document, I read somewhere in the document that the 20 year was an "arbitrary" time. And so if it really is completely arbitrary, I would throw out 10 just to stimulate discussion. It's another arbitrary time period.

CHAIRMAN SALOMON: The way I understand they went after this is you've got a 1 year point, a 5 year point and a 20 year point. Now, you've thrown in the 10 year point. Okay. So let's take this as what you have to do for a year, what you have to do for 5 years, what you have to do for 10 and do you have to do anything for 20? How about that as a basis for some discussion?

DR. MULLIGAN: I think 20 makes everyone nervous. I'm curious to directly talk about 20 versus something like 10 in terms of what's the precedent in terms of toxicities, long-term toxicities coming on in 20 years as opposed up until 10.

DR. CHAMPLIN: The obvious long-term toxicity is radiation induced cancer. And solid tumors may take even over 20 years to develop after radiation exposure. And if you assume insertional mutagenesis, it may in fact have some similar long-term outcome, you need for that end point a long time to evaluate it.

Autoimmune disease, and I couldn't give you the number off the top of my head, but I would think that would be a much smaller -- probably 5 years would be plenty to look at autoimmune outcome.

And so in situations where mutagenesis would not a concern, a none integrating plasmid, perhaps in that situation 5 years might be a sufficient follow-up. If mutagenesis is a concern, then you probably do need 20.

DR. SAUSVILLE: That word exempt is even more pertinent to this field of so-called Von Economos' encephalitis and the latent incidence of Parkinson's. I mean, what it was, whether it was an exposure or a virus is clearly epidemiologically relevant beyond 20 years.

DR. BISHOP: Indeed, I wanted to concur with Mr. Champlin. In your briefing document I think we outlined scenarios for Hodgkin's Disease where some of the problems with leukemia may not appear until about 5 to 9 years afterwards and we plateau at 15 years. Problems with thyroid, breast and other solid malignancies will not become apparent until about 15 years following therapy. And this is data that's pertinent to this conversation because if, for example, as you pointed out you're looking at a single

event occurring at the time of therapy that could lead to oncogenesis, this may not be apparent until many years later.

The 20 year period was actually discussed at the last meeting and it was recommended that this would be an appropriate time frame to look at.

The other thing I wanted to point out is the outline that we've proposed in the tier 1, 2, 3 system really pertains to potential policies that would apply to gene therapy for long term follow-up. It does not at all address the safety data that would be collected as part of a traditional phase 1, phase 2, phase 3 trial which is critical to the development of each product.

So, clearly, when I used the word exempted there, this was a word that was used by this Committee last time with this particular example and the idea from that is not to exempt patient follow-up from safety follow-up that would be specific to the particular product, but exempted from a requirement, a broad policy requirement or broad requirement that would be outlined in the guidance document that would try to be an umbrella to catch all potential scenarios.

DR. CHAMPLIN: One would hope that the

long-term follow-up beyond 5 years could be like on a post card and nothing that's more onerous than that, because clearly you're looking for major late events. And the big problem is one gets increasing numbers of people being followed in the long-term is just the enormous amount of paperwork for often a smaller negligible return. So you really want to make that aspect of the follow-up very simple and straightforward and, hopefully, not very labor intensive.

DR. BISHOP: I use the word questionnaire rather than post card.

DR. MULLIGAN: So to try to move ahead --

DR. SIEGEL: If we want a target, it'll be easy to target for those that carry risk factors such as insertion or replication or latency where we know what we're targeting. For this class you're going to have provide some guidance as to what we're going to want to target in the long-term follow-up for these particular types if we go to long-term follow-up.

As of yet, the reason for the long-term follow-up we've heard is just that it's gene therapy and we're worried. And so if we're worried, I don't know is it worry that a post card is going to solve? Are we worried about cancer and if so, then we don't

want 1 or 2 year, we want 20 years? Are we worried about everything, in which case we would want --

CHAIRMAN SALOMON: Okay. We gave you that. I mean, Dick proposed that -- and I was just letting the discussion go on before trying to come up with a consensus, and I'm not ready to do a consensus yet. But what Dick proposed was that if the risk or the putative risk was mutageneses, that you probably needed a 20 year horizon. That if it was autoimmunity, you could capture that within a 5 to 10 year horizon. So that was his way of dealing with your question.

DR. MULLIGAN: I think it would be useful to go back now and look at what is long-term according to the vector, for instance. So if it's a cancer risk, I think there is a consensus that 20 years is a sensible type of thing. And we could then arbitrarily say for integrating vectors, mutageneses, insertional activation the "long-term follow-up" has to be on the order of that.

If it's a vector that has potential for autoimmune disease, we might decide that long-term follow-up is a 5 year long-term follow-up.

For an ex vivo I think that's a very reasonable way to do it rather than have one long-term

follow-up.

CHAIRMAN SALOMON: I agree. I think that's where the Committee's going.

Now, I mean I had some specific questions like why is the plasmid vector looking at table 2 in tier 2? I mean, it's very low integration potential and it's not replicating, it's not latent and we're not requesting long-term follow-up now. How did it end up in tier 2 if this as a test for the sense of this system?

DR. WILSON: That's, I think, what we've been hearing from the Committee that you didn't want to have any gene transfer categories going into a long-term follow-up situation that didn't include collection of this kind of safety data that we've just been talking about. I thought that was the conversation that we had in November with the exception of the ex vivo cells. And you've reiterated and actually now expanded that discussion to now include those --

CHAIRMAN SALOMON: So the way I would think about the discussion today, I would put plasmids in tier 2 --

DR. SIEGEL: No, no. That's the opposite of what you're telling us. That may be why you think

tier 1 is too low.

Tier 2 is the low risk products, the ones you told us we didn't need to worry about. And now you're telling us these low risk products we should be doing clinical follow-up. That's why they're in tier 2.

Tier 1 reflects that this Committee said that there's some things that are not replicating that are going into cells that are just going to last a short period of time where we don't even need to do that clinical follow-up. We can eliminate tier 1 if that's your sense.

CHAIRMAN SALOMON: I think that you're getting the idea here and what you'd exactly end up doing is okay with me. I mean, in other words, either you put plasmids in tier 1 and you add some long-term follow-up in tier 1 or you leave plasmids in tier 2 and there's nothing that I know of in tier 1 right now.

DR. MULLIGAN: Well, I think we were on to something before when you're thinking of the different long-term. If you go back to the tier 1 and make Jay less nervous about what would be some long-term follow-up for a tier 1 thing.

Let's take a tumor vaccine, you would make

the case there's not a risk of insertional activation, therefore there's not this long-term cancer risk. Therefore, there's certainly not the 20 year follow-up necessary. And so we come up with what is the long-term follow-up necessary. And that satisfies, I think, our interest in having some reasonable follow-up. And so let's say it 5 years or something like that, you happy?

DR. SIEGEL: I'm happy with whatever advice I get that's scientifically based. I think that the problem was maybe some misunderstandings about what we meant by tier 1 and tier 2. But as I'm putting together what the advice of the Committee is, if we were to eliminate tier 1, which is probably an extremely small number of things in any case, but then look at what we've put into tier 2 and say that 20 years may be longer than needed for some of those; that within tier 2 we can recreate a tier 1 of those that we only need 5 or 10 years because they're not significant cancer or latent infectious disease risks but have other risks that could be addressed shorter, that's where we would wind up.

CHAIRMAN SALOMON: That's fine. That actually works. I was just saying that in November the examples that we were giving, which is why I stuck

plasmids in tier 1 and was saying all the things I was saying, was that's what the Committee was trying to tell you, was that an ex vivo gene transfer with a plasmid into a cell that had a very short survival in the patient would be an example of what we thought a tier 1 would be. Not with no follow-up, though. Okay. Anyway.

DR. SAUSVILLE: But there are uses of plasmids where they're being put into artificial viruses and run systemically. It's very different than that.

So, again, merely saying something is a plasmid should be X or Y I think is ludicrous. I think it needs to be based on the usage that you're contemplating.

DR. MULLIGAN: I mean, I hate to completely change the way I categorized these things, but if you didn't do it by vectors but you actually did it in terms of the issue; that is there are long-term follow-up issues that relate to autoimmune disease, that relate to cancer. And although they breakdown somewhat in terms of vectors, I think we're hearing that it really depends. It depends on what gene it is and so forth.

Couldn't we come up with a tiering system

that's more based on the nature of the safety risk and not so specifically tied to that issue?

DR. SIEGEL: The intent here is basically--

CHAIRMAN SALOMON: To be honest, that's what you're trying to do.

DR. SIEGEL: That it's not based on the vector per se, but on specific characteristics of the vector that link closely to those risks. At least that's what the Committee said in November, that whether the vector can be latent, whether it replicates, whether it inserts the genetic material, and the rest of those things.

CHAIRMAN SALOMON: Right. And, Jay, I think that the answer is that that is what this tier system is. I mean, what they've done in table 1 is give you the tier. It's not by vector. Then they gave you in table 2 what vectors fell into the tiers.

DR. MULLIGAN: Yes, but I think we're talking about gene products that are independent of vector that lead to certain sorts of safety issues, right? You'd have to figure by gene product then and not by vector, right?

So let's say an autoimmune issue can be given by different vectors, then they fall into the

different categories, but that risk we may now be saying would require less of a follow-up than the 20 year.

CHAIRMAN SALOMON: I think the difficulty here, and there's no way to solve it today, is just what you bring up, Richard. And that is that in addition to the class of the vector and what the vector will do; integrate, not integrate, become latent, not become latent, all of which is relevant risk wise is in addition the gene product being delivered. But I mean I think everyone here knows that. I mean, if you put in an anti-A poctosis gene product, that would be completely different than the same vector delivering, I don't know, a cytokine.

DR. MULLIGAN: I actually just think that the most productive way to go ahead is to talk a little more about the different time periods that would constitute a long-term follow-up, autoimmune versus cancer. I actually think if we could come to some consensus about that, that's a better template than to add in okay, now what poses a autoimmune risk.

Let's take cancer, what poses a cancer risk is certainly an insertion. And that'll categorize retrovirus vectors or AAV.

CHAIRMAN SALOMON: Growth factor, right?

