FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Meeting of:

BLOOD PRODUCTS

ADVISORY COMMITTEE

87th Meeting

Open Session

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P R O C E E D I N G S (8:04 a.m.)

Agenda Item: Welcome.

MR. JEHN: We would like to welcome you all to this 87th Blood Products Advisory Committee meeting. I am Donald Jehn, the executive secretary for the meeting.

Today's meeting is open to the public until approximately 3:30 p.m. At this time, I would like to have the committee members go around the table and just introduce themselves briefly, giving their name.

[Introductions made around table.]

MR. JEHN: Thank you. Before we begin, the committee members not in attendance today will be Dr. Quinn, Dr. Szymanski and Dr. Manno. Again, I would like to thank you all for attending this meeting.

Dr. DiBisceglie actually is a new member for his first time here at the meeting.

At this time, I would like to have Dr. Allen and Dr. Epstein come up to the podium here.

DR. EPSTEIN: Jim, it is my bittersweet pleasure to award you a plaque in honor of the service that you have rendered to this committee both as a member and then as a chairperson, from February 2002 to September 2006. It seems like only yesterday.

I just want to express the thanks for the Food and Drug Administration to you for this generous service on

your part.

You have set a high standard as a chairperson and we are very grateful for all the effort that you have put into this enterprise on behalf of the health and safety of the American people.

To a certain extent, it is premature to give you a plaque first thing in the day, because we still have a meeting ahead and we are not through with you yet, Jim. Again, our very sincere thanks.

[Applause.]

MR. JEHN: thank you, Dr. Epstein. Before we start with the meeting, I have a conflict of interest disclosure statement to read.

The Food and Drug Administration, FDA, is convening today's meeting of the Blood Products Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972.

With the exception of the industry representative, all members and consultants of the committee are special government employees, SGEs, or regular federal employees from other agencies, and are subject to the federal conflict of interest laws and regulations.

The following information on the status of this advisory committee's compliance with federal ethics and

conflicts of interest laws, including but not limited to 18 US Code, section 208 and 21 US Code 355(n)(4), is being provided to participants in today's meeting and to the public.

FDA has determined that members of the advisory committee and consultants to the committee are in compliance with the federal ethics and conflict of interest laws, including but not limited to 18 US Code Section 208 and 21 US Code Section 355(n)(4).

Under 18 US Code 208, applicable to all government agencies, and 21 US Code 355(n)(4), applicable to certain FDA committees, congress has authorized FDA to grant waivers to special government employees who have financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest, section 208, and where participation is necessary to afford essential expertise, section 355.

Members and consultants of the committee who are special government employees at today's meeting, including special government employees appointed as temporary voting members, have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their employer, spouse or minor child, related to the discussions on July 13 of

topic I, a product approval discussion and recommendation of the safety and efficacy of hepatitis B IGIV for the prevention of recurrent HPV disease, after orthotopic liver transplantation, sponsored by Nabi Biopharmaceuticals, and topic 2, a general matters discussion, an overview of the research programs of the laboratory of bacterial, parasitic and unconventional agents, division of emerging transfusion transmitted diseases, office of blood research and review.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda also includes updates on various topics. In accordance with 18 US Code Section 208(b)(3) no waivers were required for the discussion on July 13.

In addition, there may be regulated industry and other outside organization speakers making presentations. These speakers may have financial interests associated with their employer and with other regulated firms.

The FDA asks, in the interests of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. These individuals were not screened by FDA for conflicts of interest.

Dr. Louis Katz is serving as the industry rep

acting on behalf of all related industry and is employed by the Mississippi Valley Regional Blood Center. Industry representatives are not special government employees and do not vote.

This conflict of interest statement will be available for review at the registration table. We would like to remind the members and consultants that if the discussions involved any of the products and firms not already on the agenda for which the FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that you may have with any sponsor, products, direct competitors and firms that could be affected by the discussions.

Thank you. Right now I will turn it over to Dr. Allen, the chair.

DR. ALLEN: Thank you, Don. I just want to note that there will be a quiz on the applicable CFRs before we break for lunch today. So, be prepared.

