these are primary infections, the mortality is quite high and pneumonia and hepatitis are most frequently associated with these.

In contrast, I think, adenovirus infection in AIDS patients we see a lot of asymptomatic shedding if you look for it, the incidence of disease is quite low. I mean, all we have in the literature are case reports of documented invasive infections. But I've never seen a serious adenovirus infection. I've seen lot of AIDS patients, so the incidence is quite low in comparison.

And, similarly, in the cancer patients, again, adenovirus infections are a lot more common in the pediatric patients than the adults and there are only case reports in the literature. Again, much less common than in the solid transplants and the bone marrow transplants. So most of these patients do not have a problem with severe disease.

We have no specific treatment for

adenovirus. In the case of transplant patients, if possible, we try to discontinue any possible immunosuppressive therapy. We do not have any antiviral that's been documented to be of benefit, although Cidofovir has the best in vitro activity.

This is a very broad spectrum nucleoside monophosphate analog. It is active against many other viruses. It has some in vitro activity against adenovirus, however, they've also documented the development of resistance in vitro. It is active in a rabbit eye model of adenovirus infection.

And there are only case reports of responses coincident with the administration of these antivirals, including case reports of hemorrhagic cystitis in the bone marrow transplant patients that have responded to IV ribavirin or vidarabine. There's a case report of colitis in an unrelated bone marrow transplant recipient who did not have

a response to IV ribavirin, but whose symptoms resolved on cidofovir within two weeks. There is also a case report of adenovirus colitis and cholecystitis in an AIDS patient that responded coincidentally with the administration of cidofovir.

So, I think that it is somewhat encouraging, but these are only anecdotal reports, so as things stand, we really do not have an effective antiviral therapy for this adenovirus.

Immunotherapy -- probably plays a limited role. I will give IV immunoglobulin to patients if I am concerned about adenovirus infections. They do have very good titers of neutralizing antibodies to the endemic seratypes not, for instance, the Group B seratypes that some of these patients may have run into problems with. There is also a case report using donor lymphocytes in a bone marrow transplant patient with a good response.

What do we know about the immune responses to adenoviruses? Based on our clinical experience, certainly, we can presume that cell-mediated immunity is quite important because most of these severe infections occur in hosts with cellular immune defects. As I mentioned, neutralizing antibodies are felt to be protective against reinfection with the same seratypes, so there are seratype-specific, and that may be one thing to look at in patients pretreatment with gene therapy vectors and, as I said earlier, by age ten most individuals do have evidence of antibodies to the common sera-types.

Looking at healthy adults, just about everyone also has detectable memory T-cell responses both helper and cytotoxic. Two adenoviruses and what's been shown is that unlike the neutralizing antibodies that are seratype specific, the T-cell responses seem to be targeted, in part, to epitypes

that are conserved across different seratypes.

What is the pathogenesis of adenovirus infection? Clearly, it's a lytic virus. It can directly kill susceptible cells. Is there a component of immunopathology? We don't know. There is evidence for a persistence that I will present.

Adenoviruses were originally isolated from tonsillar tissue in asymptomatic individuals and we do know, also, that they can be shed in stool for weeks to month, post-infection. There are also cases of transmission documented from donor organs that I'll mention and, also, clear cases of reactivation in bone marrow transplant patients.

There are handfuls of cases like this. Renal transplant patients with hemorrhagic cystitis where they are antibody-negative pretransplant and they

seraconvert. Consistent with transmission from the donor kidney or, less likely, a primary infection. There are cases of pediatric liver transplant patients with -- who have developed Ad5 hepatitis where a majority of these patients are seronegative pre- transplant and the donors are antibody positive and with the early time of onset, again, points to a probably transmission from the donor organ.

In regard to reactivation in the bone marrow transplant patients, there are also handfuls of cases reported -- patients with Ad5 hepatitis where there was Ad5-specific neutralizing antibody present in pre- transplant sera, which, again, would be consistent with reactivation of endogenous virus. I also have some data with some of the Ad35 cases from the Milwaukee study, where all the adult patients had neutralizing antibody pre-transplant, again, consistent with

reactivation.

What are the mechanisms of persistence? We don't really know. Do they remain episomal in long- lived cells, such as lymphocytes? It's possible. It's of interest that the seratypes 11, 34, and 35, which we see in the bone marrow transplant patients to reactivate. Is it possible that they can establish persistence more readily? There is some recent data that they seem to infect hematopoietic cells more efficiently compared to other seratypes. Is there a low-level control replication in tissue? There's another possibility and do adenoviruses integrate?

There was a very limited discussion about the adenovirus early region 3, earlier. This region is deleted from most of the vector constructs, but it's a very interesting region that codes for programs that actually downregulate the host immune responses by a number of different

mechanisms. And may act to reduce immunogenicity in natural infection and/or facilitate persistence.

What are these reservoirs? Again, lymphoid tissue, we mentioned tonsils, maybe they're -- the lymphoid tissue in the gut may be a reservoir. No one's really looked at that. They're -- the kidney and liver, based on the cases of probable transmission from organs in transplant patients. And then there's also some PCR data in tissue such as the lung and brain.

Are lymphocytes a reservoir? There was old data that PBMCs from most individuals were strongly positive for Ad2 by Southern blot hybridization. I looked at a large number of PBMCs from children and adults using a nested primer PCR for Ad2 and I did not detect this -- 72 out of 73 were negative using primers to both E1A and hexon.

There are handfuls of reports such

as this looking at E1A -- detecting E1A by PCR in lung tissue, such as in this case in this report where it was detected in 20 out of 20 biopsies from lung cancer patients. In comparison, E1A was detected by *in sito* hybridization in only two of these patients. They detected the E3 region DNA in half of the patients and the author suggested that this was evidence that, perhaps, E1A might be integrated into the host DNA. There's also one report in brain tissue, where they detected E1A in microglial cells in seven out of seven patients. One of the problem with these studies is they don't really have good negative controls.

As was mentioned, we have an experience using a live wild-type -- type 4 and type 7 vaccine in the military. It's enteric-coated, it's given orally. It's been shown to be highly safe and effective, so this is an example of the safety of administration of wild-type adenovirus, but

the caveats are it was given by a specific route of administration, orally. And it was given to healthy military individuals.

Issues of RCA in gene therapy vector preparations include the fact that we really don't know what the minimum infectious dose is. It's likely dependent on multiple factors, including in particular, route of administration and the presence or absence of seratype-specific antibody. I would be somewhat concerned about giving RCA to a naive individual, say, a child, a four-year-old-child, who may not have been exposed to adenovirus or, in particular, Ad5 and does not have any neutralizing antibody. I think that's different than giving it to an adult whose been exposed. The severity of disease is also likely dependent on the route of administration we don't have any information about.

I mean, it's different than a

natural infection, which is acquired orally or respiratory -- by the respiratory tract. We're giving the vectors perennially, we're injecting them into the liver. We really don't know anything about how RCA would affect the severity of disease given by these other routes of administration. Clearly, the status of the cellular immune system is a factor and also the seratype.

As we talked about, there are techniques now to truly significantly reduce levels of RCA from Ee1 deleted vectors using altered cell lines that may reduce recombination events. Also, I think there's going to be a lot more interest in using the gutted and helper-dependent vectors and these, obviously, need to be purified away from the E1 deleted helper adenovirus and whatever RCA is contained in them. And, as was implied, all of these preparations still have input viral proteins, the coat proteins and that does not address the significant

issue of the acute reactions, which I think you will see in all of these vectors.

Then the issue of recombination: It's certainly theoretically possible that this could occur in vivo, as well, as has been suggested. And this could occur with persistent adenovirus, as well as duly acquired adenoviruses after the treatment with vector therapy. It's probably not of great clinical significance and, presumably, these patients will have been immunized or boosted and will have a very vigorous immune response to adenovirus by the time this occurs, but it's still a theoretical possibility. And that's it.

(Applause)

DR. SALOMON: Thank you very much for a really nice presentation. If I had that many slides, we'd be here tomorrow. So I think you did very well. Are there specific comments, Abbey?

MS. MEYERS: Well, I just want to

ask, if a person has a gene therapy treatment, as an outpatient, and goes home and maybe they get no symptoms from the adenovirus or maybe they get a little cold, some kind of respiratory thing, but they have a kid in the house who has asthma, who is taking steroids or his wife is taking something for a normal immune disease. Does it put the other people at risk, the rest of the family?