I mean if I put in a growth factor and put it in the liver, just making something up, and it sits there and kicks out a growth factor for the next five years, that's a cancer risk, right?

DR. MULLIGAN: I think it's the only way to go about this is to -- I think most people would be most comfortable by us, I think, giving a sense of whether there is this blanket 20 year long-term follow-up or whether there's a tier system in terms of the length of time of that long-term follow-up.

CHAIRMAN SALOMON: I'm okay with the tier system. I'm just saying that there's a lot of different things, not just integration is going to be risk with cancer. That was my only point.

DR. MULLIGAN: If you're treating a metabolic disease where the gene product is not oncogenic, you know, Goucher's Disease or something. I mean, you wouldn't need 20 years of follow-up for that, per se. I mean, in terms of the cancer risk you may depending on the nature of the vector, but the gene product, per se, would be considered safe.

CHAIRMAN SALOMON: Right. Yes, that's actually a really good point. That's an example of where the gene product wouldn't be as important or would be relevant, but it would be relevant in a

positive way in terms of the risk implications.

So I think what we're saying here, again now trying to bring some consensus, is that what we're concerned about is that we make a reasonable demand of sponsors in gene therapy for long-term follow-up, not unreasonable demands. And I think in that regard the Committee and the FDA is on the same page.

Twenty year follow-up seems to be a consensus for gene therapy protocols that have a cancer risk, and we would have to take those -- cancer risk would have to be decided. Yes, it's certainly going to be influenced by the vector itself, insertional, mutagenesis being the example that we've given several times, but it also could be mediated by the gene product being delivered, in an example of the growth factor I mentioned or an anti-A poctosis gene product.

Then there is autoimmunity, and in that we feel would probably be managed well into a 5 to 10 year follow-up.

And then there would be examples in which 5 years or less intensive follow-up would be adequate. Be, for example, cells that were modified ex vivo that had relative short lives that could be at least targeted and demonstrated in the patient that it was

given. And under those circumstances that would be, perhaps, suitable for no longer than a 5 year follow-up period.

Are we okay there?

MS. LAWTON: I just want to say for the record I don't think stating a 5 year follow-up is appropriate for all of those tier 1 level. I think that still has to be on a case-by-case basis that we look at some of that. And 5 years may not be appropriate, that's all.

CHAIRMAN SALOMON: It may not be appropriate being too short or too long?

MS. LAWTON: Too long.

CHAIRMAN SALOMON: Well, I mean, I guess there I don't know how to go any further. I mean if you give us a specific product, then we can have a discussion on what basis scientifically you're going to prove that less than 5 years is okay. And if you can, I'm a scientist, just show me the data basically.

Suzanne, you give me a desperate look a minute ago.

DR. EPSTEIN: I think it's kind of hard to put a time limit on autoimmunity and it's hard to put a limit on which products do and don't have a risk of generating autoimmunity. That's all. I don't object

to your guess. It's as good as any guess.

CHAIRMAN SALOMON: I think.

DR. CHAMPLIN: You know, I don't know off the top of my head the latent period following exposure and the development of autoimmune disease in this type of scenario. I mean, there's probably data out there. Vaccine autoimmune diseases that occur.

My impression is that these occur relatively quickly and that 5 years would be on the outside of the risk period. But if somebody knows more than me, I'd be happy to hear it.

DR. EPSTEIN: Well, if you look at vaccine, then you're only able to say you think it was causative. If you assume some kind of temporary relationship, that's very hard to answer and those studies have not really been done properly, and they're being attempted now.

But when the cause of autoimmune conversion is unknown, might be some virus, some environmental exposure and so on, it can be extremely delayed. It's just not known.

DR. O'FALLON: In the breast implant controversies there were claims that the autoimmune response was 9 or 10 years after the implants. I think 10 years is barely long enough.

DR. MULLIGAN: I think that this issue of the case-by-case is going to be taken care of by the FDA and the IND. So I think that this policy issue, we can't do on a case -- it has to be kind of a crude sort of arbitrary 5 years, 10 years sort of thing. And that doesn't effect in any way, really, how the FDA wants to specifically for a particular IND decide how long they want to follow-up. Because otherwise it would be impossible for us to come up with something.

CHAIRMAN SALOMON: I think my feeling here is we've given you a consensus. It hasn't really varied that much from the beginning.

I don't know if it's exactly what you wanted, Jay. But I think it reflects our best sense of what we're willing to publicly commit to in a field in which there's very little data. And in fact, I should just point out that my comfort is diminished in that, for example, we heard yesterday that the most common cause of adenovirus infections in transplant patients, and that's also in the paper that we got, was basically reactivation, which means adenovirus is latent. Yet when we look at table 2 it's marked as no latency.

So, I mean, there just is -- that may be that adenoviral vectors so far as we know has no

latency, but that doesn't seem to be the biological situation. So I'm just saying that even with the most expert people in the world working on this stuff, we're not even really clear about the details.

DR. SIEGEL: I'm sorry, I'll let you speak in just a second.

But let me just say because you seem -- in asking what I wanted and saying it's the most you're willing to commit to, there seemed to be some inference that I was asking for something less stringent. I just want to be perfectly clear that I was asking for something that was clear and science based. And that in fact what you're recommending to us now, as I understand it, is substantially less stringent than what we've designed based on what you recommended last November in the sense that we designed a program in which there would be 20 years of clinical follow-up because of all these uncertainties about what all these -- for the vast majority of trials. And now you're telling us for significant numbers we should be considering 5 and 10 year follow-up. The only issue of less stringency is for that extremely small number where we said we didn't even need that, you're saying no those should also have 5 years of follow-up.

And I hear what you're saying. If I've said something differently, tell me I'm wrong, but --

CHAIRMAN SALOMON: One thing you're wrong about is I don't believe that anyone up here has given you any sort of percentages for how many things would we think needs 20 years follow-up and how many specific protocols would need 5 year follow-up, and anything in between.

I think that what the Committee doesn't want to do is tell you every single gene therapy protocol until otherwise notified is a 20 year guaranteed follow-up or a 50 year guaranteed follow-up.

DR. SIEGEL: You haven't given us percentages. You've given us science based guidance that if there are not specific oconlogical concerns, that most of the other types of concerns for long-term follow-up don't require that long a follow-up. And if that's what we're hearing and if that's your opinion, then that's something that we can implement. And I'm just saying that's a move toward to less stringent.

Because you were asking are you not giving us -- suggesting that I wanted you to give us something less stringent than what I -- I just wanted to make sure we were clear on the motivations. You

heard my negative reactions to proposals only because I wasn't sure what they were. I think there was a communication problem. And because there was a suggestion that they weren't based in science. And recognizing that, I think you're right. I know you're right, especially in this field, that we need to address public concerns, not just scientific concerns. You have to address public concerns in a scientifically valid way because if you simply say we're going to do long-term follow-up not on the basis of scientific concerns but public concerns, you have then not a clue where to start at what you follow-up on. You know, we should archive every organ specimen and do full examines and x-rays and everything on everybody forever. If there isn't a scientific basis, then you don't know where to go. And we're stuck implementing something where we don't know where to go.

I'm much happier where we are now with the discussion that is based on -- can be as conservative as you want it to be, but it fundamentally needs to be based on risk so we know how to design it to be appropriately conservative.

CHAIRMAN SALOMON: Well, I think essentially that's well said, Jay. I mean, what the

Committee is trying to say is if you're worried about malignancy risks, then we're looking at 20 year follow-up. If you're worried about autoimmune risks, Suzanne's comment taken into context and appreciated, we're talking about 10 year or so follow-up. Depending on other risks that might be defined with other projects, maybe 5 year follow-up is okay. So we're just trying to give sponsors and the FDA the flexibility in a field in which a lot of the rules are not known.

DR. SIEGEL: Latency and latent infectious risk is one we haven't specifically discussed time lines on, but that's another area where you have to estimate time.

DR. MULLIGAN: It's just I'm not sure if we want to at this point talk about any of the vectors. Do you want to do the -- I just had one point specifically about the adeno vector that echoes in a different way what Ann said.

And that is, you know, the vectors, although they're in various stages of getting into work very effectively, those would certainly be a latent case. There's no question. And the pox -- I can't cite any studies, but there's clearly nonpermissive pox viruses that upon infection do not

kill, necessarily, the cells. Now how long they persist, I don't know. I don't know the information.

But certainly adeno would have the potential to give very long term gene in the guttedadeno form. So I think that's -- I would see that more like an AAV type of situation.

DR. NOGUCHI: I think what we really are saying is that science can take us to perhaps a couple of weeks ago, because that's when the latest science is. And that the public concern, there is some basis for the reason that you're right, science doesn't know everything. We only know what we know. And it's very hard for us as scientists to know what we don't know and predict what it's going to be. And that's the precise point about your guttedadeno.

DR. MULLIGAN: Well, I'm just saying that you actually simplify things since they were kind of out lyers in the old tier 2 system, maybe they shouldn't be exceptions. It just makes it simpler.

CHAIRMAN SALOMON: I think we made some progress on that.

Now there are a series of very specific questions, some of which we kind of addressed. It's 11:15. I'm trying to figure out how to do this.

What I would suggest, but again this is

for discussion, would be to spend another 15 or 20 minutes and try and go through these four specific questions that haven't been addressed and then -- no. What do you want to do?

DR. WILSON: It just seems to me that at this point that may be mute since we really need to go back nd revamp our systems, our proposal. And so I think for the sake of time, if that's all right with you, Dr. Siegel, that we're happy with the discussion we've had and we need to, obviously, refine our proposal taking into account your comments today.

CHAIRMAN SALOMON: Jay, that's okay? Philippe? All right.

DR. BISHOP: We'll be back.

CHAIRMAN SALOMON: I was afraid of that.

DR. SIEGEL: I think Amy also, she described a process as well that involves a lot of scientific and clinical and pragmatic input into what's collected and how. And there's no question this is going to be a process. Nonetheless, while it's being designed we're also doing it. You know, we don't have any choice but to be implementing while we're designing, and so these are useful discussions and I think we'll come back with something that reflects our interpretation of today's discussions for

further discussion.

CHAIRMAN SALOMON: I think that's great. And I think that maybe in not the next one, but maybe soon we could get some specific protocols presented to the Committee. I think at this point the concerns that I've expressed before is that there's nothing that sharpens the mind than a real protocol to deal with.