We have got a busy agenda this morning. We are going to start with a number of committee updates. The first will be a summary of the May 9-10, 2006 meeting of the department's advisory committee on blood safety and

availability by Dr. Holmberg. Welcome.

Agenda Item: Summary of May 9-10, 2006 Meeting of the DHHS Advisory Committee on Blood Safety and Availability.

DR. HOLMBERG: Thank you, Dr. Allen. Also, I would like to comment from Health and Human Services, and thank you for your services over the last year.

The important information that comes from the BPAC and goes up through the department is very critical, and we thank you very much for your service.

The advisory committee for blood safety and availability addressed an issue at the May meeting as far as what the strategic plan should be for the upcoming years.

One of the things that we catch ourselves in very often is the idea of where are we going. Very often, not only in the government but also in private industry, there has to be some sort of a realignment of priorities, and also the direction of different people.

One of the things I learned when I was in the private sector --and I realize I have a colleague in the back of the room that knows probably what this really means -- but poshun(?) is a Japanese word that means going in one direction, sort of like a compass point.

That is the whole idea, is to try to move blood

safety and availability together in one direction. The goal of that is obviously for blood safety. We also know that, with availability, if the blood is not available, then it is also a safety issue.

As you all know, Secretary Thompson resigned over a year ago and Secretary Leavitt was confirmed to take his place.

One of the things that Secretary Leavitt put together was a 500-day plan, a 500-day horizon. His comment to the department was, the President of the United States has given me a clear mission, to help Americans live longer, healthier and better lives, and to do it in a way that protects our economic competitiveness as a nation.

Secretary Leavitt put together actually some vision statements and visions that he saw the department going in and that he would like to see us accomplish.

There were quite a few different guiding principle for reaching those various missions. That is, first of all, the care for the truly needy, foster self reliance, national standards, neighborhood solutions, collaboration, not polarization, solutions that transcend political boundaries, market before mandates, protect privacy, science for facts, process for priorities, reward results not programs, change a heart change a nation, and value life.

There are six elements of the plan. First of all, to transform the health care system, to modernize medicare and medicaid, advance medical research, secure the homeland, protect life, family and human dignity, and improve the human conditions around the world.

So, the question at the May meeting was, how does the blood safety and availability complement the Secretary's 500-day plan.

One of the things we do in my office -- and I say office with a small o because I am in the office of public health and science in the office of the Secretary, but blood safety and availability is responsible for convening groups and obtaining consensus on issues.

For instance, in collaboration with FDA yesterday we had a very good workshop on malaria and trying to convene people together to be transparent in a lot of our thoughts, and also to develop policy and also products.

The first part of the plan was, what can be done to improve blood safety and availability as part of transformation of the health care system.

First of all, the committee felt that we really needed to have strong guidelines and direction as far as process for policy.

We also needed to look at what were transfusion practice, donor recruitment, retention, and a big one that

we have been talking about for years and we feel we are behind the power curve when it comes to looking at other countries, especially other developed countries, is where are we with biovigilance.

As you see, it is biovigilance, not hemavigilance. Hemavigilance, a lot of the developed countries have undertaken hemavigilance to look at just the blood system.

We see it not only being the blood, but to be broader than the blood, being biovigilance to include organs, tissues, progenitor cells included in that biovigilance.

The next issue is, what can be done to modernize medicare and medicaid as it pertains to blood safety and availability.

Dr. Sandler is in the audience here and he is one of our committee members. He represents the hospitals. Primarily, one of the things that we hear all the time is the reimbursement issues.

Definitely, with modernization of medicare and medicaid, with the medicare modernization act, there have been significant changes.

Even as I speak this morning, there are plans later today to have a hearing at Ways and Means Committee on the part B plan of medicare, the MMA, and especially

looking at the average sales price for various drugs and pharmaceuticals, such as the IGIV.

So, the committee looked at the reimbursement issues. I must say that what we did was, we actually had working groups break down.

We closed the meeting actually during the meeting and had working groups then convene to work on each one of these issues to come up with thoughts.

