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FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BIOLOGIC RESPONSE MODIFIERS

ADVISORY COMMITTEE

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Richard C. Mulligan, Ph.D.
Alison F. Lawton, Industry Representative
Mahendra S. Rao, M.D., Ph.D.

Consultants:

David W. Gaylor, Ph.D.
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Guest:

Amy Patterson, M.D.

FDA Participants:

Jay Siegel, M.D.
Patricia Keegan, M.D.
Steven Rosenthal, M.D.
Philippe Bishop, M.D.

C O N T E N T S

P R O C E E D I N G S

Opening Remarks and Introductions

DR. SALOMON: Good morning, everybody, in the beginning of a three-day session that begins today, Wednesday, October 24th. If you were expecting anything but the FDA's BRMAC committee meeting, you are in the wrong room. I just can't imagine anyone coming all the way out to Gaithersburg thinking they are coming to a different committee. My wife is happy. Supposedly this is safer.

Before doing anything else this morning, I wanted to begin something I just feel a personal responsibility to. We have been together, many of us, for a very long time and in a way that kind of creates a type of family, and one of our family members, unfortunately, was caught up in the September 11 tragedy. What you see here is a picture of Lisa Raines, who was vice president of government relations for Genzyme. The picture was kindly provided by Alison Lawton, to my left. Lisa was often in the audience. She interacted with many of us. I have met her on several occasions here. She was very active with FDA and Bio, and before she went to Genzyme, she was very involved

in a lot of different things. So, her interactions went far beyond just the BRMAC committee. Anyway, just at a time in which so much has happened to us, it just seems inappropriate not to take a second to recognize this woman and the tragedy that engulfed her along with the rest of the country.

Well, on to hopefully better things today. I think what we will do just to start off is quickly go around the table and introduce ourselves, and then we will get the meeting going. Can we start on the left?

DR. RAO: I am Mahendra Rao. I am at the National Institute on Aging. I work with stem cells in development.

DR. CHAMPLIN: Richard Champlin, I am the Chairman of the Department of Blood and Marrow Transplantation at the M.D. Anderson Cancer Center.

DR. HIGH: Kathy High. I am the Director of Research in the Hematology Division at the Children's Hospital in Philadelphia.

DR. GAYLOR: David Gaylor, Sciences International. My area is biostatistics and risk assessment.

MS. LAWTON: Alison Lawton. I am the industry rep on the panel. I chair the solid and

gene therapy committee for PhARMA and work for Genzyme.

DR. SALOMON: Dan Salomon. I am at the Scripps Research Institute and work in experimental medicine. My interests have been in cellular and organ transplantation and tolerance to gene therapy.

MS. DAPOLITO: Gail Dapolito, Executive Secretary for the committee. Seated to my right in the FDA section is Rosanna Harvey, committee management specialist.

MS. KNOWLES: I am Kathy Knowles and I am with a small non-profit company in Seattle, Washington, Health Information Network. I serve as a consumer representative for the VPAC committee and I am serving in that role today here.

DR. PATTERSON: Amy Patterson, Director of Office of Biotechnology Activities in the Office of Science Policy at NIH.

DR. ROSENTHAL: Steve Rosenthal, medical officer, Division of Vaccines, FDA.

DR. BISHOP: Philippe Bishop, medical officer, CBER, oncology.

DR. KEEGAN: Patricia Keegan, Division of Clinical Trials, CBER.

DR. SIEGEL: Jay Siegel, Director, Office of Therapeutics at CBER.

DR. MULLIGAN: Richard Mulligan, from Harvard Medical School.

DR. SALOMON: Thank you all, and I would like to greet Dr. Gaylor, joining us from biostatistics. We will need you, and Ms. Knowles, thank you. Let's move right along to Gail, providing us with the conflict of interest statement.

Conflict of Interest Statement

MS. DAPOLITO: This statement applies for all three days of the meeting. This announcement is part of the public record for the October 24-26 Biological Response Modifiers Advisory Committee meeting.

Pursuant to the authority granted under the committee charter, the director of FDA's Center for Biologics Evaluation and Research has appointed Dr. David Gaylor and Ms. Katherine Knowles as temporary voting members for the discussions on October 24. In addition, the CBER director appointed Drs. Jonathan Allan, Kenneth Cornetta, Michael Emerman, David Gaylor, Katherine Knowles, Jeffrey Kordower, Clifford Lane, Bruce Torbett, and

John Zaia, as temporary voting members for the committee discussions on October 25 and 26.

To determine if any conflicts of interest existed, the agency reviewed the submitted agenda and all financial interests reported by the committee participants. As a result of this review, the following disclosures are being made:

In accordance with 18 U.S.C. 208, Drs. Richard Champlin, Katherine High, Richard Mulligan, Clifford Lane and Jeffrey Kordower have each been granted a waiver which permits them to participate in the committee discussions.

Drs. Champlin, Cornetta, Lane, Mulligan, Salomon, Sausville and Torbett have associations with firms that could be affected by the committee discussions. However, in accordance with current statutes, it has been determined that none of these associations require the need for a waiver or an exclusion.

Ms. Alison Lawton is serving as the non-voting industry representative member for this committee. She is employed by Genzyme and, thus, has interests in her employer and other similar firms.

In regards to FDA's invited guests, the

agency has determined that the services of these guests are essential. The following interests are being made public to allow meeting participants to objectively evaluate any presentation and/or comments made by the guests. The following individuals are employed by industry and have interests in their employer and similar firms:

Drs. Dale Ando and Gabor Veres are employed by Cell Genesys. Dr. Inder Verma is on the board of directors of Cell Genesys and Dr. Susan Kingsman is the founding shareholder of Oxford Biomedica.

Dr. Amy Patterson and Dr. Marina O'Reilly are employed by the National Institutes of Health, Office of Biotechnology Activities. Dr. O'Reilly also has a financial interest in an affected firm.

In the event that the discussions involve other products or firms not already on the agenda for which FDA's participants have a financial interest the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the public record.

With respect to all other meeting participants, we ask in the interest of fairness that you state your name, affiliation and address

any current or previous financial involvement with any firm whose product you wish to comment upon.

A copy of the waivers addressed in this announcement is available by written request under the Freedom of Information Act.

DR. SALOMON: Before we get started again formally, again, in terms of ground rules here, I have always started by encouraging the audience to participate. My feelings are that the purpose of this advisory committee is both to focus the expertise on the panel, but also to bring to bear as much of the community's opinions and thoughts on these complicated subjects, particularly the one today on long-term follow-up. So, I hope that nobody in the audience will be inhibited to get up and I will do my very best to recognize you promptly, and would encourage that at all times.

To the committee members, I would also just say that we will attempt to reach consensus whenever consensus is possible. If my attempts to reach consensus are failing or I am wrong, then I am expecting you guys to, you know, bring that to my attention. I certainly never would want to pretend I was reaching consensus and not do it.

The other thing that I think would be

important is that a vigorously defended minority opinion is absolutely appropriate. So, even if I am saying something at the end of a section that sounds like a committee consensus if, at the end, you don't personally believe it, then I think it is very important to stop and articulate those issues and not feel that there is any pressure from me as chair to hold any particular party line.

Then I guess we should get started. To begin with, Philippe to begin the discussion of long-term follow-up: gene transfer protocols for clinical trial participants.

Long-Term Follow-up:

Gene Transfer Clinical Trial Participants

DR. BISHOP: Dr. Salomon, members of the committee, good morning.

[Slide]

This morning's presentation pertaining to long-term follow-up of subjects in gene transfer studies has been broken down into three parts. The first part, I will read you briefly, is a summary of prior BRMAC discussions focusing on statements or at least generalizations that are pertinent to today's discussion.

[Slide]

I will move on then to discuss areas of clinical concerns that pertain to gene therapy and are relevant to the long-term follow-up of subjects enrolled in these trials and, I will turn it over to Steven Rosenthal who will discuss issues of special considerations when discussing epidemiologic databases.

[Slide]

So, first some background information and summary of prior discussions.

[Slide]

It is important to understand that today's discussion is in the context of current FDA guidance pertaining to long-term follow-up of subjects in gene transfer studies. It is important to realize that as of today the only guidance that we have pertaining to long-term follow-up of these individuals is limited to studies that involve retroviral gene vectors. This guidance document has been discussed at great length at prior meetings here, at BRMAC, and is also available on our web site. For those of you who have not had opportunity to get intimate with this particular document, I would invite you to visit the FDA web site for that.

[Slide]

It is in that context that discussions in November, almost a year ago, November of 2000, took place. At that time, I think it was clear that the committee told us that efforts to gather information pertaining to the long-term risks of exposure are necessary not just for retroviral vector studies but for all of gene transfer products and, rather than focusing on vectors types, it is important to maybe consider the properties or the characteristics of vectors, and maybe this is what we should utilize as the basis for further discussion when discussing long-term risks for participants.

[Slide]

With that in mind, FDA proposed a three-tier system based on vector characteristics at the April, 2001 meeting.

[Slide]

Let me review this three-tier system. The three-tier system essentially categorizes vectors according to their characteristics or their properties into one of three categories. The first category would be considered low risk; the second category intermediate risk; and the third category

this event. If the reverse transcriptase comes along here and crosses over in the common region of the cPPT, between the vector and the wild type, you would get the crossover event but the result would be is that you would get a truncated gag/pol.

Another event is that if the reverse transcriptase here would cross over in the RRE region, you would have a truncated envelope. This event would probably take two events to occur but you could imagine that if, basically, the reverse transcriptase picks up this antisense payload and then puts it back into the virus, you would still get a wild type. Yes; its phenotype would be changed because now it would contain envelope sequences that could possibly confer an X4 phenotype strain to this virus but, nevertheless, it would be a wild-type HIV.

[Slide.]

But, in order to address the sequence issue of increasing the pathogenicity of the virus through recombination between the vector and the wild type, I just want to make one point--a few points, but one point here. The backbone of the vector contains regions of HIV that are highly conserved; the LTR, this packaging gag, cPPT and

focus on the most important information that would be relevant to long-term follow-up of subjects involved in gene transfer studies.