DR. SIEGEL: Perhaps what we can do is some specific marked up protocols if we want to do it publicly. Not specific real protocols.

CHAIRMAN SALOMON: We can do role playing, maybe.

DR. SIEGEL: There's enough of them that we could do.

CHAIRMAN SALOMON: I'd like to play -- well, I'll just tell you later what I'll play.

So at this point I just ask, is there anyone in the audience, the sponsors, that having listened to the conversation today feel that some comment is appropriate? I certainly don't want to exclude you from all the fun. Okay. They'll take anything we come up with.

And the heck with you guys. Twenty years.

I just want to go on record that the problem, and we've said this before, is just practical

implications of this is that even if we go to let's say 10 year follow-up -- I don't even want to get into the dramatics of 20 year follow-up -- for an investigator at an institution whose may not even have tenure at the time that they're proposing this sort of thing, to demand that the institution in signing off on that person's NIH grant or -- well, yes. Or arrangement with a biotech company that isn't a big multinational pharma company that would be definitely around in 20 years, that my dean would have to sign off on this -- I just have no idea how that -- I just can't imagine that happening. I just don't see how that's going to happen. And so there's a real practical issue that really scares me here. I mean, I'm doing what's right in saying these things up here, but the other part of me is going "Oh my, God."

DR. CHAMPLIN: Realistically what centers are going to have to do is to create an office where you're going to have a staff of people and as part of a contract to do a gene therapy trial is to provide the 20 year funding for that office to do the long-term follow-up. And the responsible thing is also to be sure that that follow-up beyond the 5 year point is very short and so it doesn't become onerous on anybody. And so it needs to be are you alive, do you

have cancer and have you had a major illness in the last year, and that's sort of it.

And there's sort of an irresistible impulse of organizations to create longer and longer forums and you get a 50 pager for your annual follow-up, and that just is going to be unworkable. But as long as one can keep it short and sweet and really to the very succinct, it's probably doable.

CHAIRMAN SALOMON: The frightening thing here is, I mean what Dick's saying is correct. We could have institutions make groups up that would follow this. The first question is is that bigger institutions, of course, will have an easier time of doing this than smaller institutions. And that is not a prejudice or a bias that I'm very comfortable with creating. But we are going to create that.

A second thing would be right now if we implement these, I'm afraid that these rules will get implemented much more quickly than any sort of change in the way the NIH funds my grants. And I just can't see how the NIH is going to give me funding for 20 years, you know, based on my follow-up. And in the absence of that, you're basically knocking us out of gene therapy, and I'm helping in this Committee, which I realize.

DR. CHAMPLIN: But it could be $10 a patient a year or something if it's a very simple long-term follow-up.

CHAIRMAN SALOMON: Right. But correct me if I'm wrong, but I don't think that there's a mechanism right now at the NIH for me to ask for $5 at .50 cents a dollar for the next 10 years -- I mean .50 cents a year for the next 10 years. I don't think I can do that.

I mean, I have to account every year. So they'd either have to make some congressional thing that a grant could be 10 years long, which I can't wait for that one. It just worries me here that there's a lot at stake here --

DR. SIEGEL: Well, it worries us. That's part of my concern about being science based, because the more that we ask for the less research will be done. I think there's no question, or the dollars won't be spent and other aspects of research that could have been done. And so we are defining with the help of this Committee is that minimal amount of long-term data that's necessary to get adequate safety collection -- and certainly our philosophy as discussed in November, it would be to try to simplify the long-term data collection and focus it again

scientifically around those items that are of specific concern. That said, however, first of all we'll focus it around safety, but there are going to be other efficacy and activity questions that people have already raised. But also I can't imagine we're talking -- what it took to track patients to collect data from them, to put that data together to submit it to an agency in a database, I don't think we're going to be talking about $10 a patient.

CHAIRMAN SALOMON: No, I was being facetious and so was Dick, I think. But the point I'm trying to say is this isn't a science base issue now. I want to make sure that's really clear. I'm not talking science.

Yes, everything you said is correct; we want science based reasons for doing things, at least as Phil says, to the extent that we know.

I'm not talking about science now. I'm talking about practical policies. If you go forward as we're recommending you to do, and at anytime in the next year or two, you know, we get this finally down to an implemented policy, that day if there isn't equal efforts on the part of the NIH and other funding agencies to deal with the issue that this creates, an unfunded mandate to the FDA is really annoying. An

unfunded mandate to academic scientists in gene therapy is a tragedy, because you close us down.

DR. SIEGEL: We won't close you down, you just won't be able to conduct business in a manner that you consider appropriate and safe, right?

CHAIRMAN SALOMON: We won't be able to conduct business according to a manner in which you'll allow us to hold an IND.

DR. SIEGEL: And what you're telling us is we should require you to do it, right? Let's just be clear about that.

CHAIRMAN SALOMON: I understand.

DR. SIEGEL: That's why we're here talking to the public so that we don't impose on a community requirements that they think are inappropriate.

CHAIRMAN SALOMON: We got it. I'm not making you out to be the bad guy here.

DR. SIEGEL: I misspoke, because sometimes we do inappropriately impose requirements that people don't consider appropriate. But we certainly want input from the communities involved.

CHAIRMAN SALOMON: I'm saying if you do this appropriately and we don't go to the NIH and Congress and the other funding agencies and make sure that this is done correctly and that we get the

support from these agencies, the day you do this it's an unfunded mandate until we do it and it'll kill the gene therapy in academic medicine.

DR. SIEGEL: If it does funded, then funds will be used for this instead of something else, and that's important to know.

DR. MULLIGAN: I think that two the event that this was a science based discussion, we did come up with something, I think the next chapter is exactly now whittling that in a practical fashion. And the practical fashion is titrating now down requirements the nature, the complexity requirements to a point that in everyone's judgment will allow gene therapy to go ahead.

So I really was looking at this in a very philosophical and a science based way and not factoring in whether this would kill gene therapy. But I think from my point of view, which may be different than Jay's, I actually think that there is some sort of negotiation, practical negotiation that now has to be done based on this to see whether or not anything we would propose could actually be carried out.

For instance, you know you'd really love to know if all the institutions, how many deans or

whatever heads of hospitals would possibly agree to something like this.

CHAIRMAN SALOMON: Well, I'm agreeing you will have a lot of difficulty. So I don't know that we're really disagreeing.

The question here is if as we discussed it today, we go beyond 5 and start talking about 10 and 20 year follow-ups for specific categories of gene therapy or gene delivery protocol, that's all I'm talking about. If we do that, that day the absence of funding arrangement to cover that will essentially take many of us out of those types of gene therapies. That's all I'm saying.

DR. MULLIGAN: I'm just saying that I think that now the next thing we ought to address, not at this meeting, but we need to address exactly the precise road map for trying to implement something like this.

CHAIRMAN SALOMON: My point. Yes.

DR. SIEGEL: Well, that's important because, in fact, we've had these long term requirements in place for some years and they haven't -- the amount of data for a variety of reasons, many very valid that we've collected, have not really been satisfactory. And so I think one of the important,

and perhaps the most important condition as we talk about focusing these, is not so much it's not just focusing and so that the research is possible, but focusing as to data that we actually believe can be collected. And when you talk about that system where the university makes the commitment to do this, the thing that runs in the back of my mind is, you know, there's another concern. Not whether or not they'll commit to do it, but whether or not they'll do it once they've committed to doing it. You know, even with the best of intentions if we have a system that without much of an enforcement and that isn't very actually accomplishable, it's not clear how much data we're going to wind up collecting.

DR. MULLIGAN: In fact, I would argue that this issue enforcement, you're going to have to give us a better sense of that, too, because that'll certainly influence the administrators if they are making obligations and there's a very clear cut enforcement guideline, they're going to be very worried.

DR. SIEGEL: Well, we're exploring that. Suffice to say from the FDA point of view our regulatory relationship is largely with sponsors, secondarily with investigators and very little with

institutions. We can require the sponsor to commit to do certain things. If they don't do it, we can take certain actions. Although if they're out of business or dropped the product, there are limitations in the strength of that hammer in terms of our ability to require certain actions. We've sought additional factors in certain cases, like civil money penalties. We can continue to seek those.

But not to go into details, the importance is to know there's limitations in what we can do, although there's a significant amount we can do. But, again, it's largely with the sponsor. And when we're starting to talk about the institution, there's more limitations, although the NIH, obviously, has more relationships with institutions and to some extent may have some other abilities that will need to be further explored.

CHAIRMAN SALOMON: Amy and then Ed.

DR. PATTERSON: Yes. So this is an important issue. I didn't want to leave untouched Dan's comments about NIH funding. And as OBA is not a funding entity of NIH, I'll make my comments on this fairly brief.

But I think it's important for everyone to understand that NIH funds a number of long-term

follow-up studies longer than 5 years, 10 years, 20 years. Epidemiologic studies.

Your proposal to do long-term follow-up needs to be part of your initial application, and it needs to be scientifically meritorious and well founded. And it would be on those principles that long-term follow-up would be funded.

The second point is that I think that this discussion about NIH support and the scientific merit of the studies that are contemplated underscores the need to get much broader input and expert input into the design of these studies and the types of data collected. I mean, the Committee's discussion here is a good start down that pathway, but I think we really need much broader in depth consideration of how to design these studies; what are the end points, how will the data be reported particularly because again you may be looking for rare events and you're going to have to be able to look at that data critically.

DR. SAUSVILLE: That in a way does dovetail with a point that I wanted to make in that in this formulation of how to go after these long-term results we've factored into the participation of institutions, universities. And certainly where the university was, as we discussed yesterday, party at

some level to the generation of the product, one can imagine that being relevant. However, that's not always the case. And, in fact, some biotech companies have actually not gone through universities but gone to individual investigators at free standing hospitals, etcetera.

So by that way of thinking about it, then this type of mandate falls solely on the shoulders of ultimately the small company that is going to potentially regard that as an additional impediment to being in this field. And, indeed, what was just injected by Amy, the idea that scientific merit would go into this, obviously if this was put into a study section context, those interests could be quite diverse from those of the industrial sector.