Advanced medical research, what research needs to be targeted to improve blood safety and availability. One of the things that was very interesting about even the committee, the working group, I should say, but a working group that addressed this issue, was that several members of the committee were also part of the NHLBI strategic planning the day before.

So, we really got some good input as far as what NHLBI was doing, and also some of the blood priorities that were being set forth with NHLBI.

I have to say that NHLBI, although they are not officially represented on the committee, they are in the audience at every one of our meetings.

So, they do hear where the blood community is going and looking forward to different research aspects of that.

The committee really felt that there needed to be

prioritization funding for promising new technologies and also a strategic research agenda.

Secure the homeland. You know, every time we do have a disaster, especially after 9-11, we learn more and more.

As I tell people with Katrina, from lat year, there was enough that everybody could take blame. I like to say, instead of taking blame, let's take responsibility for what happened or didn't happen.

So, really, what this working group did was look at the integration of the blood plasma system into the public health infrastructure.

Because we do not have a nationalized blood program, we do have a private heuristic approach to supplying blood within this country.

So, therefore, blood is really not a critical infrastructure, but it is a critical element of the health care infrastructure. Also, what we looked at was risk communication and disaster planning.

One of the issues that the committee had not identified back in September of last year when the elements of the strategic plan were put together, were improve the human conditions around the world.

I must say that, although this is not officially part of the strategic plan as proposed by, or recommended

by, the advisory committee for blood safety and availability, one of the things is that we are very involved in trying to improve conditions around the world, especially in the developing countries.

One good example of that is the activity that Health and Human Services and also the State Department is doing with the PEPFAR in Africa and the Caribbean.

So, what is the process that we move forward? Firs of all, we have to draft a strategic plan. We have the various elements of the plan, a lot of critical thinking that has gone into the plan.

Now we have to put it into words and we also have to draft a tactical work plan, and this will be re-submitted to the committee and then submitted to the Secretary and then we will implement it.

Now, what is the time line on all this? I can't tell you right at the present time. Like everything else, we have a lot to do with very little sources.

So, we are moving ahead on this and hopefully in the net couple of months we will be able to present something to the committee and have the committee look at that. Thank you very much.

DR. ALLEN: Thank you, Dr. Holmberg. Questions from the committee? Okay, thank you, Dr. Holmberg. We will move on then to our second presentation which is a

summary of the July 12, 2006 FDA workshop -- that was yesterday -- on testing for malarian infections in blood donors, by Dr. Kumar.

Agenda Item: Summary of July 12, 2006 FDA Workshop on Testing for Malarial Infections in Blood Donors.

DR. KUMAR: Thank you and good morning. This workshop happened yesterday. So, I was trying to work on this last midnight. So, I hope you will bear with me if it is not very organized.

As you see here, we called for this workshop on testing for malarial infections in blood donors. Just before I get into that, I think a little bit of background is in order.

As I said, it is a little bit disorganized here. So, I will jump two slides and then come back here. So, some background here.

The incidence of transfusion transmitted malaria in the United States is at an all time low. We get about one case every other year.

Also, currently, there is no laboratory test that could be used to screen blood donors for malarian infections. So, how do we protect the blood supply from malarian infections?

It is done through donor deferral policies, based

on the travel, residence or history of malaria of prospective donors.

In the process, we do lose a lot of donors. There are approximately 150,000 people are deferred every year, donors deferred every year.

So, now efforts are being made on how to make it better. So, we have various screening tests available. So, we started looking around recently. There are good reasons why we don't have available tests. We will go into that in a second.

Before we go into that, some European countries and Australia in the last few years, have started to test deferred malarial by an ELISA that detects antibodies to only two of the four malarial strains.

I would like to remind you that, in this country, at least in the past, we have found all four species of plasma malaria.

So, briefly, in the United Kingdom, individuals who had malaria or a history of prior residence in endemic countries, are deferred indefinitely.

That is in the absence of this test. Now they cannot donate blood once they have this class. All prospective donors are deferred for one year.

So, basically, travelers are deferred for one year. Then they are tested with this ELISA and, if they are

negative for antibodies, they allow them to donate blood, but they are not tested for at least six months after they return. In France, what they do is, they test four months after they return from an endemic area.