In part, there is a notion that there is a critical need for the gene therapy community to be an active participant in these efforts, and in order to include compliance we really need to be able to zero in on those issues that are most critical.

[Slide]

With that in mind, the FDA left the April meeting and put together a working group to further define the clinical concerns that relate to gene transfer studies. In addition, we wanted to be able to address the duration of clinical follow-up that would be appropriate for the specific areas of clinical concern.

[Slide]

Additionally, this working group was asked to take into consideration some of the advice that came out of the April meeting, which is not that it is just important to vector characteristics but it is also important to take into consideration the duration of gene product expression, the mode of administration, the targeted tissues and, of

course, patient-specific vectors.

[Slide]

With that in mind, we put together a multi-disciplinary group at the FDA, involving individuals with varied types of expertise in oncology, hematology, neurology, immunology and, in addition, we involved our experts in clinical toxicology and molecular biology as well as virology. Because we are talking about epidemiologic databases as maybe one of the future goals, we also involved Dr. Rosenthal, who will address you a little bit later this morning. It was important to keep our liaison, RAC liaison, informed of our activities and, therefore, Stephanie Simek was also apprised of our discussions.

[Slide]

The working group met and agreed that the four clinical areas of concern is consistent with what the committee had already previously articulated, and that is, namely, that malignancies, hematologic disorders, autoimmune diseases and neurologic diseases are the areas that we should be focusing on when discussing risks of gene therapy studies, long-term risk of gene

therapy studies.

[Slide]

So, what I would like to do this morning is to go through those four categories and highlight the information that has been already discussed in your briefing material, and maybe highlight those important examples that you may find useful to today's discussion.

[Slide]

DNA and RNA viruses have been studied as important causes of human cancers. For example, the HTLV-1, the human T-cell leukemia virus is known to be the causative agent for adult T-cell leukemia, or there are other viruses such as HIV, HPV and hepatitis C viruses that have been associated, or strongly associated with several malignancies, such as non-Hodgkin's lymphoma, Hodgkin's disease, cervical cancer and hepatocell carcinoma. It is important to note that DNA and RNA viral vectors are commonly used in gene transfer studies.

[Slide]

Some mechanisms for viral oncogenesis have been described. Among these, I have highlighted four potential mechanisms. The first,

transformation by transgene expression, and I have highlighted here HTLV-1 tax, interacting with the NF kappa-B and potentially other transcription vectors to up-regulate the transcription of a large number of cell genes like cytokines or cytokine receptors such as IL-2 and GMCSF, as well as transactivating the expression of c-myc, c-fos, c-jun Ap1 and others that could essentially lead to a clonal outgrowth and a malignant transformation.

Insertional mutagenesis -- probably the prototype or example would be ALV integrating in the vicinity of c-myc and then leading to an up-regulation of c-myc transcription, eventually contributing to the development of a non-Hodgkin's lymphoma.

Hepatitis C virus can cause chronic inflammation and the release of inflammatory molecules that recruit maybe other inflammatory cells. Maybe the generation of toxic reactive oxygen radicals can trigger proliferation and responses by surrounding tissues and may represent an important pre-condition for carcinogenesis or the development of de novo cancers. In this model the increased proliferation potential of cells increases the opportunity for replicating the

errors that can occur over time and the loss of normal cell function leading to oncogenesis.

The "hit and run" hypothesis is more controversial but here I have highlighted a recent example for adenoviruses. Here, the adenovirus-5 E1A protein with the open reading frame E4, open reading frame 6 can potentially lead to an initial insult to the cell that eventually can lead to transformation. So, in this instance I think it is important to understand that this concept raises the possibility that an initial event triggered by this viral agent can lead to tumor development in the absence of detectable viral genes or protein expression, viral protein expression.

[Slide]

An example of retroviral-induced insertional mutagenesis leading to T-cell lymphoma has been discussed previously at this meeting. This has occurred in non-human primate studies that were published in 1992 by Donahue.

As a result of recombination events between the vector and packaging and protein sequences and a replication competent retrovirus was produced. These viruses were incubated in purified immunoselected CD-34 stem cells from

rhesus monkeys who were used then to reconstitute these myeloablated non-human primates. Six to seven months later after the transplantation, three of eight of the stem cell recipients developed a rapidly progressive T-cell neoplasm. The analysis of the lymphoma showed that they were clonal; that there was common to these lymphomas the insertion of the retroviral DNA. I think it was concluded from these studies that there was a clear association between the replicating viruses and the development of lymphoma.

[Slide]

It is important to understand that we have experience in oncology with second cancers or treatment-induced cancers that can take years before clinical presentation with a second malignancy. For example, in Hodgkin's disease it is well known that leukemia can appear five to nine years following initial therapy, but these leukemias can appear up to thirteen years following the treatment for the Hodgkin's disease.

Leukemia is not the only cancer that can appear in Hodgkin's disease -- bone cancers, thyroid, lung, stomach have all been described as second cancers related to the Hodgkin's disease

therapy.

Breast cancer is another example where it is well-known that second cancers can arise. Second cancers of the uterus, the lung, the esophagus, connective tissue and thyroid can appear up to fifteen years following the initial breast cancer therapy.

Testicular cancer is the third example that I have chosen for you and there leukemia, lymphomas, stomach, colon cancer, pancreas, prostate and kidney cancers and also thyroid cancers can appear up to twenty-five years following the testicular cancer diagnosis.

[Slide]

Before moving on to hematopoietic disorders, we would infer that some of the mechanisms and some of the injury that occurs secondary to chemotherapy could be similar to some cellular injuries that could arise out of gene transfer studies and, therefore, it is plausible that second cancers will not appear until years to decades following the gene transfer protocol, participation in gene transfer studies.

[Slide]

Moving on the hematopoietic disorders, it

is well-known that viruses can induce hematologic disorders. As an example of an acute event, parovirus B19 can cause anemia and it is usually associated at the same time that you have viral infection. However, HBV can cause aplastic anemia months following the HBV initial infection. With HIV, isolated or combined cytopenias can appear months to years following the HIV infection.

[Slide]

When discussing hematopoietic disorders, it is important to understand that the progenitor cells are self-replicating and can give rise to HPC descendants. These progenitor cell descendants are very important and critical components of the blood and the bone marrow, and these cells are essential to human life.

[Slide]

Cytopenias could be related to gene transfer-related hematologic disorders, as well as malignant leukemias, all conditions that could appear months to years following the initial exposure. There we would invoke mechanisms that would be similar to what is known of viral-induced hematologic abnormalities.

[Slide]

Moving on to neurologic disorders -- gene transfer vectors and the administration strategies that can lead to neurologic disorders that we identified are highlighted on this slide: integrating vectors, vectors with long latencies; vectors with prolonged transgene expression; and vectors with immunogenic reactions are all gene transfer strategies likely to represent the gravest risk to the CNS.

[Slide]

When talking about the central nervous system, it is important to realize that the CNS is a highly specialized organ that has a lot of redundancy in functional capacity. Many known neurologic disorders require significant damage before being clinically evident.

[Slide]

Neuronal injury may go on for years before being clinically detected, and I have highlighted three examples for you. HIV dementias can occur a long time after the initial HIV infections. It is well-known, because of latency, that prions can incubate for a long time before CJD becomes apparent. Then, I have highlighted diabetes to demonstrate that it is not just the CNS that we are

concerned about but also peripheral neuropathy being one of the concerns and, again, you know, the same principles that it can take a long time and a lot of neuronal injury before you have clinical symptoms.

[Slide]

Moving on to autoimmune disorders, environmental and other xenobiotic agents that can cause autoimmunity have been described. For example, viruses and bacteria can induce antibody-mediated autoimmune diseases via molecular mimicry. Group A strep causing rheumatic fever and infectious mononucleosis causing ITP are two examples of such infections that can cause autoimmune diseases by molecular mimicry.

[Slide]

But there are other mechanisms for autoimmune diseases. For example, the unmasking of the autoimmune disease gene may be a similar mechanism that an insertional vector can unmask an oncogene. Here we are unmasking a gene that can essentially be up-regulated to cause autoimmunity. I have already described examples of molecular mimicry. There are also examples of humoral autoimmunity and T-cell mediated autoimmunity.

T-cell mediated autoimmunity is an important mechanism for autoimmune diseases. For example, the down-regulation of T-cells can normally suppress responses to cell proteins, essentially causing a shift from TH-1 to TH-2 cell balance to predominance of the TH-1 cell subsets. This imbalance of TH-1 and TH-2 is thought to be a general mechanism that is associated with many autoimmune diseases, including multiple sclerosis and the Hashimoto parovirus virus.

[Slide]

Immune responses to gene therapy vectors or transgene products are possible, and similar mechanisms as those I have highlighted in the earlier slides are plausible. The risk may relate to vector characteristics, the duration of transgene expression, route of administration, as well as the host specific factors.

[Slide]

The clinical manifestation of autoimmune diseases that result from environmental insults may take months to years before they are clinically detected. For example, systemic lupus may appear with a median of 19-25 months following the exposure to minocycline, but the clinical onset can

range anywhere from three days to up to six years following initial therapy. Another example would be exposure to silica which would cause scleroderma which could occur several months following the environmental exposure. Similarly, we would think that gene therapy-related risks of autoimmune diseases could take months to years before they become clinically apparent.

[Slide]

So in summary, the long-term follow-up of gene transfer participants should focus on four clinical areas, and I think we would agree with the committee's prior recommendation that these gene malignancies and neurologic disorders with the notion that they may take years to decades before clinical diseases or disorders become apparent. Whereas hematologic disorders and autoimmune disorders are likely to represent risks and clinical disease development that would be maybe with a shorter time frame, maybe months or years following the gene transfer study therapy.

[Slide]

We have previously proposed a three-tiered system to assess the risks to subjects that were based on vector characteristics and, still today,

we believe that this three-tiered system should be the basis of our ongoing discussions.

With that in mind, I will turn the podium over to Dr. Rosenthal who will address special considerations pertaining to epidemiologic databases.

Epidemiologic Considerations in Developing a Database for Long-Term Follow-up of Subjects

DR. ROSENTHAL: Thanks very much.