So, I think there are a number of complex relationships here that are being mixed together. I guess I share the concern that there needs to be broader input because the effects of a rule that is -- or a policy that is not responsive to all these different possibilities could, I think, be very problematic.

CHAIRMAN SALOMON: I'd also point out that in terms of Amy's point, yes, there are examples of long-term follow-up, but most of us are applying for

R01 grant awards in which, as far as I'm concern, there's no way to ask for ten years of funding on a 5 year grant award.

So the point still is that there has to be some sort of NIH decision made, and I hope it's not that every gene therapy protocol has to go to some special type of study section or some special sort of application. But, I mean, that's the kind of thing that we have to think about.

DR. O'FALLON: I think there was a passion around the table that if we don't do this, we might destroy gene therapy. Now there needs to be an equal passion that all of us to work together to keep this simple enough that it doesn't destroy gene therapy. And I think we really got to concentrate on that simplicity.

DR. PATTERSON: Ida. one more passion, and that is that we do it right and really design the studies well.

CHAIRMAN SALOMON: I think we just need to keep straight the idea that designing the studies is not as important as the long-term follow-up issues; that part has to be designed well. Right? I mean, I don't think that there'll ever be or is it appropriate to seek consensus on how to design all gene therapy

trials for the rest of the world.

DR. SIEGEL: Well, I assume maybe you're talking about epidemiological studies that go across those studies.

CHAIRMAN SALOMON: And I was trying to clarify -- I agree with that part. And that's what I was trying to clarify.

Okay. Well, a little passion is good.

So, amazing, albeit you could point out that we didn't have the break that we were supposed to have, but I'm going to avoid that and take credit for the fact that we're only 5 minutes off schedule to introduce Dr. Noguchi.

Okay. I did make a major goof here. Okay. No, Dr. Noguchi, you're not introduced.

So what Gail has just pointed out to me is that we have two prior requests to address the Committee as part of the open public hearing, and I would invite anyone else in the audience that this would be a time that they could also step forward.

So, talking about timing here, what I guess that -- and I the way, it makes more sense -- Phil, just before you leave. What I was thinking of doing was having the open public hearing and then break for lunch, come back and start with

you. Would that be okay?

Then we're going to have the open public hearing. We're going to have a break. And then we're going to go to Phil instead of lunch. Okay. We'll work on that.

Okay. Just to show you how flexible we are, I wish someone would tell this to my wife how flexible, I mean. Is that we're going to have a break now, and then we'll come back and do the open public hearing and go right into Dr. Noguchi's thing.

Thank you all. See you back in about 15 minutes.

(Whereupon, the meeting was adjourned at 11:40 p.m. until 12:00 p.m.)

CHAIRMAN SALOMON: Find our seats. We can get started with this last set of the session.

Okay. One of the things that -- I was told that the break is just from the Committee. That there was some concern that we weren't being efficient enough in recognizing speakers. And to that extent, that's my fault as Chairman. That's one of the things I'm supposed to do well. So, I apologize to everybody and we'll make more of an attempt to be looking around.

If people can help me by not just sort of

jumping in and find the people who are speaking, who want to speak in some sort of order, that would be helpful as well.

Okay. So, this last of the session begins with -- I believe we just go in order, right? Okay.

So I'd like to ask Dr. Sally Seaver of Seaver Associates to step up and address the Committee.

DR. SEAVER: Thank you very much for the opportunity to address the Committee. And since the manufacturing group is being very quiet, I decided I would speak out. And let me tell you first a little bit about my different affiliations.

I'm, as you realized, a consultant. I work with people on all sorts of biological products. And I work with them on issues relating to the manufacturing and control of those products, including working with responses to the FDA.

I'm also chair of a committee at the United States Pharmacopeia, and it's the committee on gene therapy, cell therapy and tissue engineering, and also chair of the whole complex actives division, which includes that committee and five other committees in biotechnology, blood products, vaccines and dietary botanical dietary supplements.

And finally, many people know me from organizing various conferences, quality aspects and manufacturing aspects in the biological fields.

Today the opinions I'm giving are strictly my own. I'm not representing anyone or any of these other possible modes, or any client.

And I want to comment on the disclosure, the proposed rule that Dr. Noguchi will be discussing in a few minutes on the disclosure for xenotransplantation and gene therapy.

I read the 70 pages and as with most proposed rules from the FDA or final rules, I very much appreciated the first 61 pages that sort of discussed the rational for the rule and the sections of the rules. And the message that came through to me was that what the FDA was asking for people to disclose were things that were not confidential, that were very often disclosed anyhow. And that it would help assure the patients of the safety of trials.

Therefore, the issue I have that I'd like to address today is a section that's on page 67 of that whole long 70 page disclosure, and it's section 601.52(c)(6) where it actually lists the information you disclosed. And it's a multi-inch paragraph on what they want. And one of the things listed is

ancillary products used during production.

And let me back off a bit and bring people up to speed on what ancillary products are. And basically they are components used during manufacturing that really should not be present in the final product. And so they can include growth factors, cydicines, media formulations, antibodies used to purify a cell fraction or a gene therapy product. The actual bioractor and cell culturing device has been suggested by the FDA as possibly an ancillary product. Agents used to purify the product, which could include the columns, the enzymes you might use, and as I said, media components.

So, in general this if you really -- one iteration of this is basically everything you use to manufacture this product.

Now the conflict comes in in the other wording where the FDA said that you can hold confidential information back. And let me give you some examples in this area and let me state right here that most companies consider this information highly confidential.

So, for instance, if I'm in adenovirus and I've been producing and my 293 cells beginning, the fact that I've now moved to a "better less replication

competent producing cell line" like PerC6 cells potentially would have to be disclosed. The fact that I've moved away from using cesiumchloride to separate by virus two columns and how many columns I use because after all, none of the column resin should be in the final products so that they are by definition an ancillary product. What enzymes I might use to chop up my xenogeneic product or remove DNAs from my product, both gene therapy and xenogeneic might have to be disclosed, and quite frankly sometimes if it's simply benzonase, it has been disclosed.

But in organizing conferences, I can tell you that our ability to get people to discuss in detail their production schemes is usually not that successful. And even for approved products most of the time if the company goes and discusses in particular a purification process, they very often don't disclose which product it is. If you're clever, you can figure out which one it is. But in the general disclosure it's not there.

If they disclose which product it is, they very often don't disclose all these details like media formulations, exactly what purification they did, etcetera. And I'm including companies that have really delivered a lot of information to the public,

including Genentech. If you watch very closely when they exclude some really important details, they don't tell you which product.

And what I'm concerned about this rule is that it links the product with the exact media you might use, saline, etcetera, etcetera, and method of purification. And when I'm concerned is that this is going to cause a lot of disputes, a lot of extra time both on the part of the client and the FDA, and potentially even some appeals.

Some of my clients, they don't have a lot of problem disclosing media because they say fine, I'm just using the standard media or something like that. But they're very sensitive about the way they purify. Other clients I have are like no, I'm not going to tell them anything about the media. I consider that highly confidential because we've discussed what we might in a response to this rule. But I don't mind on purification because it's the same purification that I've heard Joe Blow talk about.

So, it's very company-to-company dependent on what people consider confidential. And it's also not clear how much detail the FDA is asking for ancillary products, and it's not clear that it will be applied uniformly for each reviewer to reviewer for an

application.

So, in conclusion -- and finally, even if it were -- if you do give some of these ancillary product, it's not clear to me personally, and therefore I can't explain it to my clients, how the patient is necessarily going to be able to interpret this information. All right. How do they know the difference between DMEN F-12, somebody's proprietary media? Okay.

So, in conclusion, number one, I'd really urge the FDA preferably to delete ancillary products from this list of things to disclose. And if they want to include it, to please define exactly what you mean by ancillary products. And I hope, Phil, you'll do that in your next section.

Please help the sponsors understand why you want this info and for what purpose. And please expect some appeals.

I believe ancillary products should be disclosed in the IND. They should be discussed with the FDA. They should be shown to be safe before you start the trials. That's not what anyone is disagreeing with. What we're disagreeing with or concerned about is the disclosure of information that's often which most people consider highly

confidential.

Thank you.

CHAIRMAN SALOMON: Thank you, Dr. Seaver.

The next speaker whose requested time is Dr. Michael Werner and representing BIO.

MR. WERNER: Thank you.

I'm actually not a doctor, but thank you. It's the easiest -- I'll take an honorary degree.

Well, good afternoon. Thanks for the opportunity to provide comments on the proposed rule from FDA concerning disclosure of certain data from human gene therapy an xenotransplantation experiments.

Michael Werner. I'm Bioethics counsel for BIO, the Biotechnology Industry Organization. BIO represents more than 950 biotechnology companies, academic institutions, state biotechnology centers and related organizations in all 50 states and 33 other nations.

The biotechnology industry, as many of you know, has historically supported public discussion about the implications of new technologies. Company have recognized the need for and the value of this kind of public discussion and public dialogue. And this principle has been taken to heart in particular by gene therapy and xenotransplantation companies.

Biotech companies doing gene therapy research have participated in public discussions about their clinical trials at meetings of the NIH Recombinant DNA Advisory Committee for many years. And when appropriate, companies doing xenotransplantation have also participated in public meetings about their experiments.

Although BIO supports public dialogue, we have some very real concerns, however, with the FDA proposal. According to its preamble the proposal calls for the vast majority of material submitted along with an IND to be made public. The proposal seems to be predicated on the notion that this information is already in the public domain, and that is simply incorrect.

Although gene therapy and xenotransplantation companies have made some information publicly available, the type of information to be disclosed under the FDA proposal is much broader in scope.

Release of the vast majority of IND data would provide potentially misleading information to the public and could also lead disclosure of trade secret and confidential commercial information. This could cause serious competitive harm to the companies

trying.to develop products using gene therapy and xeno transplantation to cure disease and reduce human suffering.

Now, over the years companies engaged in gene therapy and xenotransplantation have been forthcoming about their research. However, as the industry matures and companies get closer to commercializing products, issues concerning public release of confidential commercial information become more salient.

Simply put, routine disclosure of this information will make it significantly more difficult to develop products that can be brought to market. In the end, patients will suffer because potentially lifesaving products either will be delayed or won't be commercialized.