So, with that in mind, we called this workshop with a very specific question in mind. So, we asked for public discussion of scientific development that might allow us to implement donor testing from early infections as part of a pre-donation testing, others as follow up testing to reduce the donors who are deferred for the risk of malarial infection.

So, we came up with these questions. We did a lot of deliberations and we wanted to get some clear matters out of this workshop. So, we asked these questions.

So, what are the main sources of the infection that is in the U.S. population. Precisely what are the donor populations that are causing transfusion transmission of malaria in the United States, and mostly looking at the current populations.

What are the risks and benefits that would be of implementing a blood donor screening test in lieu of risk-based deferrals. That is what we are doing now, apparently.

Available and emerging technologies to test blood donors for malarial infections. That is keeping the future in mind also.

Then potential effect of implementing such a test. If we do a model of universal testing for all blood donors -- that is, everybody is tested -- or do we test only a targeted population for people who either had a history of malaria or a possible exposure to malaria.

So, I would just like to use the workshop data base to tell you what we got out of this workshop. So, Dr. Goodman gave the welcoming remarks, and Dr. Nakhasi delivered the introduction and overview of the workshop.

Then we had three scientific chairs and one round table discussion. I am not going into the details of this. Basically, we looked at the global problem of malarial infection and how has it affected the U.S. blood supply here.

I am going to present a summary of a few of the talks here, the ones I targeted for today. This is the talk from Dr. Monica Parise at CDC.

So, the picture that is emerging now, that in the past we used to get the donors that used to have malaria, half of them used to be U.S. travelers, malaria-naive travelers, and the other half used to be immigrants coming from other countries.

Now the demographics are changing. What we are finding now is that travel to Africa accounts for only .6 percent of the U.S. travel in 2003 data, but 66 percent of

all malarial infections in this country, clinical cases, were caused by these travelers, the people who went to Africa, and 59 percent of these cases were falciparum cases.

So, most of the malaria that is in this country is coming from Africa, which is not surprising. For the last 15 years or so, 17 years, 93 percent of malarial deaths in U.S. travelers were due to falciparum, and 73 of those were acquired in subSaharan Africa.

Again, looking at the transfusion transmission issues especially, since 1990, more than 15 years of data, there are 16 cases there. So, less than one case more recently every year.

One of the donors was a U.S. traveler who went to Kenya. One was an immigrant who had lived in this country for a long time, was visiting family and friends in Africa. The others were immigrants.

So, out of those 14 infections, 12 of 14 were acquired in Africa and 71 percent were falciparum. So, that showed us very clearly -- and this is one thing we got out of this workshop -- the group of the donors that we need to target most are the immigrants coming from subSaharan Africa, probably born there or have lived long term there. So, that is one thing.

So, the second session mostly targeted on testing

for malarial infection but still looking at what technologies are available, the current ones and even the future ones.

So, this is a talk by Newmarket Labs. It is a company in the United Kingdom that made the ELISA test that is sold in Europe and Australia. It is the test that they use currently.

It is based on two malarial antigens only from two species, plasmodium faliparum and plasmodium vivax. So, this is the test that is currently used. It is based on their sensitivity claims currently that there is 94 percent sensitivity for falciparum, 100 percent for vivax.

Now they are working on a new one. So, what they are finding is more antigens are better. So, if there is only one antigen, the sensitivity is 70 percent. That is the falciparum antigen.

If there are two antigens, the sensitivity increased slightly, three antigens, it becomes 82 percent, four antigens brings the sensitivity to 99 percent. So, they come to us with this was the test that probably would be more appealing to us.

I gave a talk yesterday. I had been asked this question repeatedly, why there is no DNA based test. That is what is used for most of the viral infections for blood safety.

First of all, the malaria parasite is highly infectious. There is some report that a single infected red cell can cause an infection. So, how does one look for one infected red cell in a unit of blood. So, it is a sampling issue here.

What we concluded was, I presented that most of the people I read, that sensitivity is not an issue. We can detect up to two parasites in an ml of blood. The problem is that it still leaves an unknown amount of parasites in a unit of blood.