DR. FLOMENBERG: Well, I -- I would just refer to the earlier talks that were presented. We -- there have not been examples where they have found wild-type adenovirus shedding after treatment with the gene therapy vectors. So I would not think there would be a risk to the other family members.

DR. CHAMPLIN: Although adenovirus can cause severe disease in the most profoundly immunocompromised patients, most -- even bone marrow transplant patients

handle this infection very well, and it's only the ones that have failing grafts or mismatches that are most profoundly immunocompromised that we see these kind of overwhelming infections. And so that, on the question list, you know, the disorder is sort of listed in the, you know, intense immunosuppressive area, I think probably are, perhaps, overly conservative, because most solid-tumor patients or most people on steroids with autoimmune disease are not coming down, that is naturally, with fatal adenovirus infections. And it's really the, you know, the most critically immunosuppressed transplant recipients.

And even in the organ transplant area, perhaps, other can speak to this better than me, it's more of an issue of the graft being affected and possibly sensitized for rejection as opposed to systemic adenovirus infections causing pneumonia or other tissue infections.

So, it's the rare patient that really has the overwhelming infection and they have to be profoundly immunosuppressed.

MS. DAPOLITO:

DR. FLOMENBERG: Yes, I would agree with that.

DR. BLAZER: I think an interesting point in the presentation was that the children were at higher risk after transplantation, at least early. And if one tries to put this together, children, in fact, make T-cells more readily than adults and yet they don't have, necessarily, antibodies -- high antibody titers going into transplant. So, one could potentially envision three phases of response: The initial antibody response that helps to clear the virus; then an innate immune system response, like, natural killer cells, which adults and children make very rapidly after transplant within two to four weeks; and maybe that's why the disease -- invasive

disease risk is low; and then a final phase of a T-cell response, which happens later and puts the adults at greatest risk because of the persistence of this virus and their inability to produce new T-cells as rapidly as children.

So, as we look at the immune response and identify risk patterns, I think, part of this is asking how much virus do they have to respond to and when do they have to clear it and what are the multiple -- if there are three different mechanisms of clearing the virus, then there are three stop-gaps in preventing a disease. And you may have to have a disability of all three, depending on the viral load to really be susceptible to an invasive disease from this virus.

DR. SALOMON: Just following-up on that, I mean, that certainly would go along with the correlation with GVHD and with T-cell therapy, that would fit that. Is

there evidence that -- actually -- so an hypothesis that would come out of what Bruce just said is that the time of onset of adenoviral disease would be different, perhaps, in the children, which might occur early, versus the adults, which might occur before they develop a T-cell immune response. Is there any evidence that the timing of onset was different in these populations?

DR. FLOMENBERG: I'm a little confused about what you're postulating, now. I mean, clearly, in our Milwaukee study, the children -- the time of onset was a lot earlier for the children than the adults. Do they reconstitute their immune response quicker, is that what you're --

DR. BLAZER: I mean, the children will make new T-cells that are thymic derived earlier than more robust than adults --

DR. FLOMENBERG: So you think it's

immune mediated?

DR. BLAZER: So the dichotomy is the fact that the children were more susceptible than the adults and the time of onset was earlier than the adults and the children aren't making as much antibodies because they haven't had as much exposure. So there may be this issue of this initial wave of an antibody response requirement and then depending on that -- and K cells come back quickly, and maybe that's why most people don't get disease.

And then the fact that GVHD T-cell depletion in adults are susceptible, particularly for late onset disease means that the T-cells have to have some immune response later to completely wipe out the disease or to protect against continual exposures.

DR. FLOMENBERG: I would probably look at it a little differently. I would suspect in the children that they may just

have higher viral loads of persistent virus and/or some of it could be primary infection, that may be why we're seeing it a lot earlier, they have higher residual -- they've been exposed to it earlier -- closer in time and they may have more residual virus that may reactivate earlier. I doubt that within 30 days there's that much difference in the immune reconstitution compared -- in the children compared to the adults.

DR. BLAZER: So, that brings up is there -- have there been any good correlations between antibody neutralizing titer pretransplant and risk of reactivation in the first 30 days post-transplant?

DR. FLOMENBERG: I don't think it's been specifically looked at. As I said, in the few cases that have been reported, a fair number of the bone marrow transplant patients do have evidence of neutralizing -- seratype-specific antibody

pretransplant more consistent with a reactivation of an endogenous virus.

DR. SALOMON: Estuardo? Oh, I'm sorry, yes.

MS. MEYERS: I just want to -- are you saying that the only people who are at risk from the adenovirus are transplant patients?

DR. FLOMENBERG: No, you can -- a healthy individual whose naive can develop a serious adenovirus infection. I mean there are fatal cases of pneumonia in healthy infants and children. It's rare, most people handle these well and they have a self-limited illness. The majority of the severe infections occur in the highly-immunocompromised patients.

MS. MEYERS: But there's no danger of contracting it from a person who has had some kind of gene therapy treatment, it's not --

DR. SALOMON: Abbey, we can't

answer that question. We -- we've been given data today suggesting that the danger is low and it's not been measured yet.

MS. MEYERS: Mm-hmm -- okay --

DR. SALOMON: They've looked for it.

MS. MEYERS: The cystic fibrosis cases, where they had an overwhelming reaction to the adenovirus, is that applicable here?

DR. FLOMENBERG: Again, yeah, I think most people would agree that a lot of the acute responses are due to reactions to the input co-proteins.

DR. SALOMON: Estuardo.

DR. AGUILAR-CORDOVA: I was wondering if there was any data on -- I know you said that there was no data on the infectious dose. But once these patients that have been documented that have disease caused by systemic or by localized adenovirus, is there any data on the kind of

viral load, be it from fluids or from tissue that may be correlated with that disease onset?

DR. FLOMENBERG: I am not aware of data, Marshall, do you know?

DR. SIEGEL: In the cases where livers or lungs or kidneys have been thought to actually transmit the infection, is there any information on the quantitative viral load in the transplanted organ?

DR. FLOMENBERG: No, no one's really looked at that. It would be interesting to look at some of these reservoirs.

DR. HOROWITZ: There's probably very little. Even when you look at a fatal case of adenovirus hepatitis, if you look at viral inclusions, for example, there are relatively few cells, it's -- it looks like it's not an overwhelming viral infection, it's the host response to a relatively small amount of virus, so I wouldn't think there

would be a lot, but I mean, I don't -- it's not been measured.

DR. HIGH: Since the numbers do seem to be an important consideration here, I was wondering, is there -- is there any data about size of inoculum? I mean, for example, in respiratory droplets or any, I mean, is there any information that would give us numbers?

DR. FLOMENBERG: I'm not aware of that.

DR. AGUILAR-CORDOVA: What about on the size of inoculum that had been used, albeit in an oral dose, but the size of inoculum that's been used in vaccination protocols? I also think there was some intranasal vaccination that was done in the early seventies, as well. Do you know what kind of doses those were?

DR. FLOMENBERG: No, I don't know. But, yeah, we could certainly get that information, in terms of the vaccine

inoculum. But, again, I mean, I guess my concern is you're giving it in different routes.

DR. AGUILAR-CORDOVA: But also --

DR. FLOMENBERG: An inoculum, you know, we talk about numbers of particles, numbers of RCA may mean something different when you're giving it orally versus intravenously or intrahepatically, but we just have no information.

DR. AGUILAR-CORDOVA: Yes, I was wondering, in some of these children that do come down with it, though, when you take just blood or serum, one can culture that from there is that correct?

DR. FLOMENBERG: It can -- rarely, I mean, people don't routinely do it, but there have -- you can, occasionally culture it during an infection. So, it probably does cause a viremia, people haven't really looked closely for it.

DR. HOROWITZ: Well, your one

patient that was positive in your PCS study of lymphocytes, was a patient who had active disease --

DR. FLOMENBERG: No, these were healthy donors. I did also, I did find it in -- I looked at two patients with invasive disease and they were strongly positive --

DR. HOROWITZ: Right, right.

DR. FLOMENBERG: In PBMCs, but amongst the healthy donors, most of them were negative.