For decades FDA has kept the information contained in an IND confidential. In fact, the existence of an IND is confidential information. The Congress and the courts have consistently endorsed the public policy reasons for this approach. But this proposal represents a dramatic, and to our way of thinking, troubling change in FDA policy.

It's important to note that BIO has proposed a plan regarding the disclosure of data from

gene therapy trials. Under the BIO plan oversight agencies would have access to data from clinical trials according to FDA time tables for reporting of adverse events and serious adverse events.

A committee of experts at the agencies would analyze the data, recommend regulatory action if necessary, and make a public report. And we continue to believe that this would provide the agencies and the public with important data while protecting trade secrets.

BIO and its member companies are engaged in a thorough scientific, legal and competitive review of the FDA proposal. We'll be filing official comments that lay out our thoughts in more detail.

Thank you very much.

CHAIRMAN SALOMON: Thank you very much.

Is there anyone else in the audience today that would like to add their comments to the public docket?

Yes, sir. If you can step up and identify yourself.

MR. McKAY: I'm Malcolm McKay, Vice President of Quality and Regulatory Affairs for Cell Genesis, a gene therapy company.

Very briefly with regard the proposed

system for long-term follow-up, we urge you to consider the original plan that FDA put forth with the three different tiers and then allow the sponsor to have individual discussions with the FDA based on scientific merits as to whether or not that company fell into tier 1 and was exempt from long-term follow-up, or tier 2 or 3.

It might be that we might be in tier 2 for phase 1 and phase 2 and then go back into tier 1 for phase 3.

With regard to the public disclosure of INDs, Cell Genesis supports FDA's ability to discuss these issues in public, and we intend to write to the docket with our comments. But we are concerned about the issue of publishing an entire IND, the amendments and the annual reports on the Internet. We believe that that form, sharing the information with the public, will not serve the public.

An IND is a very complicated document. The flavor of the IND often changes with subsequent of submission. And so the public wouldn't know where to look to find out what's current about a particular IND or a particular clinical trial. And we've proposed that the FDA allow us to use integrated summary format. It's friendly, it's consistently familiar

with NDA's and it would give the company an opportunity to summarize the pertinent information in a succinct and easy to follow manner.

Thank you.

CHAIRMAN SALOMON: Thank you very much.

I certainly won't comment on any of the stuff that we're going to talk about now, but just in terms of your comment on the long-term follow-up rule, I think it is the intention of the Committee to allow the FDA based on scientifically driven data reporting to negotiate what the follow-up for a vector should be. I don't think anyone on this Committee suggests that as data evolves and our understanding of gene therapy improves, that that shouldn't be an option.

Dr. Noguchi.

DR. NOGUCHI: Thank you very much for staying as long as you have, and of course, for the continued public comments that we've heard. While I won't speak directly to the comments because, after all, we're still awaiting an evaluation of all the comments submitted to the docket, I would encourage everyone here don't let Florida happen again. We take all comments. We look at each one carefully. There are no chads and each voice counts.

It is my privilege, actually, to be able

to talk to you about the proposed rule. This is an effort that has involved literally tens if not close to a 100 different individuals both currently at FDA and previously at FDA, including several of our guests around the table.

And I'd like to go through, first, a little bit of the philosophical aspects of it and then to go through some of the details in, I hope, a short time.

Now just to speak to the complexity, in fact Dr. Seaver correctly points out many things are involved in a gene therapy experiment. This is an example of a report that was in *Nature* several years ago, or I guess last year, in which there was very encouraging data presented that perhaps a certain type of immunodeficiency disease, that GammaC-R for X-SCID or severe combined immunodeficiency might actually be treatable by a gene therapy. But to do that peripheral blood mononuclear cells were taken out of the -- in these cases, these are the type of individuals that literally live in bubbles, cannot leave the hospital and there is no treatment for them, unlike the first gene therapy patient in this country.

They run over an FDA approved or an FDA regulated column that has monclonal antibodies and

other regulated product into a Petri dish, which is another FDA regulated device. You take a viral vector, obviously another FDA regulated biologic, put it on fibronectic coated plate. Fibronectin itself is a regulated product, as is the flash. This is transduced, but that can't be done unless you also have stem cell factor, Fit-3, Interleukin-3, PEG-MDF, all of which have or will be used in clinical trials as a single entity.

You put those altogether and what you come out with, with a fairly high level of transduction are cells which are now expressing the gamma-c receptor. And in several cases very encouraging results are seen. Several of these children that actually left the hospital, they've been vaccinated, they're going to school.

Desirable outcome, extremely complicated background on how we get there.

Part of the reason and the need for a disclosure rule on gene therapy and xenotransplantation is that these are products of nature as biologics. Even as far ago as Sr. Francis Bacon, "Natura enim non imperatur, nisi parendo," or basically "Nature cannot be ordered about, except by obeying her." A different way of looking at that is

we only know what we know as of yesterday and tomorrow we'll probably be shown that we're wrong. Or another way to put it is "In nature there are no rewards or punishments; there are consequences." And our FDA reviewers and others always say "For every intended consequence, there are a 100 mostly unknown unintended consequences that we must address."

And I'd like to go through some of those that we've seen through the years.

Edward Jenner, for example, was a brilliant scientist. He said he saw some -- the maids who milk cows never got smallpox, but they had these funny little pox marks on their arms. And he said I'm so convinced that I can vaccinate people and prevent the disease, that I'm going to do the classic experiment. I'll treat my children first, then myself. Which he did. And fortunately, his children were protected. And this became a fairly widespread type of treatment, but it almost died an early death because in Italy there's an epidemic of syphilis because the transmission was done from lesion to lesion to lesion. And the needle got contaminated with syphilis somewhere along the way. Again, we didn't know what we didn't know.

In 1901 was the start of biologic

regulation where a horse named Jim was used to prepare antiserum for diphtheria. Now diphtheria was a therapeutic that was very, very useful and could reverse diphtheria. More children died from diphtheria than has ever been effected by polio, so it was a devastating disease.

12 children died not of diphtheria, but they died from tetanus because poor Jim, the horse, contracted tetanus in the meantime and it was transmitted through that antitoxin.

Jonus Salk successful himself inoculated over 11,000 men, women and children with his killed vaccine. Once it was commercialized, the very first lots that were prepared when you go from a 10 liter carbide to about a 10,000 liter fermented, every forgot you had to stir the virus or else you wouldn't get inactivation of it by formaldehyde. And in fact, many of the first people that were inoculated with the first commercial version of the vaccine came down with polio.

This continues on. Once you knew how to inactivate polio, RSV, respiratory syncytial virus, was the next one to be attempted. After all, we know how to inactivate, keep everything stirred, simple.

The first time that was done when the next

season came around for RSV, men, women and children died who were vaccinated, whereas the controlled group didn't. That was because that we think now that there was something to do with T1 and T2 immunity. There is no RSV vaccine to this day. There is a monchrominal antibody as a therapeutic, but as preventative, we still don't know how to do this.

University of Pennsylvania this last year or two years ago now, an 18 year old patient died in experimental gene therapy, others received the same dose, did not have this type of an adverse event both in this trial and other trials. Do we know what killed the patient here? Human subject -- we really don't at this time.

Even a toavirus vaccine, approved in the year 2000 was with withdrawn when it was widely used. It prevents infantile diarrhea, but in a very few select cases it causes intussusception.

All this is merely to say that for biological products mother nature will let us push her a little bit, but she always comes back and tries to tell us "You know, maybe you don't want to go this particular route."

Now, this is the proposed rule to get into that. They short named it FDA as the proposed rule on

public disclosure. This is the longer official title, Availability, etcetera. It was published on the 18th of January with a 90 day comment period, so that'll be sometime this month on April 18th will be the final comments. And, again, we encourage everyone to please respond to the docket either in writing or by email. At last count we had something like 40 written comments and close 90 email comments, all of which will be read, evaluated and used to reformulate and see where we need to go with this proposed rule. Remember, it's a proposal. It's not a final.

The scope and the purpose is for gene therapy and xenotransplantation. Mr. Werner did point out that FDA for decades has had a policy for INDs. We are speaking specifically for gene therapy, which is a decade old.

Part of the reasoning behind the rule is, in fact, that gene therapy and xenotransplantation have a different experience than other areas of clinical research with FDA regulated products. They represent unique areas of clinical research that have potential for risks that are really unusual; that is it's not just the human subject or patient that may the subject to adverse. It could be the surgical team, as in the case of xenotransplantation you could

have transmission to offspring whether they're verdant or inadvertent, and things of this nature.

We've seen what the complexities of products are. It's not just a single product, it is a therapy with multiple aspects to it.

Part of the reason of the rule is to provide, actually, a consistent amount of information for public discussion and public access.

This rule, by the way, was not promulgated in response to the 1999 death of a gene therapy individual. It started in 1994 when there was this public discussion and a departmental committee, the National AIDS Task Force, that asked the question whether or not there was duplication of effort between the NIH RAC and the FDA review process. We went through a number of discussions with this, but the critical question that was asked at that time is even by 1994 there was a tradition and I would say global public acceptance by the community, by the sponsors, by the academic and especially the pharmaceutical industry to present a large amount of data that would be available publicly. This did include things that we'll get into later.

The issue at that time was could be transfer review, sole review responsibility to the FDA

and guarantee that access. And the answer is no. As you've heard by our own laws, even the existence of an IND is traditionally and by our own laws not acknowledgeable unless it's been publicly disclosed elsewhere. This, as we said, provide a consistent amount of information, it will enhance patient awareness and consumer protection. After all, if you're entering a gene therapy trial and you're not up to date on all the types of adverse events that can happen, whether they're large or small, and this goes for the sponsors, by the way. Up to date information needs to be available by one means or another.

It will help, we think, ensure accurate and up to date informed consents as they're being written and updated. And a small but a significant part of the rule is allow FDA to fully participate in public discussions.

Now, for gene therapy and xenotransplantation, we do have that full access to discuss things. Part of it is because the sponsors have been exceedingly well versed and have been willing to discuss these things knowing that the issues are going to be primarily safety related at this early stage of the game.

Now what is disclosable, and this is an

important aspect of it. Patient information not disclosable under any federal statute.