So, the other biggest problem is in the asymptomatic donors, those are the ones who mostly transmit malaria, we don't know what is the minimum number of parasite burden that is there. So, that is the biggest road block.

So, we are testing for something that we don't know what the sensitivity should be. So, what are the possible solutions?

One is to have a technology that could concentrate parasites, that is, find one infected red cell in a whole unit of blood.

Well, that would be nice if you could achieve that. Then if we could find out about the parasite burden in the infected donors who are asymptomatic carriers. The concept was there that probably the technology is not there

right now for implementation.

The third session was more about hearing about the actual experience of testing in the United Kingdom, in France, and some data was presented by Dr. Susan Stramer from the American Red Cross.

Actually, this was a very rewarding session there. Then David Leiby presented. I am just going to go through two talks very quickly here.

So, Professor Chiodini, this is the data looking at the at risk populations. The people that had clinical malaria had come back from an endemic area and were travelers.

So, in 2004 they tested close to 43,000. Around 1,200 were repeat positives. So, in this year they found about 2.8 percent of the donors. This is the at risk population here. Those are people who have been otherwise deferred. So, there is a net gain of close to 97 or 98 percent in terms of donors here.

In 2005, they had more samples to test, and the activity stayed in the same range, but slightly came down, around two percent.

So, they got 98 percent of the donors back who would have been otherwise deferred. This year so far, until June, they have tested close to 12,000 donors and, again, they are staying in the range of two percent.

Professor Garraud from France told of the French experience there. They have tested close to 75,000 donors. Again, this population is people who were travelers, that had been in malaria endemic areas.

They are finding the activity in about 3.5 percent. So, the rest are negative, and this is the donor gains for them, again.

Surprisingly, the other two people who presented their extensive data, they seemed to be very happy with the test. There were no complaints.

So, this is Dr. Susan Stramer from the American Red Cross. She had her own data. She presented the American Red Cross experience, how many donors had been deferred because of malaria risk each year.

So, how much burden was the donor deferral policy. That is the other way to view it. So, we have the data for five years here, and the mean donation rate of 1.69.

So, travel related deferrals were close to 2.4 million deferrals, something close to here, and this is the number of units they calculated lost, close to 400,000 units.

Residents were 25,000, or this number has shifted. This is the percent loss. So, one percent loss in terms of the total blood donations among travelers. The

residents is 1.69 percent. The total lost, they are calculating, is around 1.2 percent of the donors are lost because of malaria deferrals.

So, this is their own data, but the numbers seem to be the most number of donors we are losing are in this traveler group here.

That is where everybody's eyes are. Those are the donors people want back in the blood banking industry and that is where we have got to focus also. I think we have heard the message very loud and clear now.

Falciparum, we have a lot of data with the Australian experience, and because I time I have to summarize it.

So, I think they have been doing it only for eight or nine months. They have already screened around 36,000 donors and close to two percent reactive. So, the numbers from France, from the United Kingdom and Australia, they add up.

I would like to present some interesting data from the American Red Cross again. So, here is just data, the same ELISA here. He tested in non-deferred donors, a little over 3,000, 3,200 cases here, suing non-deferred donors.

So, nobody reported they had any risk of -- they were qualified as non-malaria risk donors, accepted as non-

malaria donors here.

What he found was, surprisingly, the one time 21 cases were there, the secondary reaction was 11 donors here. Interestingly -- and I found it very intriguing -- they went back and looked at the history of these donors here, and I think that is telling us something.

Our of these 11 donors, two had no travel history at all. Two of the donors were born in Africa, lived there a long time.

One had traveled to an endemic area in malaria, and four people had been previously treated for malaria more than three years ago, and at least three of them had lived or were born in Africa.

So, these are the donors who slipped through the system. Probably they were completely safe from malaria. None of them caused transfer in terms of malaria, but this is what happened, 11 people.

So, out of level, two had no travel history, but nine of them had some sort of exposure to malaria, risk of malaria, which was not otherwise detected. So, they are doing more follow up, the serology and PCR based on data from CDA.

Then came the round table discussion. Personally, I found that the most rewarding. Jay Epstein moderated this session.