[Slide]

Determining causality of exposure to drugs with certain outcomes can be problematic, especially in the context that we are talking about today, with outcomes that they may develop many years after the initial exposure, and also outcomes which are generally rare in the population, such as cancer, autoimmune diseases and neurologic diseases.

[Slide]

In general, when we try to make conclusions about causality we generally use the following criteria, and none of these criteria are sufficient in themselves for determining causality but the more of these criteria where certain associations can be made, then we are more

confident that causality does exist between exposure and outcome of interest. For example, is the association consistent? Do we observe it among different populations or among different studies? Is the association strong? Is there a very high relative risk? If the relative risk is high, that is a good argument for causality unless the methodology of the study is severely flawed. Is the association also seen in studies that are very rigorously done, for example, randomized, controlled clinical trials? If we see an association in that context we can be pretty confident that there is a causal association. Is this association specific? Do you often see an outcome with a certain exposure and vice versa? Is the temporal relationship between exposure and outcome consistent with what we know? And, is there coherence or biological plausibility? Is the outcome consistent with what we understand about the pathophysiology and consistent with data perhaps obtained in preclinical studies and in vitro studies?

[Slide]

Epidemiologists like to use the following tools to determine causality, and when we go from

the top of the list to the bottom of the list the study designs become much more convincing. On the other hand, they become much more logistically difficult and much more expensive.

Case reports, case series are easy to obtain and very inexpensive, and sometimes they can lead to good, interesting data which can help us determine causality. Case-control studies, cohort studies and randomized clinical trials -- the last really is the gold standard but is the most expensive.

[Slide]

Now, cohort studies and randomized clinical trials we consider analytical studies because they have control groups and we can safely come to certain conclusions. Now, randomized clinical trials are the most expensive and the most convincing, but these aren't the studies that we are talking about today really. These will be carried out in the future with gene therapy products, but now we are concerned really with developing a database where some long-term adverse events can be investigated.

[Slide]

A cohort study would be a reasonable study

design and has many advantages. You can study multiple outcomes from a given exposure. You can study uncommon exposures. Selection bias is less likely. Unbiased exposure data, we are confident that everyone in our database has received a certain product, and incidence data in the subject group is available. There are some disadvantages. There may be biases in obtaining outcome data, and cohort studies are very expensive.

[Slide]

One reason they are expensive is, depending how you designed a study, often rates of disease in the subject group are compared with populations that do not receive the exposure, and what is usually lacking is data in populations with the underlying disease. Comparison cohorts can be created but you need to develop a subject controlled cohort which is similar to the experimental group. You need to have the same underlying disease and, again, developing this control cohort is really very difficult, very expensive, and not readily available outside the context of randomized clinical trials.

In addition, for rare outcomes, the outcomes we are talking about today -- cancers,

autoimmune diseases, neurologic disease and associations which may have small relative risk, cohort studies are usually not of value.

[Slide]

This chart is just an example of sample size calculations, just to demonstrate that for diseases with very small incidence, such as cancers and neurologic diseases, and if we are going to be looking at associations which may be small or moderate, sort of in the upper left-hand quadrant of this table, cohort studies are going to require very large sample sizes, in the order of tens of thousands in both the study cohort and the controls.

As the disease becomes more frequent, as you move down the table, and when the relative risks of the associations are much stronger, then associations can be made with much smaller sample sizes.

[Slide]

Case series or case reports have some advantages. It is very easy to obtain this data. It is very inexpensive. For a case series or developing a series of patients that have received gene therapy products, it is very easy to quantify

the incidence of certain outcomes. The problems both with case series and case reports is that there are no control groups and, therefore, you can't really use these study designs to test hypothesis. But they are useful in many cases for generating hypotheses.

[Slide]

However, there are contexts in which case series and case reports can very strongly suggest causation. An example historically is when the outcome is so rare and so rare and so characteristic that we can make with very high confidence an association that is causal. For example, clear cell vaginal adenocarcinoma in young girls that were exposed in utero to diethylstilbestrol, this cancer which was so rare and associated so consistently with its exposure, that we are all very confident that this drug is causally related to this outcome. Another recent example, which may not apply to gene therapy studies which we are talking about today, is when a change in the event of a course is reversible when the exposure is withdrawn, and the event returns upon retreatment. A very recent example is alopecia following hepatitis B vaccination where a

child lost its hair after receiving the first dose. The hair grew back; came back for a second dose and the outcome repeated itself.

For gene therapy it is very possible that for certain outcomes if there is vector persistence or vector sequences and/or gene products can be found within a target organ of toxicity -- data like this can help us conclude perhaps with a high degree of confidence that there is a causal association.

[Slide]

So in conclusion, to develop very elaborate, detailed databases for long-term follow-up of gene therapy for analytical studies to determine causality of adverse events may not be of value. It may be a waste of a large amount of resources, especially when the events are uncommon in the general population, such as the events we are talking about today. It would be of value if the events are more common in the general population, unlike the events we are talking about today, and if the relative risks are very high. However, developing a database more on the lines of developing a case series could be very useful to reveal causality for events that are characteristic

and are biologically plausible. They would also be very useful to generate hypotheses that later down the road could be further explored in more detailed ad hoc analytical studies, and those decisions can be made later and be more focused, and usually can have a high probability of obtaining very useful information. Thank you very much.

DR. SALOMON: Thank you, Philippe and Steven. I want to acknowledge my gratitude to the staff, all of whom were recognized at the beginning of Philippe's talk. I read this paper that you created and outlined now these last two talks and it represents a tremendous amount of thoughtful work on the part of the FDA staff in this instance and I think, certainly as chair, I would like to recognize that. We appreciate it.

This is a problem that won't go away, and it is apparently, to all of us, critical to come to some sort of grips with at this point after a year of working on it in the committee. I think as a base I am finally convinced that I am not going to be able to slide by with the kind of generalizations that, you know, it is kind of a good idea but we are not sure of the details sort of thing that we have tried twice now. So, I think

that is our challenge in the next couple of hours really, to put it into a context that the committee feels has sufficient detail to allow a response to interested parties, in this case to Congress who is not letting this drop, to consumer groups, to the public who is not going to let this drop, and to all of us in the field from the biotech industry sponsors to the individual investigators that are going to need to figure out how this is going to fit into our plans in terms of funding, in terms of politicking with our funding agencies. I think that is our task, to get on the public record the fact that there are no easy answers here, that we are going to have to make some judgments. I think that in this case this is probably the one time in which vigorously defended and well articulated minority opinions are perfectly appropriate to put on the record today.

So, that is my introduction. I have struggled with this for a while and I am going to really try and do it right. I think the last comment I have is that, you know, any soldier looking at a campaign will talk about the low point. So, I think the low point so far, as chair of this committee, was achieved with this

particular question when, at one point in frustration with the implications on research, I came to the brilliant conclusion that the FDA should do it, at which point Jay very vehemently pointed out to me that not only I just violated the basic principle of the FDA, which he was absolutely right in pointing out to me that point. So, if we can get through this, I will feel like we have really gone beyond that low point for me.

DR. SIEGEL: I don't remember saying quite that, and I don't think it was a low point. I think what I was pointing out is that our opus operandi, what we do and what we are funded to do and the way we operate is collect data from sponsors who sponsor clinical trials, not to collect data from patients. To move in that direction would represent a major step out of our normal roles with important implications -- financial, social, legal, ethical and so forth, which isn't to say necessarily that all of those are negative, just that it is not a simple consideration.

I have reflected a lot on the things you have just commented on, and I do want to make a comment or two before we get into committee

discussion of these issues just as a matter of context.

Dan is right that this is a problem that isn't going to go away, but that also means it is not a problem that is going to be finally solved at one point, solved at one point in time and then we are living with that solution. We feel that it is time to move forward to ensure that sponsors have a better focused approach to getting the right information than has existed in the past and we want guidance so that we can make progress in that field.

We recognize that we are constantly learning and that there are many other areas for input, that we are not making decisions today, for the most part, that we are going to be permanently stuck with for several decades; that we need to make decisions, vet them, have further discussion. You know, maybe implement some of them but also have further public discussion of them with various interested parties and fine-tune them as we move along.

The other complex thing about this issue that we have discussed and that I think needs to be sort of in the back of everybody's mind is that the

presentations you have heard, both presentations, are focused on what sort of information we think is important to collect. There are a lot of closely related issues. Who is going to pay for collecting it? Who is going to store that information and how? And the pragmatic issue, as we have discussed frequently at other meetings, how do you make sure that you get a high rate of collection of information after a decade or two when people move, patients move, companies go out of business, funding runs out and all the other issues that we have discussed at some length?

It is important to note that, although you didn't hear those issues mentioned, we haven't forgotten that those are important issues. So, while we are dealing with this interplay of issues, it is very hard to build the information systems or the infrastructure without knowing what you are going to collect. It is very hard to determine what you should collect without knowing what the information systems and the infrastructure are, and so forth. So, suffice it to say that we have been working hard within the agency and with our sister agencies to explore all of these questions and to move forward on all of them, and you see that our

focus in this discussion is on the piece of what is the right information to collect, but I want everyone to be cognizant that we are well aware that there are important issues as well in related areas.

Finally, the only other comment I would like to make regarding this discussion we are about to enter in is that the questions you have before you were actually radically changed a number of times over the last few days. In my mind at least, that is not that important. So, we have asked you to at least comment on certain things. Maybe we haven't asked you to comment on other things, but what we need is your input on any areas pertinent to this matter that you feel would be helpful for us and that you have expert opinions on. So, as Dan has said a couple of times, minority opinions count. Consensus is important but voting doesn't necessarily matter on all of these. These are complex issues and we really want to integrate as much of the expertise we have available to us in this forum and others into the whole process.

So, please feel free and strongly encouraged to offer opinions and comments regardless of whether we specifically solicited a

comment on a particular question or not. I don't see anything in here saying, for example, are these the right four clinical areas to focus on but if you are sitting there, thinking how come they are not going to do cardiovascular disease, the fact that we haven't asked for that opinion doesn't mean that we wouldn't very much welcome it. So, really feel open and free and strongly encouraged to participate and contribute in any way. That, by the way, applies also to the public.