Trade secret information is not disclosable. We used the narrow definition that was I think 1968 by the district court. It's a productive process, it's not the idea; that is as things like incipients, and we will concede that certain types of ancillary products very well would fall into this sort of a category.

There's a limited amount of commercial confidential information and we're basing this on our experience with the National Institutes of Health Recombinant DNA Advisory Committee, the departmental Xenotransplantation Working Group and its various meetings that it's had, public meetings. And now the Secretary's Advisory Committee for Xenotransplantation.

The key factor here, commercial confidential means that information which can give a competitive advantage to a competitor that will disadvantage the innovator.

What is disclosable or what we are proposing to be disclosable. This will be product and patient safety data and related information. Included in this will be the preclinical data, animal data that

very often can help define or help guide us away from situations in which there may be potential and adverse risk.

Name and address of sponsor.

Clinical indications to be studied and the protocol for each planned study. We have heard in the past as an example that even the design of a clinical trial is commercial confidential. It puts us in a bit of puzzlement since most of the trials and certainly many of the trials in gene therapy are only gone forward when FDA has had extensive modifications implemented in that, and in many cases FDA will consider some of this to be our intellectual property rather than anyone else.

There is written informed consent for as provided in 50.27 of this chapter. Although FDA does not in itself regulate informed consent, we clearly view this as an important means of assuring adequate patient safety as we go forth.

Identification of the biological products. Dr. Seaver is correct, if we just looked at this there are a number of subparts here. I think that the question of ancillary products is a good one that we will need to address.

While we would acknowledge that some

ancillary products or things that might be considered ancillary such as a design and types of columns and how many columns are being used could be considered in the nature as commercial confidential.

In terms of the producer cell lines, what we have seen just from the few examples I've shown you, is that a cell line or a biological material that is thought to be "better or safer" very often is not. That does not mean that it's disqualified, but what this does mean is that we need to know and have everyone know what the risks of any particular biological product area. In fact, many with the exception of the RSV vaccine that we saw before where there is no present one, we have gone through many different tragedies with biological products, but it's always been on the basis of understanding, knowing the adverse events, the risks and getting actually the acceptance by the public who participate in these trials, which sometimes have very adverse events associated with them.

Biologics are different from drugs in the sense that there may or may not be a dose related phenomenon. It very well may be idiosyncratic and the person's response.

IND safety reports.

And then information submitted in the annual report. Now, if we look at the actual requirements of the annual report, the amount of information required is rather sketchy. We've gone further in this proposal to outline the types of information that has been required by the NIH guidelines which sponsors have been routinely submitting information.

One aspect that we're talking about here is the regulatory status of the INDs, such as whether it's on hold, in effect, inactive or withdrawn. Some of this comes down to the fact that far too much of our time is spent over the phone with the media trying to save "Well, is such-and-such on hold" and "Is such-and-such on hold. What does that hold mean. Does that mean somebody has done something bad." And the reality of the administrative mechanism that FDA has to really say wait a minute, we want more information is the clinical hold.

We think that in many respects, actually, this kind of information can help demystify the fact that clinical hold is not a good or a bad thing, it's a part of the process.

Then finally there is number ten, which is a clause which allows the Director of CBER on very

unusual, very rare occasions to require that even if all safety information has been provided and we have no objections on a safety basis to disallow an IND to move forward, that in fact we can invoke only by petition to the Director, a lengthy process. And if it's determined that we need ethical issues to be discussed, we need to ask the question this can be done, we think it can be done safety but should it be done at all, this would be the clause that we would invoke in order to have a public discussion such as the RAC, such as at this Committee, such as at other advisory committees.

We're making a proposal on this could be disclosed. The reason that it reads this way is for several reasons, the first of which is that it's simple to say get all this data, put it in a database and then make it public on a periodic basis. That's a useful concept if, in fact, the population is small. We anticipate that the number of patients and the number the trials for gene therapy will grow. We anticipate that some day there will be products, we could be wrong. As we do that the amount of information is going to grow, FDA is not. That can we can guarantee you.

What we are asking, therefore, and part of

this is to help assure that the sponsor will be able to look at what is trade secret, always what patient information is there and to determine what commercial confidential information is there and official and redacted version of each submission to an IND including the original IND. The redacted document would not contain patient information, trade secrets and a certain limited amount of commercial confidential information, certain limited amount.

The idea, and this again is because we don't want to get in a position where everything has to go through a Freedom of Information request, but to rather make it in a publicly available format, a proposal, is that after a certain amount of time being used to make sure this is administratively correct and is accurate, it would be forwarded to a public docket.

Now, our public dockets office has said that each IND number will be used to create an IND docket with the same number. Through the life of the IND then, this information of redacted form would be submitted to the docket, the official document which has both confidential commercial, patient information and trade secrets would continue to be submitted.

Now, this is a radical change in a way, but what it is also is a recognition that ten years of

experience of gene therapy and xenotransplantation have suggested to us that in fact public disclosure has not been detrimental to commercial development; that in fact very often even those things such as an adverse event help to shape how the field moves forward. And that in fact currently it has lead to the public confidence that up to recently we have enjoyed in the area of gene therapy.

We believe that for all the reasons given before, that if we can learn, especially from the lessons from the past throughout the history of biologics regulation that biologics are different, that they require a certain amount of openness and that science is always evolving, then in fact what can be imagined will be done. And we know this will be done with hope. It must be done with humility, and by this we mean not the hubris that our scientific decisions must be the end point, they are a part of the end point, but we have to also acknowledge that today's science, today's dogma, is going to be tomorrow's dog meat. As science changes, so does our interpretation of what is important.

And finally, as we move forward, it always needs to be done with compassion.

Thank you very much for your kind

attention.

CHAIRMAN SALOMON: There'll be T-shirts on sale in the lobby with that last one. It'll help the database.

Thank you, Phil. That was, as always, done extremely well.

I have no official questions to guide what happens now and yet there is a provision for discussion here. And so I very much have no agenda and my objective is that everyone get a chance to speak.

Abbey.

MS. MEYERS: Well, I just want to say from the patient community this is probably one of the most important that FDA has ever done. It's extraordinarily important.

And I was at the last RAC meeting and they voted unanimously that there should be more disclosure. There's some type of regulation that went through the RAC. And one of the problems is, of course, that there seems to be a general secrecy in the field. And the only thing that people get is basically the news that's released to Wall Street. And writers pick that up and they reprint it in the newspapers. And while on the one hand industry is

saying we need to attract more patients into these clinical trials, they still want FDA to keep the whole thing secret. So if you call up and ask FDA is there a clinical trial on gene therapy for some disease, they can't even tell you if there's an IND.

So, I think that the lessons that we've learned in the last 10 years since gene therapy started, which is actually a little more than 10 years, is that if biotech, agriculture industry had been as opened and there had been a forum for public discussion like the RAC for biotech foods, then we wouldn't be facing this big problem we are today. I mean, people are scared to death of biotech engineered foods. Why? Because it was done behind closed doors and it was in secret. And we can't afford that to happen with gene therapy.

I mean, nobody's going to die for lack of an engineered tomato, but you know people are going to continue to die from these horrible diseases, especially genetic diseases, which is my area of concern, unless this field moves forward. And because of the death of this young man at the University of Pennsylvania, I think that we're teetering on the edge here. That the public is losing its faith in the government handling these things right, and this is

the solution to put this out on the Internet so that people can see that 100 people went into a trial and, hopefully, 95 of them are still alive.

What frightens people is the fact that they read about it in *The New York Times* or they see it on 60 Minutes that 100 people were in the trial and a 100 of them are dead.

So, this is the solution. And I urge you all to support this solution. I agree perfectly; take out the things that might be patentable or the trade secrets, but let us know the trial is going on and let us see what the adverse events have been.

CHAIRMAN SALOMON: Alison, you looked like you wanted to make a --

MS. LAWTON: Yes. Thanks.

I actually agree with your last comment there, Abbey. Although we're probably coming from opposite sides here, I think generally I would say that we recognize the need, absolutely, for public debate and for the FDA's need to have public debate as well. And for that very reason industry's need to have public debate.

I think the big question I have is is this proposed rule the right way to do it. And my perception of the proposed rule as it is is, no,

that's not the way to do it. And I would like to see more time allowed to have more discussion around the best way to do it to provide the patients and the public with that information in the best possible form.

One thing we talked about earlier in discussing the follow-up of clinical trials, for example, we talked about the need for the scientific aspect of advising what's needed versus just what's required from a public perception point of view. And I would come back to similar type of thing around this.

During the last couple of days we've also heard, for example, there's over 200 INDs on gene therapy trials. And I'm not sure if people have any concept of just to try and get the information that you're talking about, Abbey, to go through that docket room and to look through volumes and volumes of data of 200 INDs is not the best way to get this information out to the public.

So I think from the safety perspective and what trials are ongoing, there's a better way to do this. I don't have the solution here. We will definitely be commenting to the docket. But what I really encourage FDA is that you allow the time. And

I know that you will be reading the comments to the proposed rule, but to make sure that we have the appropriate time to look at the best way to do this for all of the industry, public, patient and FDA needs.

DR. NOGUCHI: Thank you for those comments. And, of course, we are going to look very carefully and see what the next step is going to be.

Just one slight correction. The actuality of the docket is that, in fact, it will be electronic. You may come and look at it in person, but each submission as of right now for about the last six months, everything coming in is both available in hard copy as well as electronically.

MS. LAWTON: I'm just trying to get across the amount of information for somebody to have to go through to actually try and come up with a question around the safety of a gene therapy trial, for example.

DR. NOGUCHI: That is a good point. This is not at all examining any database or search capabilities. It's simply saying we have determined that for these two areas we think this is a limit of what is commercial confidential and what is not. But not anything about retrieving the information.

MS. MEYERS: Do you agree, though, that adverse events are not proprietary information, or you think they are?

MS. LAWTON: Adverse events currently are not proprietary information because they're reported. Investigators have to report them through to the NIH anyway. And, obviously, with the establishment of the safety database that is something that will be publicly available. And so that is very definitely a very important aspect that should be made publicly available. The question is again how do we do that and is it better to have expertise in looking at those adverse events and analyzing it and, again, putting it into context within the types of patient populations. All of those aspects, I think, we have to think very carefully about.