These are the questions that were put there. I don't think I will have time to go through them individually, but they were basically based on the sessions that we had previously.

So, these were the take home messages, at least what I got from here. So, the majority of the clinical infections and transmission transmitted malaria area coming from the donors who were born in or lived in Africa. So, those are the people we need to pay clear attention to.

There were serious doubts expressed over current donor deferral policy, about one year deferral for all travelers, especially those going to resorts in Mexico and clubs in the Caribbean. So, there is a lot of noise being made about those travelers here. So, we have to consider how we can help there, or whether we can have a test that can help to alleviate the situation there.

The parasite detections, I think everybody is in agreement right now the technology, although it is very good, it is not being fit to screen donors for malaria infection, just because of inherent problems there of sampling.

Antibody testing, the experience in the United Kingdom, France and Australia has found it to be satisfactory based on detection of two out of four species, and what we can do about antibody based screening in this

country.

So, we asked two very specific questions. Jay Epstein put two very specific questions to the panel. For universal testing, I think there was a mixed response. at least I didn't get a clear message, but people want to keep the issue alive. Nobody wants to close the issue here.

Especially I think I heard at least one comment that we need to be careful already that the universal testing supposes there are malarial infections in the United States. So, that may be the way to go, then.

Testing in at risk populations, also, I think we need to collect more data for the geographic based distribution, and the species that is prevalent, to decide what number of the species should be presented in the test before we can think about this a little further.

Then some members expressed concerns regarding logistics, how they will configure their data base to fit in with the target of screening in the at risk population. I think that is it. I will stop here, and obviously we will prepare a much more in depth, thoughtful summary. I was finishing this talk at 1:00 o'clock in the morning.

DR. ALLEN: Thank you, Dr. Kumar. Questions from the committee about the workshop or the report that we just heard?

It is obviously an area that is going to receive

a lot of attention and I think the committee looks forward to a more complete report coming back, as well as research on ways to deal with this issue. Thank you.

MR. ALTER: One other important thing I thought that came out is, one, we probably would not be able to get rid of the questions, but hopefully we could simplify the questions and just say which country you went to, not where, when and how in the country.

Secondly, that if testing was added to the questions, that if it is done after the fact, it would not really help.

By the time you got the testing, the donor to come back and the testing done, you wouldn't save much time off the one year deferral.

So, if testing is done, it would have to be that you were able to draw the donor at the time they gave a positive question response.

Then, if the donor was antibody negative that unit could be used and, if not, it would be discarded. This would require big changes in computerization and how to track this special group of donors.

DR. ALLEN: Yes, gain, the algorithms that will be developed would be an interesting challenge, I am sure.

DR. KUEHNERT: I just wanted to mention that, unlike most infectious disease issues we talk about, this

was more a discussion about improving availability and looking at safety trade offs, rather than the other way around, which is usually talk about availability trade offs and needing to increase safety.

It seems that the efficiency of the deferrals are really the issue and the more that we can increase that efficiency, I think the better this issue will be addressed.

We had some discussions about malaria risk mapping and trying to look at the areas of highest risk as really the ones that need the most focus.

As long as the trends continue, as far as the epidemiology, then all of that will still have the same frame.

I was struck by some of the slides which showed that really what was driving the decrease in casing was the decreasing immigration.

So, if there was a spiking immigration, you probably would see a change in the risk profile concerning transfusion transmitted malaria. So, that is probably what needs to be watched.

DR. ALLEN: And the immigration being considerably more important than just most business or pleasure travel.

DR. KUEHNERT: I mean, the traveler is what is

driving things now because there isn't the immigration issue, but if that came back and there was an increase in immigration, then you would see both of those issues have much more equal weight. Right now it is the travelers because of the decrease in immigration, at least the way I saw it.

DR. ALTER: The main goal of the meeting was to give Mexico back to Dr. Katz.

DR. ALLEN: Other questions or comments? Thank you, Dr. Kumar. The third presentation is the committee report on the office of blood research and review site visit, the review of intramural research, and I have the pleasure of giving the summary.

Agenda Item: Committee Report on the Office of Blood Research and Review Site Visit, Review of Intramural Research.