Open Public Hearing

DR. SALOMON: In fact, you anticipated, Jay, what I was going to say right now. I think very appropriately for something that has been discussed two times already over the last year and this is the third time, I think it is one of the situations in which I would welcome some general comments from people, just as I have kind of given you a little bit of my sense of it. So, if there is anyone in the audience that would like to give us their sense, just identify yourself.

MS. TICE: My name is Malissa Tice, and I am the regulatory liaison for Schering-Plough [not at microphone; inaudible] and we have conducted a number of Phase I and Phase III trials in gene

cancer. Let me just give you a little background of Schering's involvement and I have a statement, and I have a statement from Schering-Plough.

Long-term follow-up is defined as the collection of data on study participants that occur at least one year after the treatment period of the clinical trial. Numerous factors must be considered, ranging from practicality and feasibility of obtaining the follow-up data, the scientific merit of the information gathered, the analysis of the data, the creation and maintenance of the database, the financial and administrative burden on the investigators, academic institutions and sponsors. Furthermore, there is a significant burden on the patients.

As previously discussed, these factors can be overwhelming and may discourage participation in [not at microphone; inaudible] research. One more practical and efficient way to capture this information may be the creation of a patient registry sponsored and maintained by the FDA, which would allow patients to be voluntarily contacted. Data reporting would be in a standardized format in the registry to allow pooling of information in an attempt to draw any meaningful conclusions or

trends. It is important to define what information is being required above and beyond the safety and efficacy data collected during the clinical trial.

When a clinical trial is conducted, patient follow-up is included to determine the efficacy of the drug product. Additional requested data beyond the protocol prescribed length of time raises concerns that patients will be lost to follow-up, thereby rendering the data uninterpretable. In most cases there will be all these problems in determining the relatedness of the gene transfer product to adverse events detected a few years after this treatment.

Overall, the FDA needs to clarify and state what the objectives are for the long-term data. Examples are survival status, occurrence of new malignancies, as presented today, autoimmune disease, hematologic disorders or neurologic disorders. We support the basic principles of the proposed three-tiered system and feel that the length of follow-up must be determined on a case by case situation through communication and discussion with the FDA.

Each vector construct is unique and the variables associated with its use, such as route of

administration, the underlying condition and the patient population. A rigid guideline is not flexible enough to accommodate the various gene transfer clinical trial scenarios. The rationale for determining what data collection is needed must be defined. Currently, as was discussed here for the retroviruses and in the guidance, laboratory specimens are required for five years with questionnaires and telephone calls beyond that time. The rationale needs to be evaluated based on the biology of the vector. If the half-life of the vector [not at microphone; inaudible] laboratory specimens are burdensome to the patients. They have to travel, lose work time, etc. Managed care, insurance companies, academic institutions and sponsors, along with the extra paperwork and procedures find this provides little extra information or useful information.

In the case of vectors that do not persist, such as plasmids and adenovirus laboratory specimens are [not at microphone; inaudible]. Thank you.

Committee Discussion of Questions

DR. SALOMON: Thank you very much. Richard?

DR. CHAMPLIN: Reflecting on the data being collected, certainly the four disease groups that you looked at have precedent but this is an area when unpredictable things can certainly happen, and I would think almost anything goes in terms of organ targets for toxicities. Clearly, examples of late liver and kidney failure, and chronic glomerulonephritis are mostly in the autoimmune category perhaps but, clearly as one is screening for toxicities one needs to look for those things. I would think an approach would be to try to use a broad-based toxicity scale, sort of like the NCI common toxicity criteria that is used for a chemotherapy drug. As one collects information from patients, obviously you want to make that as simple and easy to pull out as possible so that somebody on the receiving end would need to translate the patient's description of their medical problems into categories by either that toxicity criteria or some other instrument.

DR. SALOMON: So, right now anyone is there anyone else who had a sort of general point? Richard?

DR. MULLIGAN: I have an issue with the definition of long-term follow-up. In the briefing

document there is a comment that clinical concerns restricted to a specific vector for a given study agent for a given study would be addressed in the study protocol would not be material to any guidance. I am thinking that this may be a very important key to separating the formal definition for long-term follow-up and many of the concerns people would have may well be covered by the individual protocol.

So, one of the clarifications in the sense of maybe a sample or two of what would be the closest kind of information for the clinical protocol that you are talking about would be like a long-term follow-up because I think if we can separate as much as possible those two things it may be easier to see the real long-term follow-up.

DR. SIEGEL: I think that is a very important issue. In fact, I think the April discussion or confusion over that was fundamental to some diffuse discussion in terms of what was needed. Each protocol for any drug, biologic or device under study includes an amount of follow-up that is dependent on both the nature of the drug, its anticipated effects and the nature of the disease. In traditional drug studies with

short-acting drugs that typically follows to approximately a month after the end of the treatment period. In biological studies, because they often have much longer lasting effects and they may have persistence of both desired effects and undesired effects, such as immunogenicity issues well after the administration of the product, it is quite common that studies persist significantly longer than that.

In our current experience for the vast majority, if not all, gene therapy products we have been asking for follow-up that extends to at least one year after the final administration. So, for the purposes of these discussions, and as reflected in the footnote on page one, and also consistent with the comment that you have just heard, we have decided to define long-term follow-up as follow-up that occurs beyond the first year after final treatment on protocol.

With that said, however -- and I think that is functional for what we are looking at when we are talking about the risks that may cross over broad varieties of gene transfer products that might share common vector characteristics or other characteristics that might call for long-term

follow-up such as we have been discussing. But, as your question is asking, we would all presume, regardless of the discussions about general principles for long-term follow-up, that if the nature of the disease being treated or the nature of the insert and the vector product being produced raised specific concerns regarding safety relevant to that specific product or, for that matter, efficacy regarding that particular product, we would require follow-up. Even when those concerns require follow-up beyond one year, we would require that regardless of this discussion.

So, the fact that you might imagine a particular insert in a particular disease where you think you would want to have, you know, five years of follow-up because of the nature of what that insert is doing, unless that is a broadly generalizable characteristic that shouldn't be driving our discussions of generalizable issues of vector characteristics as we would expect for a given disease and a given insert. We would make a case by case determination about the nature of that risk, and the duration of that risk, and the appropriate way to deal with that risk in the setting of a clinical trial.

In addition, in some sense all of our determinations will be case by case but we feel that as we look across broad classes of vectors to look for shared risks, we need to develop the guidance regarding the common expectation based on the factors that we have discussed.

DR. MULLIGAN: I think we can just say it is very, very key. It makes me feel more comfortable that we might be able to look at the long-term follow-up discussions in a slightly different way than maybe some of us have in the past because I think you are giving comfort that the good old-fashioned process of reviewing a protocol will identify things that probably would be of most concern. I think we could all come up with several specific points of things that will be done in the near future where that five-year follow-up may well be very, very important.

So, I would propose that we might want to, based on that, think of the nature of the other information. What is the other kind of information. I was struck by Dr. Rosenthal's talk because at the finish there is a suggestion of an analytical importance of the follow-up information. That is, I think you were making a point that some

of the data collection may not be that useful because it doesn't really tell you whether it really is associated with the gene therapy.

I am struck because I am not sure, in the context of the overall value, why we are doing this, why that necessarily would be the goal. That is, another goal might be simply to get raw information. From the political point of view, when something bad happens people are not going to want to know that you didn't know, no scientist knew, why this happened. They are just going to want to know that you identified this, or if you didn't identify this people are going to be very upset. So, a system that is too sophisticated because you are kind of getting rid of things where you don't really know what is going on is probably not the right system for this kind of follow-up. So, maybe I am just trying to fantasize about getting over this whole thing over the next hour or two.

DR. SALOMON: I would like to share your fantasy, Richard. Certainly, at the end of the day it will mean a lot more to me than now.

DR. MULLIGAN: But I am not so sure that maybe it is all that complicated if we begin to

separate things on the basis of real clinical information and analytical information and raw information.

DR. SALOMON: I agree very much with what Richard has been saying just now and as Jay put it. I spoke with Jay earlier this week to just get some idea about where these questions were going and, as Jay points out, they evolved quite a bit.

I think that what we ought to do now is try and follow a path to get to the end of this and the guidelines I think, Richard, you have kind of articulated. The first question and the first issue I think we need to just have some sort of official opinion on is do we agree -- you know, do we advise, not getting yet into the details of what long-term follow-up us but just in some form that we can feel comfortable with, can we say to the FDA, to the public, that we believe long-term follow-up for gene therapy clinical investigation is appropriate? If we can get past that first question, and then begin to get at what would be the appropriate context and kind of information and, in so doing, try again to articulate where the issues are and some of the practical obstacles that sponsors, individuals and biotech industry

experience. Then, maybe we can get to the end with talking about what database, or what we would require in terms of long-term follow-up in order to be responsive.

DR. RAO: I just wanted one more clarification. So, if we just take an example using something like lentivirus and say that that is retrovirally induced, it is going to persist and the hope is it is going to persist for the life span of the individual in some sense. Then certain long-term follow-up will be covered just by the clinical protocol itself as an individual protocol and we are not going to worry about that as an issue. Right? If this is just a follow-up for unanticipated effects, in some way can we be preemptive in collecting information which might give us clues to what would be common effects across many such viruses or many such drugs?

DR. SIEGEL: Well, I guess there are two ways in which I could look at your question. One, there are issues that are specific to a specific trial and those things that you want to collect for all lentivirus and that is, in fact, what we are answering. There is another issue, and I am not sure if it is what you are asking, is it collected

as a matter of in the protocol or some other matter? I am not sure if that was inherent in your question.

DR. RAO: Yes.

DR. SIEGEL: I guess what we would envision is that if we feel for lentiviruses that it is appropriate to collect information about malignancy for some period of time, at the present point in time we would ask that protocols would include that as part of the protocol. That is the way we, in the FDA, see that things happen. At some future point in time some group may put together some multi-center cohort study and database that deals with that in some other way. You know, we have heard discussions and suggestions about that and, as I have said, we have discussions and lots of different avenues at the same time. So, if you are saying protocol specific issues versus general lentivirus issues, yes, that is what we are focusing on but we would think either issues would essentially addressed in the protocols we would expect to see.

