a great outcome of this session, is that if the community agrees that injecting the cell of interest, or the cell gamish of interest into immuno-compromised

mice with an infarcted or dysfunctional myocardium, and the endpoint is an improvement in systolic function--if the community agrees that that's true-North and a good bio-assay, then that's a wonderful outcome of this session to use as a surrogate gold standard.

If it doesn't--

CHAIRMAN RAO: Dr. Harlan, we're going to come back to models, and so I really want to--

DR. HARLAN: Okay.

CHAIRMAN RAO: --try and keep that--

DR. HARLAN: But it if doesn't, then I endorse what Dr. Kurtzberg said about a working group to try to come up with--

CHAIRMAN RAO: Yes. Specifically to manufacturing.

DR. HARLAN: Specifically to manufacturing--and to Dr. Rieves' comment--a number of benchmarks were discussed, including some potentially onerous ones--were they to be applied to every patient's cells. And, in fact, some of the assays that I was suggesting, such as testing for in vivo efficacy in hind-limb ischemia clearly could not be applied in a workable timeframe to testing an individual patient's cells prior to