DR. SALOMON: Okay, I think then that what I'd like to do is break for lunch. Last time that we were here, it took less than a half hour to eat downstairs, they're rather efficient. So, what I'd like to do is try and meet back up here in 30 minutes, you know and, obviously, I'll be pragmatic about it if it seems like it took us longer.

(Whereupon a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(1:45 p.m.)

DR. SALOMON: I want to thank everybody for being very efficient about lunch and joining us back up here, that's good. A couple members of the Committee and it may also apply to others that I haven't talked to are going to need to leave within the next 45 minutes to an hour. So, I think one of my jobs here is going to be to begin and to have a very focused discussion the specific questions and then once we've addressed those, we can relax a little bit as the time goes on and talk about some of the broader issues that came up during this morning's conversations.

I'd like to welcome Dr. Flomenberg to the table and thank her for that -- the microphone's still open there, so our other speaker's and anyone else in the public who wants to make a comment at this point are welcome. This is the -- what we call an

open public section of the meeting. We've not had any specific requests for anyone, but it's still part of the procedure here to make that offer open. So. Gail tells me that the offer has been open, so we're okay, then, I managed to. Okay. All right, guys.

I think it was really clear from the discussions this morning that there are several different layers of discussion that we should have and nobody's trying to say that there is any particular relative value or merit to those levels, but we are going to answer these specific questions. Because, otherwise, I get all kinds of grief, appropriately.

So, let's just first, answer these questions, and then I will back off and the conversations can go in a, you know, more in a natural way. So, I apologize to everyone for a short period of time, but.

So, question number 1 is: Should recommendations regarding acceptable levels

of RCA in the adenovirus gene transfer products be the same for all clinical uses?

And in thinking about that question, let's consider the following patient populations as they might differ in their relative risks. So, we're talking about different levels of immunocompromised patients and this now picks up on the themes that we were discussing as triggered by Dr. Flomenberg's comments, as well as themes that were touched on by Dr. Sublett and Dr. Hutchins.

So, yeah, I think everybody gets it, so what does the Committee think -- Dr. Rao.

DR. RAO: Shouldn't it be even more focused and say just the two choices that we really have before the Committee, right? It's 30-fold different or remains the same, right, in terms of RCA levels, right?

DR. SALOMON: So, what kind of

discussion do you want to have? Richard?

DR. MULLIGAN: I'd like to -- before we get to this, get a definition of recommendation. I'd like to hear from the FDA what -- what a recommendation really is, because I think that will turn out to be very important here, rather than people arguing about whether there is or isn't a different risk associated with something. As I understand a recommendation, it is a general guideline to guide the development of the production method and testing and so forth. If we take it as that loose a definition, then it may be easier to give general principles. I think a general principle might be, is there enough risk assessment information to make weighing risks a valuable part of the criteria that's one thing. But if you say it's a recommendation, you know, you can go in and make the case, then what you really want to hear is the arguments that people will make

when they come to the FDA, that is, they'll say, yeah, I know, I have this wrong ratio or helper content, but this is in a very, you know, safe population, immune competent group.

DR. SALOMON: So, Richard, let me tell you how I'm thinking about this, and we can see whether we're on the same page. To me that's more question 2 than question 1. So, question 1 is saying, is there going to be a difference in the risks of replication competent adenovirus by patient population? Question 2 is asking what kind of experiments or data would you do to set that risk and in context of that would be the question of do we have enough data, which I think is what you're asking?

DR. CHAMPLIN: Well, I don't think so because I think the first one is saying should it be based on just setting a common guideline or should it be based in risk fashion?

MR. SIEGEL: Let me try to clarify that. What we would expect and let me ask the review staff to correct me if I'm wrong -- but we would expect all manufacturers to set a specification for, you know, a test specification for RCA testing and usually that would be a release specification where when they -- if they fail to meet the specification the lot would not be releasable. Now, we provide a guidance, not a rule, but a guidance in -- as to what that specification should be.

At the present time, the guidance is a single -- at a single level that is independent of what the clinical use is. Whether we have more than one guidance, depending on clinical uses or whether we have one guidance, which as with all guidance -- all things of its nature can be modified as appropriate for clinical use, I think we'd come to the same end.

So, the question before us is,

more or less, as I think you characterized in your second option, that industry or manufacturers are indicating and, I think appropriately, that the levels we're setting do place some considerable burden on both testing and also on production lost. And in some cases might seek and find useful a more -- a different standard or a looser standard and then the question comes -- and they can propose any standard, and they might well, as you've suggested, propose a different specification based on the fact that it's -- that there's low- perceived risk because of the nature of the target population. And, in order to deal with those -- whether it's dealing with those requests or setting different specifications, the guidance that this Committee provides and the expertise regarding whether that should be done and how it should be done is what we're seeking.

DR. SALOMON: So, can we, I mean,

I -- okay, if you're not totally satisfied, then that's fine, but I think what I'd like to hear is the opinions of the group based on what, obviously, the expertise you bring to the table and what we've heard today, whether you think that there is a higher or lower risk of RCA administration in different kinds of patients, the immunocompromised patients, bone marrow patients, cancer patients, children, et cetera. I think we -- we have some data and, you know, people should have a comment on that. And then, secondly, whether or not we -- based on that presumption of overall risk in any patient population with RCA, because we've been given data on that, whether we should be, you know, how stiff and how flexible we ought to be in setting criteria. Which I think gets -- segues to where you're going Richard, right? So, can we just start with, sort of, the first concept, what's your impressions now, what's

your expertise on whether or not -- what's the risk here -- is this a big deal, a little deal, no deal?

MS. MEYERS: From what I heard this morning, and I'm just a layman so all I can do is interpret what I heard is that there seems to be a higher risk for bone marrow transplant patients, a higher risk for children in general. And there's a lower risk, but there is no population where there is no risk. So, in some people who are perfectly healthy, they can still get a life-threatening infection from the adenovirus. That's what I heard this morning.

So, in looking at this rule and saying why is there a need to change it, seems to come down to financial. I mean, some people, companies would like to save money by not throwing away so much of their sample, and I don't think that the financial reason is enough reason to change the rule.

DR. SALOMON: Well, I mean, I agree with everything you said, that's a good -- you made your point. But the problem here is that the last conclusion you made that the only thing driving it is financial, is probably not fair. In that if there is little or no risk, then putting a gigantic financial and practical burden on the companies isn't justified. So that's --

MS. MEYERS: Right.

DR. SALOMON: I mean, so that's what we need to discuss right now.

MS. MEYERS: But --

DR. SALOMON: If we decide that there's a really high risk or that there's a really high risk in a specific patient population, then we can go on to the next part of it, which is what Dr. Mulligan was saying is, where should we set that limit, realizing in a real world that that's going to have it's implications on the whole field.

MS. MEYERS: See, I would think that the only place that there is no risk -- if we could find a population where there's not risk and you could guarantee there's no risk, I'd say go ahead and change the rule. But we can't do that.

DR. SALOMON: So, let's -- let's continue discussing it from around the group to what extent do you think there's risk? Alison and then ----

DR. LAWTON: Let me just throw out something and see what reaction I get, because just in general, from the presentations this morning, I would say that the proposed limit of the 1 RCA per 3 times 10 to the 10, is too overly tight for certainly category C and potentially category B of patients, given the information that we've seen with regards to the risk around that type of level.

DR. SALOMON: So, you've put B and C, just for everyone else, you're referring

to mildly immunosuppressed patients and patients with genetic defects, right?

DR. LAWTON: Yes, sorry, I'm looking at an old version of the questions, that have B and C actually written on them.

DR. CHAMPLIN: The, you know, adult patients who do not have one of these major transplant issues going on, the risk, almost, is zero. I mean, you know, there's never anything that's truly zero, but it's, I'm unaware of adult -- normal adult patients having severe infections from adenovirus. And, in fact, it's the opposite.

That's the problem; you have immune response that limits the -- your retreatment of patients with adenoviral vectors because of a vigorous immune response. So, I'm not sure we have a problem.

You know, as we talked about this morning, the toxicities that have been

observed are probably to the total viral particles, probably from something related to the proteins on the virus and not the recombinant virus, per se. And so, one is reacting to a theoretical problem that, at least, has not been documented to have occurred in any patient.