MS. MEYERS: Well, I want to just register my feeling that there should be no delays in this. These regulations or changed regulations, whatever you do about all these little questions, the main thing is information about adverse events should go on the Internet. And the reason is that when the Gelsinger family agreed that their young son should go into that, they had no idea that animals had died in the preclinical testing. They had no idea that people who

were in the test before them had abnormal liver enzyme levels after the test. And they need a fighting chance. Patients need a fighting chance.

And when you're sitting there and thinking about whether you should put your child or your mother, or your spouse into a trial and if you're not getting the whole truth in the informed consent document because, of course, IRBs are overworked and under funded and everything else, we need to know the whole truth. The patient community needs it. Otherwise, it's going to end up on 60 Minutes and the whole field is at risk.

CHAIRMAN SALOMON: Again, I have no agenda today but to make sure that everybody gets a chance to comments. There are lots of issue that we could get into that I don't think really we're set up with the time today to do that and to try and define, for example, a universe of what should be in a public disclosure or how it should be shown to families, should be on a web, you know, what is it that you'd find when you opened the website. I think those are the kinds of details that have to be worked out between the FDA, between the sponsors in industry and done in a way, Abbey, that responds appropriately to your concerns that accurate, interpretable, accessible

information be available to patients. And I think that's, from my limited view at this point, where the real concerns are.

You're not going to be able to allow a family member going to a website to interpret complex results in an animal model. It's not appropriate. It's not fair. It's not going to communicate, nor is it going to contribute, I think, to what you want; a sense of reassurance that everything's on the table.

So I think those are the issues, those are the details that are going to need to be worked out.

DR. SAUSVILLE: I'd like to share those thoughts and actually extend them to the extent that in both biologics and in so-called small molecule drugs the nature of the preclinical toxicology studies are actually to cause, if possible, toxicology, toxic effects. And I must say I'm very concerned that the undiluted and uninterpreted and unfiltered information of that type could be very problematic and actually hinder patient access to otherwise very reasonably constructed clinical trials.

DR. SIEGEL: What, of course, would go on the website would be -- what is proposed is some redacted versions of what comes to the FDA. And I think for a similar -- notwithstanding the fact that

we have rather sophisticated scientist sponsors in general for similar reasons don't like to send us undiluted, unexplained animal data. Our animal studies come with explanatory summary reports and interpretations.

DR. SAUSVILLE: Right. What I just heard is that there was a desire for an Internet disclosure at one level of either of what actually is, and even if you extend this to adverse events, the initial occurrence of one adverse event in a clinical trial, again, taken out of a clinical context, could be very problematic. I mean, the usual rules for stopping clinical trials actually call for more than one adverse event.

So I think this is a very complex area. And while I -- I mean to be clear, I mean I'm very both personally and professionally amenable to the idea of a constructive dialogue to how to do this. One has to be concerned that access that without interpretation could ultimately be deleterious.

CHAIRMAN SALOMON: Richard and then who else.

DR. CHAMPLIN: So I always support that the patient should have access to reasonable information and be aware of pending adverse events.

One has to keep in mind a couple of things.

The specific organ toxicities in animals often are not reproduced in man. It's very dependent on the species and the metabolism of drugs. And so if liver toxicity occurred in the dog, that doesn't necessarily mean that it's going to happen in humans. So one can be mislead if there's detailed information about toxicology data in other species.

The other issue is you're of course interested in the observed versus the expected. And in given disease state there's a background of adverse events happening in leukemia patients, for example, undergoing chemotherapy. And that when you get the raw adverse event data, it's not clear exactly how much is truly attributable to an investigational agent and how much is to be expected in the standard treatment of those patients. And so one has to somehow keep this all in context, and whatever information is provided has to be given with the balance of that overall discussion.

CHAIRMAN SALOMON: Amy.

DR. SIEGEL: Well, the rule suggests that trade secret information and patient identifiers would be redacted. Other than that, the documents would be essentially what is submitted to the FDA would be

submitted also and redacted form for posting on the Internet.

Is there some commercial redaction?

DR. NOGUCHI: A limited amount, yes. That's the proposal.

CHAIRMAN SALOMON: Any and then --

DR. PATTERSON: I wanted to make a comment because I think it's an important issue about providing an analysis and context for information that's provided to the public on what Ed was just talking about.

There has also been out for public comment a perhaps synergistic or complimentary proposal from NIH regarding the reporting of adverse event and other safety information to NIH. The interplay of these two proposals is something that I think needs to be explored further. But part of our proposal that would involve FDA cooperation or collaboration and input is the establishment of a national data assessment board that would meet in close session and would look at all the data reported, would look at the data being entered into the comment database between the two agencies, and would report out perhaps on a quarterly basis to the RAC and on an annual basis in some sort of written summary report of the findings and report

the information in context, do analysis across trials, across vector class, across clinical indications.

So, I just wanted to put that on the table that I think the federal agencies are sensitive to the fact that merely putting up raw information is not necessarily beneficial.

MR. GROSSBARD: Elliott Grossbard.

Something that Dr. Siegel said prompted me to think of unintended consequences. And you're quite right that on many submissions sponsors in describing toxicology studies, for instance, indulge in a fair amount of what might be called spin control, and the FDA reviewers are very sophisticated and I've over the years come to see how it just kind of gets ignored or blown off and handle in appropriate matter. Reasonable people can disagree.

In a redacted version if companies were to indulge themselves in this kind of activity around safety studies, this could lead to an interesting interchange with FDA, something short of a labeling meeting perhaps, but a discussion about whether the company's interpretation is appropriate for presentation to the public and lead to kind of an ongoing engagement around a scientific interpretation that could be a distraction in many ways.

CHAIRMAN SALOMON: Alison.

MS. LAWTON: Just to follow-up on that comment. I think that's part of what I was trying to get at as far as we need more time to work through how we do this and how the timing of the information is made available, how the information is made available. Because that's one example where information that could be made publicly available immediately would be with a company's perspective that might change in the future once the FDA's had a chance to look at it. And so the timing could be key.

Likewise, with adverse events. You know, a serious adverse event may have a very different perspective when you first get that to having follow-up information to find out actually the reason that serious adverse event occurred.

So, they're both examples of why we need to really sort out the details around the processes and how the information is made publicly available.

CHAIRMAN SALOMON: I just think a point following sort of where Abbey was going, is that yes, of course. And I support that, as I already said. However, we also shouldn't go so far as to say that if data is there that maybe isn't fully interpreted or understood, often times because it might take a year

or two or 20 more events to really put it into context, that's not necessarily an a priori argument not to have that in the public domain in some form. Because we shouldn't assume that patients and patients' families can't go to the investigator in the process of a true informed consent and say "Well, you know, at the website I read about such-and-such and I'm concerned about it."

I don't necessarily see that as any sort of a negative thing. That is, in some sense, very positive aspect of a partnership between the physicians -- we're asking the patient and the patient's family to take a risk. And I think that what we have to fight for, too, here is reasonable, responsible information transfer, but still not fight for no information transfer until it's 5 years later and it's happened 25 times, and we know the exact molecular mechanism.

DR. SIEGEL: Well, it should be noted it's not envisioned that the patients would be the only consumer of this information. There are other investigators, that there are physicians and so forth.

CHAIRMAN SALOMON: That's important context. Thank you, Jay.

Michael.

DR. O'FALLON: Phil, I think you said this process which lead to this massive document which I memorized every word of, of course, has been 6 or 7 years in the making, right? So certainly sponsors have participated, is that not correct?

MS. LAWTON: No, that's incorrect. No.

DR. O'FALLON: They have not?

DR. NOGUCHI: No. This particular rule, as many rules do, they go through a number of interactions. While we can say it started a number of years ago, events certainly propel it one way or another.

We have indicated that we would be proposing this rule for some time, and even on that scale other events have interfered or gotten in the way, other priorities come in there. So, it's -- no. In this particular -- this is a proposed rule. This has no part of a public discussion and it's not by any means meant to be the final, but it is meant to be the beginning.

DR. SIEGEL: It's the nature of the rules we have by which we can make rules, which are governed by law. They're not just rules. And that in order to ensure that there's a fair public input and we're not getting input from some people and not others, and

whatever, that while it was several years in the making internally there were broad general discussions. It's at this point that the proposal is out, which is really only a limited period of time, for more formal input on the specific proposal.

MS. CHRISTENSEN: Janet Christensen with Targeted Genetics.

I think that one of the issues that -- I've actually read this so many times I could probably give you chapter and verse. I think a lot of us have in preparing our comments to the docket.

One of the concerns, however, is that when you start talking about criminal prosecution for perjury if the redaction is not appropriately carried out, I find that personally very scary. You know, I'm going to do my very best job, but if we don't see eye-to-eye, I may be criminally prosecuted. And that's one of the aspects of that proposal that I find very concerning.

When you do that in there, besides being the full employment act for regulatory lawyers and regulatory professionals, which I must say I have some bias towards, we have to start bringing in legal staff. And we are in order to be prospectively protecting our interests and keeping me out of jail,

okay. I like my freedom.

I think that you inadvertently lay on a tremendous amount of additional bureaucracy and legal review to ensure that we are following the law. And for that reason I believe that there's a figure in -- as proposed as having an impact of about $840 a year to each company. I would suggest that with this additional legal review, not only for intellectual property, not only for securities and exchange information, and as well from the regulatory law perspective, that figure is going to be significantly higher.

So, that would probably -- and I would encourage everybody on the Committee to take a good look at that particular aspect. Because I think that can have -- I think it has a potential to significantly have a negative impact on working with the agency. I think we've worked very well with the agency, as well as NIH, but we'd like to continue to maintain those relationships. But when you put the threat of prosecution in there, it has a quelling effect.

Thank you.

CHAIRMAN SALOMON: So the question I had in follow-up to that is who will do the redaction? I

guess in one version that I had heard, and this is by no means quoting anyone in the FDA, but in one version I heard was that reaction would be actually done by the companies, which I thought was brilliant because that way the companies (a) could control what they redacted and therefore you didn't have to have any fights or issues, and of course it was a tremendous savings in FDA activity, which I also thought was positive given the sparse amount of funds.

So if redaction is being done by the companies, and again this is a question not that I'm saying that anyone from the FDA told me they would do that, why is this an issue then of perjury and -- I didn't follow that.