DR. ALLEN: Good morning. I don't know if they scheduled this purposely for my last committee meeting or not.

I had the pleasure almost a year ago, July 22, to chair the review committee for the office of blood research and review, review of intramural research.

The committee was composed of a broad base of people with various background and experience, including committee members, those with basic science research

backgrounds, clinical research backgrounds, blood collection experience and backgrounds, as well as industry backgrounds. The committee members are listed on the right.

The purpose of the review was a periodic review of progress and performance of the OBRR research program. In fact, this was the first one structured in this way, however.

The intent was an over-arching summary of the research program's goals and support. It is not a focused review of individual investigators and their work, which is done through a separate review process.

To conduct a review, we did the following things. We evaluated background information about OBRR and its function within the Center for Biologics Evaluation and Research.

We studied written research program descriptions, voluminous materials. Actually, I think we had a couple of binders of materials.

We did have a chance to review the report on the research programs at CBER that had been conducted back in 1998.

We looked at the curriculum vitae of the investigators. We looked at selected publications and then we had oral presentations, questions and discussion in an all day process.

I just quickly go through the 1998 report because I think it has useful background information. At that time the review committee strongly endorsed, first, the fundamental need for basic science research at OBRR to support its regulatory mission and, second, adequate funding of the research program to assure its success and its ability to attract first rate scientists.

I think it is not a secret that, even at that point in 1998, there were significant concerns expressed about the level of financial support through congressional appropriations, and the need to find acceptable alternative sources of funding for the research program activities.

By way of background, OBRR maintains an active laboratory research program. It is integral to FDA's critical path research initiative.

It is mission focused to enhance OBRR's regulatory functions and is primarily targeted at current regulatory issues, but with the flexibility to respond to new regulatory concerns and safety issues.

I think we will hear next a report on that, as we listen to the west nile virus update which, again, obviously was a problem that was not a problem that was anticipated and planned for prospectively. That is an example of the kind of flexibility that the OBRR needs in this arena.

The principal investigators and senior research staff at OBRR expected to spend about half their time on research activities and about half their time on regulatory activities.

That, in fact, is a balance that is rarely achieved. It does not account for regulatory time frames and priorities which take precedence very frequently, and it certainly does not account for other significant and time consuming activities such as management and administration within a complex structure at the FDA.

Evidence of the research program's success, just some brief summary statements. In total, the senior scientists in OBRR regulatorily publish more than 50 articles per year, most of it in the peer reviewed literature.

They have abstracts accepted at scientific meetings. There are progress assessments on external laboratory site visits, which uniformly, during the period of time I have bene here, have uniformly been very favorable, and commend the work that is accomplished and the scientists accomplishing that work.

OBRR staff sponsor and organize workshops on specific topics of importance, such as the malaria workshop we just heard about.

From this intramural research review, overall, in

summary, OBRR research programs merit high grades for depth and quality of research.

Research agendas have been diversified and productive. Research programs are directly applicable to the FDA's critical path of biologics product development.

In comparison with the 1998 CBER review, the OBRR research programs were believed to definitely have improved in terms of focus and relevance to mission, quality of the research being conducted, and the diversity of funding sources, for example, through developing innovative alternative funding sources and establishing collaborations, which were an important way of getting the resources to accomplish the work that needed to be done.

Let me, as this point, go through the recommendations from the committee. First, the OBRR intramural research site review committee strongly supports the FDA's continued emphasis on the importance of having a strong intramural research program to support its critical path program for effective and efficient regulatory activities.

Having experienced and active research scientists involved, both in the regulatory process, and in the development and evaluation of scientific knowledge critical to the support of the regulatory activities is both sound and an essential component of the regulatory process, a

process that facilitates the approval of biological products, and protects the health and safety of the American public.

Two. The OBRR senior management and the research scientists are highly commended for the depth and quality of the research program that was presented at this review, especially considering that each investigator is simultaneously responsible for a huge regulatory work load.

Both divisions, the division of emerging and transfusion transmissible diseases, and the division of hematology, have developed productive and diversified research agendas that have increased in value over the years despite both budget and personnel restrictions, and both divisions have contributed to the critical path program.