So I would support the concept of not being overly restrictive. You would like to, you know, reduce contaminants in a product as much as is reasonable, but you wouldn't want to be throwing out half of your lots for no reason in the situation where we haven't see a symptomatic case. So, certainly for the B and C, the immunocompetent categories of patients, I would see no reason to change from the current, you know, standard of what -- 100 or whatever the units were to a more rigorous standard that would really impede the development of the field.

DR. SALOMON: So, we'll go

Estuardo, Richard and Joanne.

DR. AGUILAR-CORDOVA: I think that, you know, part of the discussion is, of course, always based on the cost risk benefit type of analysis and what's the risk is somewhat indeterminate and I don't think that even though we have data, what the risk is not. It's the majority of people that get exposed to adenovirus -- wild-type adenoviruses on a daily basis do not come down with fulminant viremias that cause any disease.

So, I think we have a fairly good impression for immunocompetent things. We also have some data to show that there are severely immunocompromised people may have no way to keep a check on viremia and so, I think we can't really analyze what the risk would be -- at what level an infectious dose would come.

So the first issue would be that there is no data to know what the risk would

be and how to evaluate that. And as if that weren't enough, really, when we're talking about these ratios and these new specifications, they really would be based on somewhat floaty and dicey characterization methods. And so, to say that they're unachievable or too costly, they are, if one uses one method, then they may not be, if one uses another method.

So, it really becomes almost a circular argument. So, it is difficult with the amount of data presently available to make any strong conclusion. I think the only strong conclusion that I could possibly make is that with the levels of contaminants that are possibly there today, there hasn't been any significant disease. There have been some case reports of significant adenovirus related to disease in severely immunocompromised patients or neonates or infants in -- that are not immunocompromised but not in adults and the preclinical data

that is available, shows that not only the age of the animals but the route of administration and the total doses of viriants are related to toxicity.

I think those are the data on which we can base an answer that says it depends on the patient population and depends on the route of administration.

DR. MULLIGAN: You know, I think I may be saying the same thing as what you just heard, but let me try it differently. I think that there's very little at all, if any sense of the absolute risk in any of these cases. And that's the difficulty.

The relative risk is what we're championing and trying to have a heavy discussion about, but I think that's obvious that, you know, the more immunosuppressed everyone's going to say there's more of a risk. But I think that that just -- the issue of whether there's an absolute risk cannot be addressed. So I think that

because you can't address that, I would use the relative risk as a modifier when people come to the FDA to break the guidelines.

And on the guidelines itself, I find amusing that the new recommendations.

(Interruption)

So the way, as I understand the recommendation comes about is looking at what is routinely achievable, okay? And I still think that's very reasonable. But, in fact, based on all the discussion we had, we don't actually know what that number is, because, in fact, we know people calculate it differently. So, those in industry that say, you know, that 50 percent of our lots wouldn't pass, have no idea, because they don't really know what that number is.

And I think the spirit, as I understand it of the FDA, is to make it to set that guideline at a level that is reasonably obtainable. And I think that it's a very good thing to set a high

technological standard -- I think that's the purpose, in fact, of having such a guideline to actually get people to push towards having a more pure product.

But at the end of the day there's no -- no sense, I think, at all that there's any biological reason for why the level has been set, it's completely and totally arbitrary and as far as I can tell, so was the number before. So, I would just push for getting to a sense, you know, with the better reference standards and, you know, a more unified test of what is the state of the art, what is doable by people and try to set it at that point, and leave the risk as a modifier for particular cases because of the -- really, I think the lack of any real sense of how important the absolute risk is.

DR. SALOMON: Okay, Joanne.

DR. KURTZBERG: What I was going to say, has actually been said, but I just don't think the numbers we have right now

are meaningful. And so, I agree with what Richard said.

DR. SALOMON: What do you think, Joanne, with your experience, what do you think of this whole idea that our -- do you agree that there is some patient group-specific risks higher in the young children, higher in the immunocompromised bone marrow transplant patients?

DR. KURTZBERG: I mean, intuitively, with what we know about the wild-virus, you would say that, but we have no data to know if that's going to apply to, you know, modified virus, but intuitively you would identify those patient populations as a higher risk, yeah.

DR. SALOMON: Ed?

DR. SAUSVILLE: I mean, along those lines, I mean, although everyone has bought into the idea that there's more risk with the younger -- with immunocompromised patients, none of the clinical experiences

that we've actually see so far where, I guess, some of the populations could be characterized as immunocompromised has there been the suggestion that that has translated into some actual increased risk of disease.

So, I would even go so far as to say that this is the sort of thing that you have to trade off what the potential benefit or value of he scientific exercise is, versus some theoretical risk and it should be the sort of thing that should be part of the consenting process and I -- and at one level, I think this is something where the patients are going to have a voice in what they would see as their risk.

DR. SALOMON: One thing, again, I believe it's correct, at least I've heard no data in given today or in my own reading where they gave adenovirus to patients with bone marrow transplants. At least none of the data that was presented today. Are there any studies guys that they gave them

to that patient population? Because the patient populations we've heard a lot about today have been patients with metabolic disorders and those with a series of different kinds of cancers, which I think we've sort of all come up thinking are relatively low-risk populations.

And certainly I should add, wearing my hat as an organ transplanter for 20 years, I, you know, we don't think much about adenovirus and I immunosuppress the hell out of everybody with anti T-cells antibodies and cyclosporin and prednisone and cellcept (?) and other drugs, so.

DR. SAUSVILLE: I guess, I'm a little bit, I mean, again, this isn't a question that's there, but I'm a little bit more concerned about the issue raised by the metabolic abnormality patients. I don't think we have a very good idea of what drives the inflammatory or quote/unquote "immunnu" or whatever response is. I think

that's going to be far more telling as a safety issue than anything having to do with recombinant viruses.

DR. SALOMON: I think we agree with that, Ed. And we're just focusing right now on this first question.

DR. HOROWITZ: I guess it's sort of almost like a vote to sort of repeat some of the things that have been said. I mean, I think we have enough data for B and C to know through experience that there are no problems. And I think the difference between 1 and 10 to the 9th or 3 and 10 to the 10th are probably not -- certainly not significant.

So we really ought to concentrate on A and decide when and what help we can be to the FDA in terms of suggesting steps of caution along the way. After all some of the questions that some of us here feel comfortable with now, we were very uncomfortable with a few years ago, but

experience has taught us that we can -- that this is not so much of a problem.

Just for the record, you know there were two deaths reported in young men in the military presumably from adenoviruses, although the cases were not as well, perhaps, documented. They were reported in the MMWR, I think, last week. These were young people in the military who were not immunized because the vaccine is no longer available, at least currently not available, and they died during an adenovirus epidemic of respiratory disease.

Now, those were type either four or seven, which are not being considered today for vector considerations, which are mostly two or five. But I want to just -- I don't want the group to feel that that we can have an absolute no-risk situation with whatever decision we make and there are children that will develop pneumonia even with type five or sometimes with type two,

where occasionally it will die. So, you know, there's no trade-off with 100 percent certainty, but as physicians and others we deal with relative levels of certainty, which make me feel B and D are fine and -- B, D, and C are fine and we really ought to try and help by 2 and 3, we ought to help in trying to reach some steps so that we can help the FDA with that big category --

DR. CHAMPLIN: Now, I think the A category, you know, the profoundly immunosuppressed, I'm not sure a 30 percent or 50 percent reduction that we're talking about, you know, in terms of technology to limit the recombinant adenovirus is going to make a difference there. Because you've got a proliferative virus in a permissive host, where there's no effective immune response. And I'm not sure there's going to be a safe level of recombinant adenovirus if there's any, you know.

So, in that group, I would be real

cautious about doing the treatment at all. And would want to be sure that the risk-benefit relationship of the proposed study would, in fact, justify it's going forward.

DR. SALOMON: So, let me try and, I think that I hear what sound likes somewhat of a consensus, but let me try it out.

So I think we all agree that, well, there is a consensus, it would appear, that there is a higher risk in this A, this first group of patients with severely immunocompromised and in very young children, who probably haven't have a historical experience with adenovirus. And that, otherwise, in other groups, it's certainly not zero, Abbey, Marshall, we hear that. But it just doesn't seem to be very high. Anyone agree with that?