DR. SALOMON: I think what is critical here is that nothing that we do today is going to change the fact that each protocol that comes to

the FDA for an IND and, for that matter, to the RAC for review, is going to be looked at for the specifics of that protocol; for the specifics of that vector class. Things are going to change. There are going to be new technologies that we can't anticipate today. Nobody and nothing we are going to say or discuss now is going to try and change the flexibility of the regulatory agencies to deal with case by case issues now and in the future.

With that said, there are some principles that we need to decide are appropriate, and the principle that is on the table right now is just the simple principle of do we agree that long-term follow-up beyond the current one year after the last dose is generally appropriate? That is the question that I would like to hear from the committee on. If you think, gee, that is obvious and simple then, you know, we can go through this quickly.

DR. CHAMPLIN: I mean, just the precedent of, you know, chemotherapy administration and later the incidence of acute leukemia, in some types of patients it is a 15 percent actual rate that secondary leukemia develops after intensive

chemotherapy of various types, and this occurs usually in a period of a decade. So, clearly envisioning products that damage or rearrange DNA, that is a possible outcome and it would be inappropriate not to be monitoring for that in some fashion. I think the practical issue is how can you do it in an effective way and we will come back to that.

DR. SALOMON: Yes, I promise we will come back to that.

MS. LAWTON: Your question is, is long-term follow-up necessary and I guess I would just come back to I think we all agree that some level of long-term follow-up is necessary, but that comes back to the tier approach and we then get into what is long-term follow-up for the different categories.

DR. KNOWLES: I think long-term follow-up is essential. I think things have changed a lot in medicine over the last ten, fifteen, twenty years. I think the American public is going to demand it. So, I think this is an issue that needs to be addressed.

DR. HIGH: Disagreeing with this is like disagreeing with mom and apple pie. I mean,

obviously for a new therapy like this it is important to acquire long-term follow-up and I would only make the point that as we do accumulate data, so when there is twenty years of follow-up on 4000 patients, then I think the requirements change unless necessary.

DR. SALOMON: I think one thing I promised to the committee -- I promised to myself is that before we are done we are all going to make sure that we have articulated all the problems with this as well. Well, if I don't have anything, then I am actually going to say there is a consensus of this committee that long-term follow-up beyond one year after the last dose of a gene transfer vector is appropriate as a starting principle. Do we need to vote on that? Are we going to dispense with votes today? I just want guidance from you.

DR. SIEGEL: I think if a critical issue comes up and it looks like it would be useful, that might be useful. I think in general, as a general rule, advice is -- you know, votes seem to somehow discount minority viewpoints. People come from different perspectives and you need to hear voices from different perspectives. I am not sure we are really in a voting situation. We might come to a

situation where we are going to have to make an immediate decision and it would be useful for us to have a better record but I don't foresee that per se.

DR. SALOMON: I just want to do things right in the official sense as well. So, the second question is an important factor for determining the nature and extent of follow-up are the characteristics of the vector. I think everyone would agree with that. As well as, when we talk about the vectors, the class of the vector, what kind of gene is in the vector, what kind of disease the vector is being given for, I think we all agree that you can make it very complex.

The FDA has proposed dividing gene therapy products into three tiers. Everyone here is familiar with the general concept of the three tiers. So, let's deal with that next. Does everyone have the three-tier system? So, the three-tier system, tier one is low; tier two, intermediate; and tier three, high. And, I am not going to read the rest of it. You, guys, have it. So, comments on the three-tier system?

DR. SIEGEL: Let me first say we welcome and invite any comments on how the tiers are

defined or used. One particular area where we are really eager to get clarification on, and that relates to the last question, is we thought we heard in November that for the low risk products if a vector doesn't replicate and the cells aren't going to survive so it is really not too much to distinguish from any other types of therapy for which we don't have specific, generalizable concerns about long-term effects. Neither the vector nor the cells containing them are expected to be around for very long except where, as we have discussed, there might be an aspect of a particular protocol that required long-term follow-up, that one-year follow-up might well be adequate.

We went back to the committee to check if that is what we heard and I think we perhaps phrased the question somewhat differently because what went up on the board is something that suggested that such patients would have no follow-up, and I think that made a lot of people anxious. But I think the question we thought we were asking then was if you are in this lowest risk group and if you are followed for a year after the last treatment, which could be many years if it is a recurring treatment and most gene therapy today

there have been short courses of treatment -- if you are followed up for a year after the last treatment, and if you have a vector that falls into these low risk groups, and if there is a specific reason in a specific protocol for longer-term follow-up where that would be implemented, the question is, is long-term follow-up necessary in that group?

Again, I don't want to limit the discussion to that area but we are looking for some clarification. I think we asked different things and we will take full responsibility for confusion, but we are not really sure what we have heard and what we are being advised to do.

DR. SALOMON: Well, my sense of it, just to start this off, is that there are two circles here and I am trying to figure out where the two circles intersect. The first circle is, I feel very strongly, that the FDA, in its approach to this, has to have the flexibility that if approached by a sponsor with a specific vector and a specific trial where there is -- and I am not going to define how that should be because I don't think we can define that here, but where there is really compelling data that the vector or the

gene-modified cells don't survive, except for a very short period of time as, for example, in the case of irradiated cells or in the case of certain vector classes, the FDA and the sponsor should have the flexibility to suggest that there should be no long-term follow-up. That is one circle.

The second circle is this question of a generic public anxiety that extends through regulatory agencies, Congress and the public that the minute you mention gene modification, recombinant DNA, etc., that you have to do something, that that is out of the ordinary. That is the other circle. Richard?

DR. MULLIGAN: Well, I have a radical idea that may seem like we are going backwards but I don't think so. Based on the discussion that we have just had, if I look at the different tiers there may be a way to make essentially one tier -- you know, no tiers essentially. I note that in the high risk the only difference really from category two is essentially an annual physical for five years. I would propose that we talk about why we propose this and why that should be the case, and wouldn't that be something that would fit into a protocol-specific requirement? That is, based on

what you think those issues may be, wouldn't you be likely to have an annual physical? If that was the case and you dropped that, then you really look at all the tiers being comparable except for the lowest tier where, based on this very recent discussion, there is the question whether there should be any long-term follow-up.

So, the radical proposal is you might say that everyone is going to have -- and we would have to discuss what this would be, you know, the clinical question, but whatever that is going to be for anything from the point of view, as I think you articulated, you know again, if something happens to someone who has had irradiated tumor virus vaccine over ten years and has some autoimmune reaction, people are not going to care or they are going to think that it is pretty silly that, you know, the wisdom of the FDA and the group was that this was something sent from those reporting requirements, and that would be silly because, again, things might happen. If we have a system for getting this information and it is an easy enough system, a questionnaire system, then it just unifies the ability to get the information and probably gives us the most valuable thing we could

get from this which is raw info. I think just having info so that people will know that we have been looking for these things, even though we can't necessary articulate what we are going to do with that information or whether, indeed, that information is every going to draw us back to really what happened.

DR. GAYLOR: One thing that may be obvious to everybody already is that almost any late effect -- you know, the first one you won't believe is related to the study drug or vector. It is only when you have observed greatly greater than the expected that, you know, a bell rings in your mind to say, yes, this encephalitis was related to drug X or vector X. So, causality aspects really can only sort of be ascertained in the short term around the time that you are giving the drug, and if you give it and something happens you assume there is a causal relationship. As you get further and further from the exposure other things are going to happen to patients. They are going to get other medical problems and the challenge is to sort out is if that new medical problem is in any way related to the vector. So, almost never will it be obvious that it is unless it is a previously known

association.

DR. SIEGEL: We do have an advantage here though. Given some of the putative mechanisms of long-term effects, if insertional mutagenesis gives rise to a tumor ten years later you should be able to find in that tumor, you know, a clonal insertional site of the vector. You might be able to. Or, if you expect an autoimmune response as a toxicity, you might be able to find in that patient evidence of a response to the gene product.

So, I certainly agree that for the most part, except for very rare -- and this applies to everything we see, all rare events in drug studies, you know, you get one case with a rare event and it is very hard to know what to make of it and you look a little more closely. But in addition to looking for other cases and related cases, we may have molecular mechanisms to look at as well here that may, in fact, even in a single case point to causal association.

DR. RAO: Just in the interest of time, as you said, to move things along discussion, is my sense then correct that there seems to be some sort of consensus, at least for tier, one that there be no long-term follow-up required or mandatory after

one year? Is that correct?

DR. SALOMON: I think we have two things now on the table. One question was appropriately raised by Richard, are the tiers useful and I think we haven't answered that. The second question was what I started with, and that was, you know, these two circles. One circle is that there is a concept that we ought to leave open the fact that appropriately argued scientifically based decision that certain things don't require any follow-up. The other circle is when you say recombinant DNA and gene transfer in the same sentence requires follow-up.

DR. RAO: I thought that it may be useful, because even Dr. Mulligan said that in terms of doing away with the tier system, he would just suggest that there be this one tier which would be this low level tier one which, as you suggested, would give the FDA flexibility to say that this is not something for which you need follow-up. And, he proposed that at least in terms of long-term follow-up we can consider tier two and tier three as one. The difference in the follow-up is just that you have a physical annually. In that case, for long-term follow-up we can consider that as one

and then discuss it separately later. If that seems to be a reasonable consensus, then we should at least say that, yes, we all agree with the tier one idea and say that there isn't any required recommendation for follow-up and move to the next.

DR. SALOMON: That is an interesting way of taking both our questions and putting them together, and we can discuss it.

DR. BISHOP: Yes, I want to make one clarification. In tier two and tier three there is an additional very important aspect that is different in terms of what is required. Tier three, being the highest risk, was modeled upon current recommendations for retroviral vectors which includes a laboratory component to that. There, we felt that at least in the first five years it would be important to this discussion to evaluate whether or not it would be necessary to have this laboratory component. It may be a tissue or may be some blood sampling to be done. Along with that thought, really the discussion at the time that we put this together was based on the current recommendations for retroviral vector studies.