DR. NOGUCHI: Any laws that are -- or any regulations that are put forward by FDA are sanctionable; that if you don't follow the regulations, there is this whole series of steps that are available, those being one of them. If you lie to the FDA, that is against the regulation and is sanctionable. So it's in that nature where to be fair that where industry and sponsors are talking about legal counsel, we have legal counsel as well. And that was one of the -- it's not a stipulation, but they felt that it would be worth reemphasizing that

this is not meant to be a voluntary kind of a thing that it would be nice to do, but that it is in fact something we've spent a lot of time and effort determining and we feel that it's in the public interest to do that. For the out lyers there are these sanctions which are not unique to this particular rule. They apply to all FDA rules. That's really the nature of it.

I will say about the redaction, part of this it's not really -- it's on certainly CBERS part, but the device industry does have -- all 510Ks have redacted version. This is one level of clearance that is approved. And I believe it's being implemented for PMAs as well. So part of it is based on other FDA experience. The redaction is done by the companies.

DR. SIEGEL: But as part of the reasons for the underlying question, it's anticipated under this proposal that the FDA would do some checking of the amount of redaction. That, you know, some companies for competitive reasons or other reasons might choose to redact more materials than we thought were appropriate. And if that became extensive, it potentially could undermine the whole point of the rule.

On the other hand, if you acknowledge

there's limitations on FDA resources, so there have been no -- the anticipation would be that the chore of redacting would be by the sponsors with an expectation that that would be largely sufficient and with spot checking and with appropriate remedies which, in many cases, would simply involve just a telephone call and a discussion of what happened. But in some cases, it might involve more severe actions if there were problems.

CHAIRMAN SALOMON: Alison.

MS. LAWTON: Yes. I was actually just going to make a comment on the redaction as well along the lines that Jay just said, around as we heard from Sally as one example around the different level of redaction that might take place by companies. And I think one of the questions around this proposed rule is what's acceptable and what's not. And that's not clear at the moment.

You know, in the proposed rule there are definite ways to deal with that, such as putting companies on clinical holds if the level of redaction is too much or inappropriate. So those are the types of things we still have to work out the details.

CHAIRMAN SALOMON: Yes. I think in thinking about this, the concern that you'd actually

face potentially criminal investigation for perjury is -- that was good. I like drama. I didn't mean that to sound a criticism.

But I'm not quite sure that that's a very large risk over what exists right now. In other words, what I could see you being accused of perjury for is if there was an existing rule that you disclosed adverse events in animal trials or in clinical trials and you didn't, then you would of course be against the rule. But I'm thinking that's not too far from where you're at today.

So I guess I'm -- in part of this discussion not quite sure what the incremental injury is here vis-a-vis a perjury charge.

MS. CHRISTENSEN: I think the thing that caught me is in looking at previous proposed rules I've not found that language, per se, included in there. And so perhaps this is a newer trend we're going to see in proposed rules. So it's more of you don't usually find, for example, that there's -- for example, those proposed rules for GMPs issued in May of '96, there wasn't a thing in there that if you don't comply with this you'll be potentially up for criminal prosecutions. I think Phil and Jay's comments are on the mark.

But again, you know, we have to react looking specifically at the proposal as published in the *Federal Register*. So whether or not it's high drama or not, it certainly got my attention, as well as a number of other people's attention. And I think I just wanted to float that out there just so people get an idea. Because what I don't want to have happen, and this is me personally, I don't want to have happen that the synergistic relationship that we have with the regulatory agency -- the relationship we have with NIH/OBA is harmed or teased apart in an unhelpful way for the patients, for product development and moving forward. That was my point.

CHAIRMAN SALOMON: Abbey.

MS. MEYERS: It's so interesting because I run a charity, a nonprofit and I can't negotiate with the IRS. I can't tell them what I think should go into the regulations for nonprofit. IT's crazy, you know, to hear that the regulated industry wants to tell the regulators how to regulate them. That I can't adjust to it. But I wish I had that kind of relationship with the IRS.

But when you're looking at this, understand the way this happens on Main Street. People are sitting out there saying "Ah, the FDA

controls my food, my drugs, the cosmetics, the x-ray machines, the mammograms and everything," and each one of those we go in there and tells them how to regulate it.

Another thing. All of my children have been in clinical trials. I had to signed informed consent documents for all of them. The drugs they went on had killed animals. I looked at the sentence and I said to the doctor "Explain this to me. What happened here." And after I had all the knowledge that I could, I made the judgment to put them on the medicine. I'm not stupid. You can't be so paternalistic. Doctors are learning that everyday. If the patient doesn't learn enough from the doctor, he goes home and he gets on the Internet, and he finds out the truth anyway. And if I want to find out the truth about 99 percent of these people's products, I go on the Internet and I look at what they've been releasing to Wall Street. I find out more from Wall Street than I can from the FDA. Something has got to change here. Consumers won't stand for it anymore.

So tell them that the animals died and put a little footnote next to it that says "They died because they fell out of their cage, not because of the drug." But tell them the truth, because if you

don't, you increase your liability and you lose the public faith.

DR. SIEGEL: I just wanted to make clear, and I know you know this, Abbey, but when we make new regulations we are compelled and we are not compelled in the sense that we do so reluctantly to consult publicly. We consult publicly with regulated industry, and I must say in many cases we hear important perspectives from regulated industry of the implications and impact of the regulations that we may not always have appreciated. But we don't consult just with public industry -- with regulated industry, that's why we are here. We are a consumer protection organization. We're regulating industry. We want to hear from consumers, we want to hear from academicians, we want to hear from scientists. We want to hear from all concerned parties inn order to do what is in the best public interest.

I don't know how the IRS operates in that regard, but if they are able to make rules without public consultation, I would be a little bit surprised because that wouldn't seem appropriate to me.

CHAIRMAN SALOMON: Well, I think actually the comment about the IRS isn't is fair since we know that in Congress, which is a public environment, that

there is all kinds of input from the regulated industry, which is the public. And they're in the process of changing the tax laws as we sit here discussing these regulations.

So, I don't think that it's quite an unreasonable situation to have regulated industry trying to work in a partnership with the FDA as long as we realize the FDA isn't bound by anything that a specific company or a group of companies demands, but it doesn't mean you can't be heard. I think that's probably a very positive aspect of things, not a negative.

I think that from what I'm hearing here, again, this discussion wasn't intended to finish, but it seems like the dynamic that Abbey and Alison in a way have kind of set up is the right one for the next discussion. And that is how much and what kind of data should be available to the public that addresses really well exactly what Abbey wants, and that is a sense of confidence, a sense of participation, a sense of partnership and how much of that is going to be -- how much information is not going to be put on there that would be considered private, competitive. And by the way, I don't think most patients really care whether you use a real complicated growth factor mix

to get out gene transcribed trials. I mean, I don't think that's the kind -- so I think that when you really -- you know, well there isn't going to be a fight, "Well, I really want to know about the stem cell factor."

DR. SIEGEL: But, no, the patients may not care, but public discussion of safety concerns. If you want to start doing aggregate data and be able to discuss in a public forum what is the safe or an unsafe way to proceed, it might be quite critical that you know which growth factors went into which product.

And so, again, it's not simply that the patient is the sole consumer of these data, which isn't to undermine the issue you're saying, and I do think we need to carefully look at everything. But it's important to realize all the perspectives.

CHAIRMAN SALOMON: Well, I guess, Jay, what I was -- what maybe isn't either quite clear here is -- I agree -- I understand what you were saying back to me.

My thinking is is that if there's really an issue that gets brought forth to a committee like this, whether we have to close it to get at part of it, you know, that there's some secret factor that we need to know about for us to make a decision, yet

maybe isn't going to be shared with all the other competitor companies, I certainly agree with that.

My thinking was that this public disclosure policy and what we've been talking about isn't really for that sort of a user. I thought it was more for the daily experience with the whole field of gene therapy and xenotransplantation. What trials there are and what they're about, and who needs them.

DR. SIEGEL: That's a wrong perception. It's important to note that feeding into this rule is not simply making sure that things are available on the Net that patients can read or investigators, but also facilitating our ability to share with NIH data that they wish to be able to present in public, facilitating our ability to share with this Committee data that we would prefer to be able to discuss in public rather than behind closed doors, facilitating our ability when symposia are held, you know, why do these mice die at the last RAC meeting, what's going on with adenoviruses, why did Jessie Gelsinger die in a RAC meeting of November '99. Facilitating our ability to speak to information that we have in hand which may well involve a lot of that type of detailed information, and that's an important underlying reason for this. This is not to be viewed simply as a way to

put all this information for public consumption in a raw form for people to read on the Internet, although it does involve doing that and we're hearing some comments that there might be other ways to address other concerns without doing that.

You know, I want to reiterate what Phil said, and I'm here trying to explain not particularly defend any one position at this point in time. Although, obviously, I was involved in development of the proposed rule. But I want to repeat what Phil said that it's very important to us that we have as much input from as broad a spectrum as possible to encourage people.

We can insert, and I suppose insert these proceedings into the docket so that what is said here will be part of the formal record considered. But I know that there's a lot that's underlying what people are saying that isn't going said, and I would encourage people to put that out. To put that in paper in whatever detail they wish to communicate and get it into the docket, because we really do want to be able to consider all of the concerns and options as we work on this rule.

CHAIRMAN SALOMON: I think that's an excellent clarification, Jay, and that actually helps

me see it in a broader light.

I would tend to bring this to a close now. I would also invite any other comments from the panel or from the audience.

If not, I want to thank everyone who attended the meeting and contributed.

I'd like to thank Gail Depolito and Bill Freas and Rosanna Harvey, and the others of the FDA staff for whom work an incredible amount of time and energy into making these things happen. And I certainly appreciate it.

We'll see you in the next FDA meeting, which will have a title next time, right?

(Whereupon, at 1:17 the meeting was adjourned.)

CERTIFICATE

This is to certify that the foregoing transcript

in the matter of: BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMMITTEE

Before: FOOD AND DRUG ADMINISTRATION CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Date: FRIDAY, APRIL 6, 2001

Place: HOLIDAY INN
8120 WISCONSIN AVENUE
BETHESDA, MARYLAND

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.

Laurie Rossbach