DR. CHAMPLIN: And then within the A category, it's clearly the allogeneic bone

marrow transplants that are T-cell depleted and mismatched are the highest risk. The organ transplants and autologous (?) bone marrow, blood stem-cell transplants seem to be low-risk, and I would actually probably put them in the next category, myself.

And the --

DR. SALOMON: That's an excellent point.

DR. CHAMPLIN: And even the HIV patients as has been discussed seem to have a relatively low- risk of serious infection.

DR. SALOMON: And I would agree also for organ transplant patients -- solid organ transplant patients. Bruce.

DR. BLAZER: Just another quick point. I think after the bone marrow transplant patients reconstitute and if they're off immunosuppression, we immunize them, they do make responses. So I don't think it should be a moratorium on high-risk bone marrow transplant patients, but it

should be until their immune system has other evidences of normal responses.

DR. SALOMON: Right, I'll actually return to that in a second because I want to pick up something that Ed Sausville made a point of. I guess part of it is that I'm also hearing, and I think Ed captured it, that even if there is a higher risk acknowledged in these settings and both Bruce and Richard have refined that for us. That a lot of that could be handled within an appropriate informed consent procedure. And doesn't require any sort of moratorium based on the risk or the risk to the public around them. Now, that's I'm just putting that out for further comment.

MR. SIEGEL: But still, if we're talking about relaxing the standard for product testing, are you then suggesting that the consent form would say to the patient, if you want to be frank, are you willing to take a -- to receive a product

that isn't quite as clean of infectious virus as it could have been because we didn't want to have to deal with that, is that how you're suggesting we deal with in consent?

DR. SALOMON: I mean technically I don't know if I was quite going there, yet, I -- that was my next -- that was where I was going next, though. But, I mean, yeah, kind of, if you want to talk about it that way in the sense that -- the sense that if we're -- if the Committee's grappling with the idea of what's the risk to begin with and then, based on some consensus based on what we feel the risk is, how, you know, tight, and how obsessed do we want to be within, you know, the quality of -- the exact number of RCA particles per, you know, total.

So, yeah, I mean, I suppose you could put -- that's the kind of thing that would -- irrelevant to how tight you made

it, unless you made it zero, you know, it's zero RCA, which I don't think anybody's suggesting for lots of reasons. Unless you made it zero the informed consent at some point would have to say that, wouldn't it Jay?

MR. SIEGEL: Well, zero, is sort of out of the question because of the technology. I think at some point we thought we had a zero standard when people weren't able to produce doses as high as they were able to test. At this point, you can produce a lot more than is feasible to test. And all we can do is exclude certain amounts and it looks like, from the data, that we're nowhere near to achieving zero virus going into patients.

And in that regard, I want to say that based on -- aside from whether to loosen or tighten the standards, there seems to be a little attention that we need to take based on this morning's discussion to,

perhaps, rationalizing the standard because we set thee standard at what a test result shows rather than -- without accounting for the confidence intervals of that test result and we're doing tests that are at their limits. You know, if you find nothing in 3 times 10 to the 10th that tells you probably have less than 1 particle per 1 times 10 to the 10th, is your 95 percent confidence interval and you can get aberrant results if you test a little more or a little less. You can wind up approving unsafe products and holding back safer products.

So I think we'll pay a little more attention to trying to rationalize how that standard is. But that's an independent question about whether it should be a variable standard or a tight standard.

DR. SALOMON: Well, it's exactly where I want to go next. But I wanted to just sort of finish this because I made a statement for discussion and I don't believe

that we reached any kind of consensus on it. So, the question I had said, again, was picking up Ed's point is to what extent can we be comfortable that even in a -- even in what we recognize as a high- risk population, that a lot of that can be a part of the standard consent procedure.

I mean, you just say, you're here you are we're doing it in a T-cell depleted allogeneic -- you know bone marrow transplant, we're going to give adenoviral vector to you, there's going to be some replication competent adenovirus in your preparation and you are going to have this increased risk and we can't quantify it. I mean, I'm comfortable with that, but I'd like to hear what my, you know, other members of the Committee say. Richard.

DR. MULLIGAN: I would just state it differently which is that there wouldn't be any difference in criteria for the riskier thing. I mean, in a way you're

saying that. You're saying you're going to set some limit and you've maybe going to vary how you devise the clinical protocol or what you're going to tell the patients, but you're really -- you're really just saying, I think that you would not change the criteria or that's another way of looking at it to not change it.

DR. SALOMON: Yes, I mean, we'll get to that, but I guess I'm just trying to make sure that we're all comfortable with the concept that, in the absence of -- I mean, so one idea here is we know the exact answer, we set this limit, we hold the manufacturers to it and everything's great. And I'm saying I don't think we're going to come to that. We all know that.

So, if you don't have that, then what you do is -- well, we don't know the limit so you're going to -- we're just going to do reasonable informed consent and that's an appropriate place to be today in this

field.

DR. MULLIGAN: The only problem that I have with this is that once we go through the risk and then we go to how we set the dosage, and it's totally arbitrary, I mean, I don't think anyone would disagree with the fact that there's no biological basis for thinking that three-fold difference is going to make any difference, other than, you know, less is better, right?

DR. SALOMON: That's my point.

DR. MULLIGAN: So --

DR. SALOMON: Yes, no, we're agreeing.

DR. MULLIGAN: So, I'm just trying to get us to focus on practically -- we're going to get eventually to whether the one number is the right number or the second number's the right number, and I would say, it's pretty -- the concept probably ought to be what's a doable number? And that's about it, and I wouldn't make it complicated by

all these risk assessments.

DR. SALOMON: Okay, yeah, I mean that's the kind of discussion --

DR. GAYLOR: There was a bit of a discussion this morning about the guideline should be based on RCA per dose rather than RCA per 10 to the 10th or whatever. It's really the dose of RCA that's important. So, maybe we should have some discussion about that rather than about -- it's the number of RCA that's apparently important and it's not 10 to the 9th or 10 to the 10th, it depends on the dose. So, makes it more complicated, but that's more relevant it seems.

DR. SALOMON: Okay, Abbey and then Joanne and Ed.

MS. MEYERS: I just want to say handling it through the informed consent document is absolutely not acceptable, because it would come out sounding just the way Jay said, you know, you will have a more

contaminated product than the guy in the next room. And it's not right, so -- and it's a scientific concept, I think it's going to be impossible for consumers to understand.

DR. SALOMON: That's an interesting point, I wasn't thinking that there would be different standards just that you would inform that patient group differently but, yes, I can see the idea that different patients would get different amounts of RCA would be problematic.

MS. MEYERS: Yes, the RCA might be higher in people with genetic diseases than in people with bone marrow transplants and that -- it's not right, there's got to be one standard.

DR. SALOMON: Joanne.

DR. KURTZBERG: Two things. I don't see where we have any data that says a higher number of RCAs is riskier. And nobody's shown data to even say people

measure it the same way. But even if you had that, there's no data that says we know what's risky or that a higher number is risky. So, we're making one assumption and then we're making rules about other things based on an assumption to begin with and I think we need the data. And we don't have it yet, so we ought to get it.

I also think that, you know, one orphan population that might theoretically come to therapy with this kids with inborn errors who undergo algeneic transplant, but also need gene therapy because the bone marrow transplant doesn't reach all the organs that need correction. And in that population, you could consent that family, very easily and weigh the relative risks of your child's IQ will be that much lower or their bones will be that much more deformed and they would be able to weigh the risk of maybe they might get a virus versus they get gene therapy at a time when those organs are

developing and they may not be the -- as injured by whatever the underlying disease is.

I think you can consent that kind of -- I think you can have that kind of discussion and get -- give informed consent for that kind of therapy. You're underestimating the depth of the knowledge of the families that might have to make that kind of decision.

MS. MEYERS: I have to disagree with you because a parent in that position will do anything to save a child and, in fact, the Belmont Report talks about parents of dying children as being a particularly vulnerable population. And so, the concept, at that point, when they're standing there reading an informed consent document, talking to their child's doctor, they're going to sign just about anything. And for them to truly understand that there's going to be more of a possibly dangerous virus in

that product, then in the child next door who is getting it for cancer, he's going to have the idea that it might be more dangerous than what the kid in the next room is getting is -- it's not digestible to a family.