DR. GAYLOR: Maybe another way of looking

at those is whether or not those would be better put in a protocol-specific fashion. It depends what the basis for doing that over the five years is. I would say in the case of retrovirus vector that that is not just collecting random long-term follow-up. That is a real highly relevant, technical issue that I think would be very, very important. I can't conceive of any gene transfer with hemopoietic cells using retrovirus vector that people wouldn't be, over a five-year time period, trying to assess whether or not the vector was still present.

DR. MULLIGAN: What we are talking about today is what the requirements are for those protocols. I mean, this is the way the FDA -- this is their guideline to approve a protocol or give at least advice on the construction of the protocol to be sure it contains these elements. So, it is not like there are two different processes here. This is a process of considering protocols, whether they are acceptable or not and if they need these criteria.

DR. SIEGEL: I would like to address a couple of comments about public expectations, not to address what the public expectations are but the

comment that it is gene therapy so we need to be doing something, just to make sure that at least in the context that we have been viewing this in is, of course, we need to be doing something but we need to be doing the right thing. You can always do more. Not just in the long-term but even in the first year you can say, well, we are only doing blood tests once a month, why not once a week? How come we are not getting electrocardiograms once a week and thyroid function studies once a week? Why are we only getting all the routine blood screens?

So, there are two things that I think one needs to reflect on in making these decisions. If you are talking about not collecting information, it is not a decisions that, first of all, we are talking about decisions to focus resources in those areas that are going to provide the most safety rather than in those areas where they would be less efficiently used.

The other perspective, especially if we talk about long-term as a perspective we have discussed before, and most epidemiologists I have talked to believe, and I think is a matter of common sense, is given the practical difficulties of getting information, especially out many years,

asking for less may in many cases mean getting more. If you ask everybody to come in twenty years later and have blood tests and scans I think most are just going to say no way. If you ask for a one-page questionnaire you are probably going to have more of them return than if you ask for a twenty-page questionnaire.

So, the issues are not so much whether we need more or less safety information but how to get the best and most important information. I just want to make sure we are all on the same page there because I don't think we should feel some compulsion to ask for things that don't make sense. That would be harmful. On the other hand, we need to do the best job of collecting those things that will tell us what we need to find out.

DR. SALOMON: In terms of pages, I think the only thing I would say is you are a page ahead of me right now in terms of my outline for this campaign. I am hoping to get to what it is we are going to demand in the third question, and just get past this sort of concept now of do we go along with the tiers. So, just to focus on that, I know, Katherine, you had a point you wanted to make -- I would like to say two things, one directly along

the lines we have been discussing this morning.

One is, Richard, I personally am okay with this tier system in the sense that I don't think the substance of what you are suggesting is wrong either. I don't see any big disagreement between us. For me, the tiers I think may be useful to the FDA and also the sponsors approaching the FDA, and will also allow, as new information comes along, sort of picking up on something Katherine said, you could move a whole vector class down a tier and that, to me, would be a good thing as well. So, I think just from a practical point of view the tiers have some value, but I don't disagree with anything you said actually in terms of the fact that some of these things should be specific to a trial.

DR. MULLIGAN: I think in the spirit of reducing bureaucracy, I would like to have more arguments why you would want to have the tiers. That is why I am focusing exactly on what is the difference, the relevant difference, and the thing that is in the high tier is something that I would like better discussion of what the rationale for that is.

DR. SIEGEL: I would like to ask some of our FDA scientists to comment about this. What we

are proposing here, the nature of this tier system is that these are, based on the discussions we have had with the committee and our analyses of the system, these are the characteristics of a vector, the ones that you see under high, that would specifically warrant value in general for annual medical histories and archives, that it is those integrating, replicating and so forth where you might want to do that. That is what we want comment on as to whether that is an appropriate linkage. Now, there will be case by case decisions and, while not wanting to get bureaucratic, we don't want to be arbitrary. There is a value for industry and investigators to know what the expectation is before they plan what it is they are going to study and how.

DR. SALOMON: Can I make a point along that line? I am thinking to myself how would this work in practice. So, the way I would see it working in practice, let's say I have a retroviral vector that I was putting into macrophages ex vivo and I could demonstrate that the macrophages had a relatively short half-life, I would then ask, as a sponsor, to have that phased as a tier two study when I came in to do my IND. Whereas, next week we

might be dealing with one that was a retroviral vector or lentiviral vector in a hematopoietic stem cell in which there would be no question today that that would be tier three, but maybe five, ten years from now we could get rid of the tiers because they would collapse on each other. So, that is the value I see in the tier system.

DR. MULLIGAN: I don't see that. This question comes back to this issue of what should be dealt with in the individual protocol, and I am not sure I see why the specific cases that you made wouldn't be in the protocol. So, I am not seeing the generic kind of global issues for this particular point, that is, the five-year annual physical for these particular cases. I don't see that they are particularly distinguishable. I don't have a good sense of why that would be particularly necessary as a generic requirement as opposed to a case by case within a protocol requirement. That is, if you thought that there was something about the macrophages that was different than the stem cells, in the protocol you would probably want that addressed, and I would think the FDA would view the protocol and see a difference between the macrophages or the stem

cells. But, in fact, according to this thing the macrophages would be considered a tier three. Right? That is, if you are not irradiating the cells and using a retrovirus, and you are putting these into patients, even a cell with a short half-life would be considered a tier three.

DR. SALOMON: That is fair. I guess my point here was to give some flexibility that that could be a tier two but, I mean, you are right. If it turns out that in doing it this way we complicate things, then I am also not for it. So, that is the kind of discretion we need to have. Katherine?

DR. SIEGEL: Before you do that, because I think this is important because part of the question you have raised in your last two or three comments is an important one, which is why not just do all of this on a case by case basis based on good scientific judgment? And, there are attractive reasons to do that, but there are important considerations for why we would seek general principles and general guidance, if not general rules that are inviolable, and that is, first of all, people who are planning to do research, whether are commercial sponsors or

academicians, benefit tremendously from having advance knowledge of regulatory expectations. If you know when you are designing a protocol or seeking a grant or funding a research study, or whatever, that you are going to have to bring patients back and archive specimens and examine them for five years you have a better idea of what your costs are and whether or not you are willing to do that. So, it is a lot easier for people to pursue research in an efficient manner if they have some general idea of expectations.

A second reason is that when we don't put out those general principles that we work from there is often a perception, whether correct or not, that we are being arbitrary and capricious. We say we think your study requires five-year follow-up and they say, well, the guy down the hall doesn't require five-year follow-up. Why is that? And we say we can't tell you; that is confidential information. You know, they may do a different study with their irradiation machine or something. Frankly, it also is a more difficult job for us to ensure that that doesn't happen, to ensure consistency. Then if we have guidance, it would serve not only sponsors but ourselves.

Finally, it helps you understand what is in that database that you have accumulated. While there may always be exceptions, if you have a database that in general has these sorts of data on these sorts of protocols, then when you go back to analyze for incidences or occurrences, or whatever, you know that that is what is there.

So, those are some of the reasons why, although from a scientific perspective it would always be best to try to just say, well, let's deal with each one in the most appropriate way as it comes, there are advantages to try and spell out general rules, not to mention, of course, the opportunity to have public discussion, which is hard to do when everything is simply done on a case by case basis.

DR. MULLIGAN: But I think what we are trying to do is separate the kinds of information, and we are still having trouble. I mean, there is confusion. Just from what you said, you know, sponsors will want to know what kind of archival sampling but, I mean, I think that should be built into the scientific and medical review and separated from -- I think this is why we have been doing this for such a long time, we haven't

articulated a real distinction between that and the murky stuff that might or might not be put in a clinical protocol, and I am just saying that one way to do that is to make sure it is very clear that the long-term follow-up information is different. Still, based on the years of talking about this, you obviously have a lot more guidance based on all the discussions you have had about the clinical protocols and what might go into individual clinical protocols.

But I think that is the key to resolving this, separating as best we can those two classes of info. Otherwise, we are worrying about how to collect the information that probably should be in a clinical protocol in this long-term follow-up. I am just trying to set the stage so we get to the point of talking about what information we want and don't get confused with, oh gee, we can't get this information because it is too complicated; we can't be tracking these patients and getting samples for twenty years, and so forth.

DR. SIEGEL: The two classes of information you are referring to are?

DR. MULLIGAN: The information that I would say is more medical, scientific long-term

follow-up, things that are more technically directed to a protocol, issues like retrovirus, integration, persistence, from, I would say, the value of the long-term follow-up, we will come down to eventually, has to be just collecting raw information, keeping track of gene therapy patients and make it very, very simple. At the end of the day we will want to keep track of these patients. We will want to identify things that happened and it will undoubtedly be in an unorganized fashion. It will have to be, but there is greater value to it.

DR. HIGH: I would just say that actually I agree with the points that Dr. Mulligan made and it might be useful to collapse the intermediate and high tier groups. When I look at the field, it seems to me that the way most clinical trials are structured now, one does elicit information on short and medium term consequences of the intervention.

What is really lacking in the field are data about long-term consequences of the intervention, and what would be most valuable I think to all of us in terms of eventual licensing of products would be to begin to collect

information about long-term consequences, and the information we need I think could really be acquired through a simple questionnaire rather than -- I don't see the purpose or archiving samples and doing annual physical exams between one and five years. I think it is much more important to collect data out through twenty years, very simple kinds of information that is just essentially patient follow-up.

DR. SALOMON: Good. Let's go back to a question that I think we can't go forward with this discussion until we answer, and that is, are we agreeing that there are going to be cases that don't require any long-term follow-up?

DR. CHAMPLIN: I guess I have been bothered a little bit by this. I would like to say yes because we would all like to simplify matters, but the question is can you be truly sure that a non-integrating virus doesn't have a small fraction of integration going on? Or, if you are treating macrophages, you know, 99 percent macrophages, that the one percent stem cells that are in your preparation aren't going to transduce? So, even when the objective might well meet the tier one objective, is the reality of the manufacturing of

those cells totally safe in terms of the potential for long-term consequences? I would like to be assured that that would be the case and that we could do things in a simplified manner but I am just uneasy that that is truly possible.