DR. KURTZBERG: Well, number 1 I think it is. And number 2, when you're getting that kind of informed consent, you're also taking a true mortality risk with the procedure, which is greater, by far, anything, any theoretical risk you might take with the recombinant virus. I mean, you know, you have -- in some of these procedures, you have a 20, 30 percent mortality risk from one or another organ's failing just from the procedure you're doing. And I do think people can be informed.

I understand what you're saying about them being vulnerable but, nonetheless, they're usually well educated

about their child's disease, well informed about the options and they really spend a lot of time weighing all of these things.

DR. HOROWITZ: Well, in a sense, we've already been there. Because in the dose escalation, some patients will get more RCA and beginning patients will get less. So, I mean, in those studies, it wasn't said that you will get a more contaminated product because you'll have a bigger does. I mean, there was a single informed consent, I assume at the various dose level. So, in a sense, it's already been dealt with because of these dose escalation studies and not been a problem. At least in that aspect of informed consent. It depends --

DR. SALOMON: The other thing to --

DR. HOROWITZ: I mean, if you actually use the word contamination, you know, obviously there's going to be a reaction, but if you use it with more

neutral words and just describe it accurately, in a sense, we've been there already.

DR. SALOMON: The other point is that we've also set ample precedent in other clinical trials like that. Not just dose escalations but, for example, just different immunosuppressive drugs, I use them in liver transplant patients, heart transplant patients, kidney transplant patients and kidney/pancreas patients at all different dosages and different strategies. And I'm, you know, I don't have any problem explaining that, even though the risks vary, you know, substantially so, I think those things can be done.

MR. SIEGEL: But we've never really asked people to consent about the standard for the quality of the product. That strikes me as a different issue to consent on.

I want to make a couple comments

that might help put things in perspective and also to summarize and also to summarize in part what I'm hearing. First, I just want to say that with almost all new technologies, it seems like we work through these same sorts of issues of theoretical risks that either become of less concern, such as, say, murine (?) retroviruses with monoco (?) antibodies and E. coli DNA with recombinant protein. And sometimes we come up more concerned. And interestingly, there's always this tension because as they become less concerned and you think you might want to lower the standard, you get better technologies to where you can actually lower the levels and you realize that you're not just looking at safety, you're looking at quality control, and consistency control.

And it's important to note in that regard that every drug you take, every product you take, certainly everyone I've

been involved in improving -- approving, undergoes a lot of testing for maybe residual of every solvent that's been used for contaminants of all sorts of types that are potentially there. The limits in many of those cases are not set on the basis of safety determinations, they're set on the basis of achievability both because less is almost always safer, but also because going lower because it is an issue of quality control -- you know, even if you know a certain level of LPS of endotoxin in a product is safe, if one batch has ten times as much endotoxin as all the other batches did, it should raise your eyebrow and make you wonder what happened in that manufacturing.

And so based on what this Committee has said, it sounds like there is a broad consensus that there's no data on which to set a risk-based limit, as far as any data we have, except in certain

populations the risk appears to be limited and we have no quantitative data about risk at all. And so, we're going to set a limit based on feasibility or achievability. Now, one of the implications of that is -- well, there's a couple things to say about that. One is that, unfortunately, achievability limits are going to be based on particles per total particle, not on RCA per total particle not on per dose, because what's achievable is a function of manufacturing and independent of whether you're going to give a lot or a little to a patient, even though the risk may be a function per dose.

But as we've heard and as it sounds like, when we set a limit, if we set a limit based on achievability, we have a lot of options. We can set a very rigid limit that can be achieved only at, you know, at great attention and then, if you're lucky, or you can set a looser limit, where as long as you're doing a good job, you're

going to achieve it, you know, the large majority of the time. And where we fall in that spectrum will depend on, in part, on the sense of how critical a factor this is. If there's a broad consensus that, boy, the risks of adenovirus preparations are huge compared to the contributory risk of RCA whether it's 10 to the 9th or 10 to the 10th, the real risk are, you know, it's a small part of the total risk, that might feed into that.

DR. SALOMON: But I think --

MR. SIEGEL: But also, the nature of the population --

DR. SALOMON: Right --

MR. SIEGEL: Might feed into that to where, for certain populations, we may want to go one step further.

Now, as to -- just one more comment, which is does it make sense to go one step further for certain populations than others? Can we say to somebody, well,

we're giving you a cleaner preparation, or if we don't say to them than the person in the next room. I would say this, chances are that -- if you look at those two children, one of whom is in this first group and one who isn't, for example, in the hospital, we're already giving the one whose in that first group a different air environment, probably there's more gowning and gloving going on, you know, there may be filtered air, there may be -- there may be different foods, we're already exposing certain people -- you know, there are risks that every body's exposed to every day that we don't expose to severely immunosuppressed people to.

So, I'm not sure it's irrational to say, you know, a certain amount of adenovirus is something that is reasonable to have in a product, but not in a certain special population.

DR. SALOMON: I think what I want

to see us go to right now is we're not -- we're not -- we haven't lost sight of the fact that we understand that -- there has to be some kind of standard because we have to have something, I think, as Richard pointed out, I mean, you have to set some sort of standard and even in some ways one could argue a little bit of a higher standard, I think as long as it's not an absolute but, rather, one for the technology to evolve toward. And also, so that when a complication occurs, whether we thought it was likely or not, that there is a track that we can come back to that we've moved the field forward in terms of knowing.

So the question here is not whether or not we agree with the basic premise that some sort of standard could be, but I think what everyone said and, again, let's pick this up for discussion -- what everyone said is, these numbers are just not very valid, I mean, we don't have any

confidence in the current assays that have been done, you know, at the very levels of detection of these assays for technical reasons and we haven't seen, really the true correlations between multiple laboratories with the new reference standards. And I think that I hear from the Committee that I don't think we would want to give you advice on, you know, x-number of RCA per thousand particles, at this point.

Now, I mean, that was not meant to ---- discussion.

MR. SIEGEL: We didn't specifically ask for a number, none of these questions asked -- they asked you to tell us how to go about determining what this --

DR. SALOMON: And I think -- so, I'd like to hear some discussion on that, Ed, do you want to --

DR. SAUSVILLE: Well, actually, I didn't so much want to address, I did want to follow-up on this discussion that, again,

seems to be -- or could be inferred as meaning that we're going to accept cleaner, dirtier, contaminated, noncontaminated -- I mean, I don't -- I'm a little troubled with that is that we heard this morning that some levels of standard might cause up to some 50 percent of batches to be disqualified by more than one company.

And I guess I'm a little concerned that, again, recognizing that each of these entities -- these viruses are unique that we could, potentially, be creating a situation by having this notion that we're going to have one standard that's going to ensure all batches or all production lots have the same degree of quote/unquote, "cleanness" that we might disincentivize the creation of certain constructs which for some reason or another are difficult to get to that standard.

And I return to the fact that, again, this is a nuance that can be addressed in the informed consent process.

And it's not a question that a more or less contaminated it's a question of what the achievable biology is.

DR. SIEGEL: That's a good point, nobody's -- if I understand your point, that there's not a proposal on the table that you make a bunch of lots and you give the cleaner ones to some patients and the dirtier ones to another. The proposal is that a given manufacturer can achieve a given level and, depending on where they're going whether that's acceptable may --

DR. SAUSVILLE: And that's going to be, to a certain extent, driven by what they're trying to do, actually.

DR. SALOMON: Phyllis.

DR. FLOMENBERG: I agree with what has been said about there being a rather low-risk for toxicity from RCA in most cases. I would again, just like to bring up the situation of a naive patient. I mean, I have a concern about giving 5,000 RCA to a

naive child whose never seen that 5 and do we want to consider some type of prescreening of patients before --

DR. SALOMON: Let me ask -- I thought about that. So, let me ask you a question, Phyllis, if -- and, of course, to anyone else, if you had documentable neutralizing antibodies to seratype 5 using a 5-based viral vector, would that satisfy you -- would that be diagnostic and protective?

DR. FLOMENBERG: Yes, in most cases, other than the severely immunocompromised patient, I'd feel more comfortable having that information.

DR. SALOMON: And we have to keep in mind the point that Joanne made, vis-a-vis one of the target populations for this kind of the future could very much be a young or young child getting an autologous or an allogeneic bone marrow with a metabolic disorder.

MR. SIEGEL: Just as a point of information, most of our sponsors, I think, almost all are doing serologic testing and most of them are excluding seronegative patients, but some are not, and I think we heard from who are not, and I guess that's valuable information to include as a consideration.

DR. SALOMON: So, let's turn back to the question of does anyone -- so my impression right now is that the field deserves tremendous credit for picking up the mantel in 1999 and in less than, you know, in two years that's fantastic, to have developed a reference standard that'll be shipped within a year.

So, I think that's great. And until that's done and until the data is really there to discuss and even retrospectively to go back on some of your frozen lots that were given to these patients and get a real sense -- to look at

the Gelsinger case, for example with the reference lot, because now you know, you can see how it could have been 10 to the 12th, Gelsinger could have gotten 10 to the 14th r 10 to the 15th, it's possible.

I mean, I'm not saying anything like that happened, but until that happens, my sense is that, I don't think the Committee wants to go there with specific numbers. That's open for discussion.

DR. KURTZBERG: I just want to comment again on the babies with in-born errors. And I think in -- number 1 no matter what you can control in the product, you can't control the exposure of the patient. And that could, theoretically be much -- a much greater risk for recombination in vivo because the patient gets wild-type virus, which happens in kids. And I think that the relative risk of that versus the relative benefit of whatever the therapy is has to be weighed and that, there

are going to be times in those populations where the therapy still carries more promise than the risk in that you have to inform the family and the parents, but you might still go ahead with therapy and I would hate to see something put in stone that restricted the availability of that kind of therapy to that population.

DR. SALOMON: Steve, Joyce, Dr. Semmick, I mean, what do you guys think. I'm concerned that we've now dodged your number issue, and I want you guys to comment on that because if you're not comfortable with that, you need to tell us that.

DR. FLOMENBERG: Well, I think if you look at the questions, we never really asked you to discuss a number. It was what's the type of data that people need to be collecting in order to make the risk assessment analysis. It's not what is the number. That, I think, clearly, like Dr. Siegel was saying is based on what is

achievable of the manufacturing record, it's more, but is there a risk or not a risk? And if there's not a risk, then it's dealing more with, like you say, process, validation, you know.

DR. SALOMON: So, I think that you know, I think that what we're telling you is that the process that ought to happen now is this reference standard -- and it's happening, you didn't need our advice for this, I mean, what you're doing is right, the reference standard's going to get distributed, there's going to be retrospective as well as prospective studies based on the reference standard. And that I think the Committee's comfortable with that going forward.

We also accept the fact that the FDA does have to set standards for a product, that's a given and I think Abbey you should be, you know, I think that's the point you were making and I didn't want to

give the impression that we disagreed with the concept of a standard.

What we were saying is that special-risk groups would get an informed consent saying, even within that standard, you may have a differential risk. We're comfortable with that part, but not that we make all kinds of different preparations or different standards.

MS. MEYERS: I would feel very comfortable with the suggestion that people would be given some antibody tests to see if they have any kind of a -- will have an immune response to the virus. I think that's an excellent suggestion.

DR. SALOMON: That was noted and let's see what else? Yes.

DR. BLAZER: Let me ask you, even with the antibody test, there still may be, clearly, patients that you'd still want to consider this for whether you give them immunoglobulin for a period of time or --

you know, I think, I go back to Joanne's point. For the transplant population, and particularly in children, the risk benefit ratios are very long discussions but we're testing in children for their benefit the therapies that they may be the first ones that are receiving that, where we don't really know an outcome, but there's potential high benefit and there -- aside from immunoglobulin infusions, even there may be other strategies that would still allow us to provide benefit to these children and adults that would make the risk acceptable.

DR. SALOMON: Yes, I think that's a really important point, Bruce, I think we all agree that nothing that we're saying here should be an absolute prescription on anything, but it should be -- they're all contributing to relative risk.

I think the point that you are well aware of, is that you could measure the

titer in a young child before, and it could be positive and then what you do is you go ahead and totally wipe out their bone marrow and you and I both know in two weeks the -- you know, the antibody's cleared if even that long, right? And the new B cells aren't making antibody so effectively that was all irrelevant so, I mean, I agree with you that in that population there are special considerations. But those of us doing those kinds of transplants are aware of them.

DR. HOROWITZ: But in terms of the gene therapy after autologous bone marrow transplantation, we have already learned and should be careful in the future that trials not be approved where we know the expression of the gene is going to be short-lived when we know the need for the gene is going to be life- long, I mean, that issue came up with the OTC trial.

Now, there are two sides of the

story, I mean if that therapy were given to tide over a two- day-old baby for three weeks, until that child could be metabolically balanced by diet, there'd be a different consideration then if a manufacturer came in and said we are proposing long-term therapy with a nonintegrating virus.

So, with the current technology -- so I think, I mean, clearly the FDA will be responsible for assessing those risks, but I just think we should note there are differences of risk based on short- or long-term therapy.

DR. KURTZBERG: I agree but in the in born error kids when you use bone marrow transplant, you have a 5-, 6-, 8-month period before cells get to some tissues from the transplant and so you might be in a temporary situation, but where you're preventing damage until the more permanent therapy takes effect.

DR. SALOMON: Okay --

DR. KURTZBERG: Also, I just have to mentioned wearing my transplant hat, that whatever you set is going to have huge implications in terms of what insurers are going to cover. And so if you say, well it's really okay, you know for you to treat these in born error kids because we understand, but your package insert says something different, then that makes a huge public health problem or a small public health problem, but a huge problem for that population, because that caveat is in there.

MR. SIEGEL: At this point, of course, we're not close to writing package inserts, that would come.

DR. SALOMON: So let's, I mean, I think that sort of covers question 1 and a lot of questions 2. Please discuss the sort of experiments or data that you've used to set acceptable limits for RCA exposure. Joyce, you're looking concerned.

DR. FREY: I think we've all agreed that question is probably, we've got plenty of guidance from the Committee. It's -- we definitely want discussion, though, on number 3.

DR. CHAMPLIN: I hope we're collecting data on the ongoing trials on the dose of recombinant adenovirus that people are, in fact, getting, and being able, then to draw some conclusions on the safety of various levels of every components of every component of the infusion, because there's a lot of data out there from the hundreds of patients that we've seen in terms of real-life experience.

DR. FREY: Well, we are, but I think you have to understand it's also in the caveat of the ability of the assays for detection of RCA and that's why some of it, with the reference material to be able to retrospectively go back and more definitively measure that is one of the

things that we plan to do.

DR. GAYLOR: I'd like to make a suggestion for the FDA. I think we're collecting -- generating the right kind of data and particularly getting a better measure now of RCA. But it's very difficult if you're looking at data from, say, a clinical trial in advanced cancer patients, where half of them are expected to die within the next three to six months. It's very difficult to tell if you're doing any harm. And what I'd suggest, and I assume FDA's going to do this, just analyzing data from individual trials, it's going to be very difficult, but I hope you're going to put together data from two or three dozen of these trials, and not just look at incidents of disease, which is a pretty crude measure, but look at survival, not necessarily time to death, but look at time to disease or pneumonia-free days or survival type analyses that are more powerful than just

looking at crude incidents.

So I think the right kind of data is being generated, what I haven't heard is whether the right analyses of these data are being planned. I assume they are.

DR. SALOMON: I think they are.

MR. SIEGEL: Right absolutely.

DR. SALOMON: I think that if you hang in there that the next meeting will be on one of the things we're going to talk about is long-term follow- up --

MR. SIEGEL: Right.

DR. SALOMON: The databases that are being developed with collaboration between the OBA, Recombinant Advisory Committee and the FDA on just those things. I think that's really important.

MR. SIEGEL: For the record, though, one of our highest priorities is work with the NIH at building a database that will allow or facilitate those sorts of analyses as we get more experience and

larger numbers. The analyses are being done now, but on a less formal basis and, of course, as you've pointed out correctly, working on the policies for long-term follow-up it can be very tricky to make sure that you get the right information at a high reliability and that we will be discussing that.

DR. CHAMPLIN: When, you know, considering that the problem that we're talking about today is infectious recombinant adenoviruses, you know, these can be easily cultured, so, needless to say the patient should be frequently cultured in terms of trying to detect that virus directly as opposed inferring things from survival.