DR. GALORE: I am probably getting ahead of the question here, but follow-up doesn't have to be an all or nothing situation. We could do a sample of 200-300 people and do physical exams on them, and depending on what we see there we may decide to increase that sample size or we may decide to discontinue physical exams. So, it doesn't have to be all or nothing. I think we can make use of sampling.

DR. SALOMON: Okay. I guess the reason I am pushing this, and I could be wrong, is that if we agree that everything needs long-term follow-up, then there is no tier system. Right?

DR. MULLIGAN: I would agree with Dick. I have to agree with him that if the level -- well, just what you said that basically even with a non-integrating virus I think it would be ridiculous at this point to say that we can predict that there would be no reason to collect this. And, if you make the eventual question very simple,

or whatever, then it is not an impediment to have that information and it would be inconsistent with the concept not to include all gene therapy activities.

DR. SALOMON: Okay, that is a clear statement. So, taking my two circles, that could bring the two circles together. So, we have two things on the table still, but progress. It is really I think up to the FDA staff at this point to tell us what they think of the three-tier system in the context of the conversation we have already had this morning.

DR. SIEGEL: Well, I guess I hear mixed opinions. I certainly hear some subset quite concerned about the notion that there is a group where if you have one-year follow-up, you would be comfortable just to do one-year follow-up. I think we could target not too complex follow-up beyond that on that group. Although I certainly heard opinions to the contrary, I think that is something that we can work with.

One of the areas I am still seeking more input on for the tier system is the implication between tier two and tier three, and as I read this -- although, again, I would ask the experts who

devised the system to comment or elaborate or correct, some of this, it seems to me, was driven in part by a desire for samples and that, in fact, the issue of whether somebody is viremic, has an immune response or has an insert for some of these classes of viruses, even if they are doing well, whether they have those things going on over the first few years may be important information to have, particularly if they develop toxicity later on.

I have not heard this but I am reading between the lines that, to some extent, there is probably a thinking that if you are going to bring somebody by for a sample, rather than just send them a questionnaire, you might as well examine them and take a medical history while they are there. I don't know what drove what there, but I guess having heard some comments that seem to allude to whether there is a difference between these high and intermediate risk categories, one thing that might be worthwhile focusing on is while they are, in fact, high or weak, overestimating the potential value of getting samples beyond the first year in some these cases, or are we saying it should be in all cases? Bringing patients back, I

think we all agree, is a bigger endeavor than sending questionnaires. Philippe, do you want to comment on that?

DR. BISHOP: I think that when we initially envisioned this three-tier system there was a notion that there would be vector characteristics that would present a higher risk in the long-term for these subjects. The notion that coming in to the clinical institution where the expertise lies where, indeed, there is going to be a specimen collected, maybe a physical examination and maybe a directed interview of the patient by the experts that are well aware of what is happening in the field would have some value.

So, I think in terms of trying to identify flags or signals that a certain strategy or gene transfer may represent a long-term risk, we thought that certainly the clinical centers where this took place would probably be the best suited to recognize those signals. Hence, the physical exam and the direct patient-physician contact that would take place at the same time, maybe an archival specimen would be collected which could have some value for the reasons that Dr. Siegel outlined.

DR. SALOMON: So, that we be a tier three.

You are making the argument for why tier three would be different than a tier two.

DR. BISHOP: Tier three, and we felt, based on discussion that this committee had and the advice, that maybe the concerns would not be as great beyond the first five years, especially when it comes to autoimmunity and maybe hematologic disorders, although malignancies and neurologic disorders could occur much later, but most likely these would be captured in the questionnaire and would not necessarily necessitate the level of expertise that the physician at that center may be able to provide.

So, that is the distinction between tier two and three, tier three being the highest risk and maybe requiring that within a certain period -- we picked arbitrarily five years; I don't know if that is a correct number for follow-up, maybe a year is sufficient. I don't know. But we picked that, number one, because we thought that this could potentially be manageable and doable, and would probably provide the most specific information.

We had entertained at some point, if all gene transfer products needed to be monitored,

maybe combining tier one and tier two. However, I think we had heard the committee here previously expressing a need to have the flexibility that you articulated for us and, therefore, we were uncertain after the last meeting whether or not we had heard you correctly and whether or not we really needed to leave tier one intact, or whether or not we needed to combine tier one and tier two, again, tier two being just the clinical questionnaire as being a useful tool here. All of that, of course, was a thinking exercise for all of us and certainly your comments are appreciated.

Carolyn, do you want to address maybe some of the value of sampling, especially as we understood it for retroviral vectors and how that may apply to the high risks?

DR. WILSON: Yes. I am Carolyn Wilson, Center for Biologics. I wanted to give a little bit of a historical background of how we got to this particular recommendation. Actually, to go back to almost ten years ago, 1993, after the Donahue report came out there was a letter that was issued to sponsors that actually asked for lifelong follow-up of all patients who were treated with products involving retroviral vectors, and that

lifelong follow-up involved active obtaining and testing of samples for evidence of RCR infection and we recommended that three different methods be used, serologic, PCR methods and infectivity assays.

It became evident very shortly that that was a very onerous burden on sponsors to fulfill that particular request. So, back in '97 and '98, starting sort of in 1996 and 1997 actually, I think it was, we were having FDA-sponsored gene therapy forums, and in those forums we were having sessions to address those concerns with the guidance at that point.

We had proposed one of several different options regarding how to scale back that kind of lifelong follow-up for patients in retroviral vector gene therapy trials, and we were focusing again primarily on the issue of RCR and the clinical manifestations of the potential infection by an RCR. We felt that if testing during that first year of follow-up was all negative, one potential would be that you wouldn't do any additional physical examination but that you would do just data collection but not archiving of samples.

Interestingly enough, during the discussion, because we had an extensive panel discussion with extensive input from audience members, there was a strong feeling that people weren't ready at that point to give up archiving of samples, at that point. So, this was really sort of a compromise position between not doing anything past the first year if all the of the RCR testing was negative and doing everything lifelong. So, I don't know if that helps the discussion.

CHAMPLIN: Is there experience now with archiving all that dead tissue that has been worthwhile in any way? Have you find evidence of persistent virus that would then be meaningful?

DR. BISHOP: In November I think I presented to this committee some of the limitations that followed an attempt by sponsors, and I think there were legitimate attempts by most of our sponsors to comply with the guidance, and we presented an outline, and it was a pretty long outline, of the limitations that were identified in the course of a survey. We attempted to contact almost everybody that was doing retroviral vector studies at that time. So, I think that conclusions in terms of the value of having done that are

difficult to state because I think there was a lot of information that had not been collected that precluded us from really knowing whether or not there was any value to this exercise.

But there was a general sense from almost everybody that had this been done, then maybe today we would know and we would be in a better position to make statements, more definitive statements about whether or not this was a valuable exercise.

In addition, I wanted to come back to one comment that Carolyn had made, which is the collection of specimens and archiving them, one of the values of doing this is in the course of following individuals three years following gene transfer studies who develop an autoimmune disease, we now have yearly archival that has occurred where you can go back and start looking at whether or not antibodies have become apparent, or there was maybe the presence of viremia. So, I mean there are various studies that can be performed that, at the time of collection may not be obvious that would be extremely valuable once a particular clinical disorder had been recognized.

DR. SALOMON: Yes, Doug Jolly?

DR. JOLLY: My name is Doug Jolly. I work

for Biomedica [not at microphone; inaudible] ... respond to the gentleman's question [not at microphone; inaudible] ... HIV infection and [not at microphone; inaudible]... in the final go-around we had 250 patients approximately from two HIV trials and we tried to do follow-up for three years, three to five years out from the initial start of the trial, and we got about 66 patients out of the [inaudible; not at microphone] ... which is about 25 percent of patients.

I guess I would agree with what Dr. Mulligan was saying, that I think for those kind of protocols [not at microphone; inaudible] ... not too much to worry about. [Not at microphone; inaudible]. So, I would say that you really have to look at the clinical experiment to try and categorize the [not at microphone; inaudible].

DR. SALOMON: Can you enlighten us on the reason why out 350-some patients you only go, I think you said 64?

DR. JOLLY: Yes, 250 patients.

DR. SALOMON: But why? What happened to the others? Why didn't you get follow-up on the others?

DR. JOLLY: Because the way that trial was

run [not at microphone; inaudible] ... cystic fibrosis patients there are not particular centers where it is common to follow [not at microphone; inaudible]. These are patients that were recruited at various sites referred from other physicians, and so just the whole process to find these patients again is much more complicated ... [not at microphone; inaudible].

DR. CHAMPLIN: If we are getting into practical issues here, sort of doing annual physical examinations at the treatment center for five years becomes a very difficult thing to actually accomplish. We try to do this with our bone marrow transplant patients and the fall-off is just dramatic even after the first year. So, if what you really want is blood samples. You can get that without the patient having to fly across the country to come to the treatment center, and it is good to have some sort of organized interview by a physician to collect interim history and medical information and potentially get a chemistry panel to check for creatinine levels etc. that might not be symptomatic in the patients if they had mild renal insufficiency for example.

But I wouldn't necessarily think they

would need to return to the treatment center to do that. So, one would need to have in a protocol physician examination, perhaps laboratory studies and if you want samples, have samples sent but not require them to return to the treatment center.

DR. SALOMON: If we want to have a break this morning before lunch, this would be a logical time to take a ten-minute break and then come back. I think that would be good, just in terms of everyone having a chance to break for a second and come back. So, ten minutes.

[Brief recess]

DR. SALOMON: Thanks, everybody for coming back to the table. You never know with these breaks how long they will take; I always have this fantasy that they will be ten minutes. So, I thought we would try and see how much we can get done between now and 12:30. That is an hour, and then break for lunch.

So, just trying to restart where we left off, it seems like one big step to take right now would be to come back again to one of the primary questions, and that is can we -- you know, option one, there are no gene transfer protocols today that the committee believes should be exempt from

long-term follow-up as has been defined.