DR. SALOMON: Yes, I think I agree with that and I think the Introgen trial, specifically, set a pretty good example for that looking at different times. I think sometimes you're only looking at 28 days,

but in a couple of your studies, you look more frequently and I think that was, you know, that's the kind of thing that needs to be done.

Okay, so, when adenovirus is used for *ex vivo* transduction of target cells, ex vivo now, we're shifting gears a little, should RCA measurements be performed on the transduce cells, before you infuse them back in? Now, remember, we do that routinely for retrovirally ex vivo transduction of cells with retroviral vectors, you always RCR in the transduce cells, even though you also have to show that there's no RCR in the initial suit so -- the initial infectious suit. Now, what do you -- in this case, though, we are going to put in some RCA, so what do you think?

DR. LAWTON: Maybe I can just, I mean, we've just been talking about the methods. If we're having difficult measuring it in what we're adding, how are

we going to actually measure it in the actual cells?

DR. SALOMON: Are you suggesting, Alison, are you suggesting that you don't have confidence that the current detection sensitivities are low enough that if you do 10 to the 10th T-cells or something ex vivo that you're not going to know whether you got it or not?

DR. LAWTON: I mean, obviously, it's a question, yeah. And until we have better understanding of the methods and the detection levels, et cetera, I'm not sure whether you're going to get anything extra from testing those cells before you put them in. That's just an observation.

DR. BAUER: I think the thinking here was that there would be amplification if it was an RCA, so it would be a relatively sensitive method.

DR. SALOMON: If you put -- this is, again, I just don't know this, I mean,

there are people here who know the answer to this -- if you put wild-type adenovirus on T-cells or hematopoietic stem cells, which would be two logical populations for this sort of thing ex vivo, do you get replication and is it detectable?

DR. FLOMENBERG: It's very inefficient except, as I mentioned some of the group B serum types seem to be able to bind better to hematopoietic cells. But, in general --

DR. SALOMON: Bind or actually become productive infections, right? I mean, I'm sorry I'm a retrovirologist.

DR. FLOMENBERG: Not really know they get in better, but yeah, it's not entirely clear to me, but you get very little -- you don't really get -- you get very little replication in hematopoietic with adenovirus. And there are probably several steps that are blocked, including binding, internalization and then

expression.

DR. HOROWITZ: Well, that's true, Phyllis, you do have a -- produce a B cell line, right, that makes adenovirus? I think, in general her answer's correct. I mean, most lines that the adenovirus will enter will not replicate the virus and produce either any or very little progeny, but there is this EBV transform line that right, that produces adenovirus?

DR. FLOMENBERG: We isolated a BE cell line from a patient, a bone marrow transplant patient, both transformed with EBV and also had a productive adenovirus infection. But, in some cell lines, some transform cell lines, T-cell lines, B-cell lines, you can get like a jercaps (?) are relatively -- you can get some replication. But primary cells, I think is very limited in a number of steps.

DR. KETNER: But this is really the question, isn't it, I mean, you take A

patient cells, treat it with a gene therapy vector and, you know, most, you know, maybe it won't replicate it in most cases, but maybe it will in some and so I'll need a test and see whether it did in those. I mean, I agree, I think there would be an amplification, so I think it's easier in looking for RCA in the inoculum. So, I guess I vote yeah.

DR. BLAZER: Can I just ask, how long does it take to replicate and how many cells would you need to study in order to pick up anything in the time frame after which you've added the virus and before you're going to infuse the cells?

DR. HOROWITZ: Well, the minimum replication cycle is probably about 16 hours but, as a practical thing, probably about 24 hours in the permissive lines that we use in the laboratory. In some of the less permissive cells, I mean, that don't replicate as well, I mean you might have to

wait two or three, you know, up to three -- two or three days to do this assay. But definitely the data should be obtained as I think because very small amounts, as has been pointed out already could be amplified quite significantly.

Those cells that would amplify virus most likely will die and the virus would then be slowly shed extracellularly. It could be dealt with in other ways, I mean, those cells could be treated with neutralizing antibodies to reduce the risk of RCA extracellularly, but definitely the data should obtained so --

DR. BLAZER: So, if you know how many RCAs you're putting in and you know how many cells you can actually assay and you figure out the time frame, if something's even 100 percent permissive, would you be able to pick it up given the aloquata (?) cells that you'd be able to measure, would you use that as a lot-release criteria?

There's a difference between getting retrospective data and saying that you can't infuse the product without that information? I'm just asking as a question, I don't know the answer.

DR. HOROWITZ: It would be hard to do it quickly, I guess. Although you could do it by real time PCR to look at the amount of virus that was released. I mean, the problem is compounded a bit because productive adenovirus infections, the virus remains cell bound, so it might not be out in the supernatant to assay for even a few more days beyond what I've mentioned. I mean, one of the things that the manufacturers know and we all know who work with it that the virus does remain, even completed virus in cells that ultimately would die will remain cell associated for a number of days, so, yeah, I -- the time frame of speed would be somewhat compromised in terms of our ability to give an answer

within two or three days. How long do you think from a cell-point of view -- how long do you think one would have to keep the cells for transfusing?

DR. BLAZER: Most people, when they culture cells will do it in a matter of days to a week to ten days, there are some that are going three weeks, but people are trying to shorten culture periods to seven days ten days or less --

DR. SALOMON: Well, in hematopoietic stem cells, I mean I wouldn't want to go over 72 hours.

DR. BLAZER: And you can't for those, but I was even thinking of T-cells to take the extreme, most people are trying seven to ten day cultures. So you're thinking of, when you expose the cells to the virus, and then you're going to have to take cells at when you would infuse it, hold those cells, take several days to do the assays, keep the cells in culture and then

release it, you're only measuring part of the time period anyway and if the statistics are such that you're really not going to have any kind of likelihood of holding up the infusion of those cells, then I'd say get it retrospectively on the cells being infused.

But if the statistics are that you have a significant risk that you're trying to avoid, and you pick a time period before infusion and you have a sensitive enough assay, then that would -- then you could build that into a lot-release criteria.

DR. HOROWITZ: Well, of course, this experiment could be just done -- I mean it could be done, I mean, on cells that were not going to be transfused to infect them, and I don't know if anyone in the room has done those experiments could help us.

DR. SALOMON: Marshall, Beth had a point did --

DR. HUTCHINS: Yes, along those

lines, we don't have that kind of data but the fact is, I'm also on the U.S. expert committee on cell tissue and gene therapy and we've discussed this issue, actually, in terms of looking at prospective lot release and what real-life situations actually occur. And the fact is that you would probably be forced, even with your longer-term, well, maybe not with three weeks, but if you're really only talking seven to ten days at best before that gap that's your time frame that you've got to do to deal with things, that's probably not, maybe, that's on the cusp of not being realistic at all. Because with an amplification step, even if you used PCR as your read out to get very specific information and they're sensitive right off the bat, you're going to need to allow a couple of days of amplification.

I mean, most people do a minimum of three to five days as a first

amplification for RCAs and the sampling amount that you're going to be able to take, just because the number of cells you're going to have is limited and you don't want to take, you don't want to use it all up just to do this one test, you're also going to be doing other analytical methods as well, again to ensure that you knew something about what you were doing prospectively, not just collected retrospectively. I think you would actually be forced into a retrospective analysis situation most of the time.

I'm not saying you shouldn't necessarily get that data, but I'm not sure you could do it on a lot- release basis, just practical aspects of it.

DR. LAWTON: One of the things that you could do prospectively is, actually, I think somebody else mentioned it earlier is to actually look at the cell type being transfused and see whether it's

permissive ---- virus. At least understand that.

MR. SIEGEL: Let's take as a given, we have a log history of regulating cell therapies and, you know, this issue always comes up in a cell therapy, you know, it takes three weeks to do a fungal culture. Should you require a fungal culture before you give the cells? We've never required the results of a test that can't be done in a manner consistent with the manufacturing of a test.

So, let's just take that as a given, but there are times, we have some products where the cells are transduced and frozen before they're administered and you can keep them as long as you need to and so, let's just, please look at the question. Assuming, you know, and some tests can be done quicker and some cells are long enough. If it's feasible should it be required prior to release? And if not, should it be