Option two, there are some possible gene transfer clinical trials that should be exempt and we are not trying to define exactly what that should be yet. Can we deal with that because depending on whether we agree with option one, there are none that are exempt, then we can just agree on that and move forward? Then I would like to come back to sort out finally this tier thing.

DR. RAO: I think it is more like option two, that there are some trials where there shouldn't be necessarily an absolute long-term reporting requirement.

DR. MULLIGAN: I vote option one, that there are none that shouldn't have long-term follow-up. By long-term we mean longer than one year. Is that what we are talking about?

DR. SALOMON: Yes.

DR. CHAMPLIN: I voiced earlier that I wanted to be reassured that both the manufacturing as well as the concept was consistent with the goals of option one and that there was truly no potential for long-term toxicity, so I think the onus is on the sponsor to demonstrate that. Perhaps if you think that there are some that would

meet those criteria, you know, you could describe those types of studies that would meet those criteria.

MS. LAWTON: I would just like to comment that as far as, you know, if it is decided that everything needs long-term follow-up, that is fine but we also need to look at where is the highest risk that we want to try and collect information and understand, and the practicality of all of this is a huge issue and I don't want us spending a lot of time trying to collect long-term follow-up on those very low risk things and, therefore, not getting the information in the high risk areas where we really want to focus. So, that is the only comment I would make.

DR. SALOMON: Any comment on that to try to give us what your sense of the public would be?

MS. KNOWLES: Well, I wrote something down here earlier this morning during our discussion, and this is probably something that is not going to be taken very well but it sounds like in some senses FDA needs to redefine research protocols to include long-term follow-up at the front end of those protocols so that it is part and parcel of the research protocols. The sponsors know about it

up front and there is no discussion. It just happens.

DR. SALOMON: Well, I think that is definitely the premise of all of this, that we would define a type of long-term follow-up that would be applied, and would be up front, and would be applied to all protocols to the extent that those criteria --

MS. KNOWLES: Excuse me, I am not talking about just gene therapy. That is why I say it is probably not going to be well received, but I think it is something that should maybe considered at some point in time.

DR. SALOMON: Well, I think everyone would realize that it is beyond the purview of this committee to comment on any other committee's area or any other FDA activity, but I certainly think that that is now on the record.

Dr. Patterson, I don't want to put you on the spot but you have a very important role here in terms of not only your expertise in the area but your liaison with the recombinant DNA advisory committee. Can you give us some sense of where the RAC is on this?

DR. PATTERSON: Well, I think since the

inception of this field the NIH and the RAC, in concert with the FDA, has underscored the importance of long-term follow-up. I think as an agency, its mission is to advance knowledge in order to promote good health and it is incumbent on us to try to get information that is pertinent to the safety and progress of this field.

I think I have said before each of the other times the committee has discussed this topic that I think that the FDA is to be commended for the steps it has taken so far in trying to outline a paradigm for long-term follow-up, as has this committee. I want to stress that we think that there needs to be a broader consultation process before the final lines and characteristics of this framework are put in place. That consultation should include I think not only patient advocacy groups and communities, but it should also include people and agencies, such as the CDC, with expertise in surveillance studies and long-term follow-up so that twenty years from now we have data that is both scientifically valid and statistically useful, and is as least burdensome in the collection process as possible. So I would hope that this is a very important pivotal first

step to a longer-term process.

I also realize, in reading the briefing materials, that there is mention, particularly for the autoimmune diseases, about the possibility of having some of these conditions become reportable diseases. That is a process that involves the CDC. That is a longer-term process. I know that colleagues at the FDA recognize this.

I also think, in addition to the tier approach we may want to think about a phased approach to long-term follow-up. What is the short-term fix to long-term follow-up? What can do we do right now? What can we put in place now versus in the longer-term? What regulations may be needed? What changes in the local and state health departments for reporting diseases are needed? That is a longer-term issue that is going to require a much wider dialogue than what is happening here, important as it is, in this room.

DR. SALOMON: Thank you. I certainly think I can speak for the committee in saying that we would very much welcome additional discussions outside this committee. I think as you have had to come back three times to this committee to get us to this point reflects the fact that I don't think

anyone here feels that the complexity of this issue, and its impact on so many different groups with so many different kinds of interests, can be adequately reflected by anything we accomplish today or, you know, in the last two meetings. So, I agree. Do I speak for everyone? I think we would love additional consultations, and I think that is implicit in any advice we give today.

DR. CHAMPLIN: To say the obvious again, long-term follow-up is easy to say but it is very, very, very hard to do, and it is very hard to get information. It is hard to get information that is interpretable. Just thinking about, you know, if you have a questionnaire and somebody says, "I have kidney problems" and sends that back to you. How do you score that? Do you call them? What sorts of things do you do to sort that out, glomerular nephritis, bladder infection? So, you are going to get just reams of data that are going to be very difficult to interpret, and this is really going to require enormous resources in personnel, in time and computer systems and effort to sort it through probably for very little gain in the end. We hope, in fact, there are going to be few, if any, long-term adverse events and it is just an enormous

undertaking to try to be sure of that.

MS. LAWTON: I was just going to comment that that is assuming you can find those patients.

DR. SALOMON: So, trying to move this forward, what I have heard so far this morning is -- trying to seek kind of minimum consensus here -- everybody agrees that not all vectors are created equal and that we all agree with the basic concept that there is an array of relative risks for long term. But having said that, I also sense that rigidifying that in a tiered system is something we are probably not really comfortable with.

I think to move this field forward, I think what Amy suggested for the first phase would be that we have so far agreed with the concept that long-term follow-up beyond one year after the last dose of the gene transfer vector is appropriate. That is an important start.

Secondly, I think there is a general sense today that probably all gene transfer vector clinical protocol patients should be followed long term. I am not going to tell you that that is fifteen or twenty years yet. We will get to that in a minute, but there ought to be some tracking of those patients, albeit all of us are concerned

about what that will entail, and we feel that is a reflection of concerns from regulatory agencies, Congress and the public.

Perhaps if one agrees then that all should be tracked, in the future we can use that data and come back to this so that this is, as Dr. Siegel instructed us at the beginning, only our best advice for today and not necessarily for all future time, that we could agree that the tier system per se doesn't add anything and it would be just rigidified interactions. If everyone has to have some form of long-term follow-up, then we can basically not try and stick to specific vectors without repudiating the basic concept that there are going to be relative risks that will increase with certain kinds of trials and that that should be dealt with on a trial by trial basis. Can we have some discussion of that? Can we get there? Have we gotten that far?

MS. LAWTON: Can I just ask a question? Then, if we agree that we need long-term follow-up, are we willing to have a discussion around what we think is a minimal of the data that we need to collect, and then that the additional things is what is out for further discussion?

DR. SALOMON: I think that is critical. So, what I would suggest that I can be comfortable with -- again, this is just to start the discussion -- is affirming that we need long-term follow-up; creating a framework that is generic enough to cross all different kinds of trials that come forward that would satisfy, in phase one, what I think are critical issues. One is I just can't see burdening this field with such a financial involvement based on just this sort of major thing -- everybody needs follow-up -- that it just decreases the ability to do gene therapy and move this field forward because that is the last thing this field needs right now. But, at the same time, we need to be respectful of the fact that there are a lot of unknowns in this new technology and do that as well.

So, I am thinking that what we could deal with in the next half hour or forty-five minutes is what this committee feels would be the phase one, what everyone should get, and then if you want to do, you know, brain biopsies yearly on a specific trial that is between you and the sponsor on that trial and that didn't come from this committee.

DR. SIEGEL: I guess I would also like, in

light of Alison Lawton's question and some that we have, rather than accept -- you made a comment that while the tier system sort of becomes irrelevant everyone needs follow-up, but her comment was, and our approach and thinking has been that even if everyone needs follow-up attention ought to be focused on those areas of greater concern, which could lead to systems where there was either more frequent or extensive data collection based on certain factors, or whatever, and I would like to, you know, keep that on the table for discussion as to the merits of that sort of approach.

DR. SALOMON: I guess what I am trying to get at, and I am just testing the water in a way, but what I am trying to get at is affirm that the principle of long-term follow-up is there; affirm a framework for long-term follow-up that we feel could be applied to anyone in the gene transfer protocol, with the implicit advice to the FDA that the protocol details should then be left between the sponsor and the FDA staff. Then, we could finish by discussing more generally principles for that long-term follow-up, which we already have and I think there has been tremendous progress. So, that could be the last thing we do. You know, if

you want to do details, here they are. But that way at least I think the committee could get to a point where we move the field forward. We affirm, we gave a general concept, we didn't kill the field -- not to be too dramatic but I am just really scared of that. So, we could be practical, move the field forward and also give you good advice. That is what I am hoping.

DR. MULLIGAN: One thing is that we are not getting rid of the tier system but, I mean, we have spent a year talking about the tier system and I think that the concepts and principles are very sensible. So, it is a question of whether to incorporate the tier system organizationally into the formal long-term follow-up. So, I think we do agree; there is some consensus about what diseases, what applications require more or less and I think we are saying we don't want to stick that into the formal long-term follow-up because of all the issues we have discussed over the last hour or two. But I think that all of those principles are very reasonable and there probably is a consensus, or we could get at some point to a consensus on the tier principles. We probably did that several months ago.

DR. SIEGEL: Right. The tiers came out in the November discussion to try to incorporate those principles. What you are saying is you endorse the principles but it is hard to be too highly prospective and specific about exactly how to use them. I understand that. I made the case for why there is a lot of advantage to trying to be prospective and give guidance on how they are used. But I hear what you are saying.

DR. MULLING: But the other message, certainly my message is that I think there ought to be a very deliberate incorporation of some of these principles into the actual product review. That is the other part of this, a kind of a different way of thinking, that those things that are most of most concern to people that are bringing up issues, taking samples for the first five years -- you know, we maybe ought to be thinking a little differently about those.

DR. SIEGEL: Just to clarify further in terms of the way you set the goals for the end of today, surely, basically it is feasible but I question setting them too low, and there is some consensus there needs to be longer follow-up because where are we in the process? That is, I