Three. The issue of sufficient time and qualified personnel to conduct the research remains important. The environment must be competitive to be able to attract outstanding young scientists, and to retain more senior scientists as principal investigators and regulators.

These issues are critical to the continuation of an effective and productive research program that supports the FDA's regulatory mission.

Four. Among the most critical issues facing the OBRR research program is funding to support the basic

activities, including reagents, supplies and adequate equipment.

The meager budget available to OBRR through congressional appropriations to support research directly is totally inadequate to conduct even a significant part of the wide range of important program priorities for which the office is responsible.

Five. Other options to increase the research budget through resources outside the FDA, although difficult and time consuming for OBRR staff, are essential.

Opportunities for collaboration and to seek acceptable funding sources must be pursued, although this must be done within the confines of the research priorities established by OBRR.

Just to emphasize this point, obviously FDA can't go to the regulated industry and seek direct support for research activities.

Alternatively, unlike NIH supported scientists who have research ideas that they want to pursue, regardless of the specific mission, the FDA is very tightly constrained in terms of the direction of the research and the research priorities. These obviously limit the funding potential also.

Six. Adequate laboratory space and equipment are clearly essential components of a strong and product

research program.

The inability to assure these in the future could have a definite impact on future research activities. These issues need to be addressed as funding is sought to support the research program.

Seven. As was noted during the presentations and discussions, it is imperative that OBRR have the flexibility, capacity and resources to address new scientific and regulatory issues that become apparent at any point in time, perhaps as a crisis.

Planning for these is difficult, especially when OBRR is also being faced with decisions about trying to develop a more focused research program.

These issues must be factored into the decisions that the agency needs to make about future research program directions.

Eight. Given the current realities of the research funding limits, the committee recommends that OBRR must decide whether it should try to maintain a broader array of research activities that attempt to address the responsibilities within its mandate, or whether it should focus on a smaller number of research topics and priorities, allowing staff to develop greater expertise and critical mass in fewer areas.

If this model is adopted -- that is, a more

focused, limited research program, OBRR could define a research matrix based on the potential for collaborating effectively with academia or industry through contracts and other mechanisms.

The committee recognizes that this approach also requires funds and other resources that may not be included in the budget.

This is a difficult recommendation. I think it clearly shows how the committee was, I don't want to say split, but was not necessarily unanimous in whether the focus should be a very tight, controlled, here are the areas that we give the highest priority to, or whether it should try to cover the broad array of responsibilities that OBRR has.

Nine. A related issue is the need for OBRR to define the best mechanism for identifying research priorities to be pursued, either through intramural research or outsourcing. A good mechanism may already be in place, but it was not discussed with the committee.

Ten. OBRR needs to be attentive to the potential or perception of bias introduced into the regulatory process by intramural research findings that are portrayed as FDA policy positions when, in fact, they are not formal policy positions.

Eleven. The visibility of the OBRR research

program is an important aspect of its broader acceptance and support.

Despite the meritorious work that is accomplished, there seems to be little appreciation outside the FDA for the extent and quality and importance of the work that is being accomplished.

It is important for OBRR to define and exploit opportunities to expand their visibility. Certainly information available through the new web site may be one opportunity, as are workshops, scientific presentations and publications and other venues.

Every opportunity should be taken to provide strong links between the research program activities and the regulatory capabilities that this research supports.

I will add here that I think it is obviously incumbent on each one of us, who are not FDA staff, to try to get the importance of this message across to congressional leaders and funders.

Twelve. To directly enhance funding to support research activities, OBRR should work with FDA and department leaders to identify creative funding mechanisms.

Establishing a research endowment fund, for example, that could be funded by major philanthropic organizations, private donors and regulated industry might be one example.

There certainly are examples of this kind of activity both at the NIH and the Centers for Disease Control, where there was congressional authorization to establish outside endowment funds and foundations to support research and other activities that were not directly supportable or supported by appropriate monies. I think this might be a model that should be pursued by the FDA, and there are others also.

Finally, the committee strongly supports the FDA's emphasis on a strong intramural research program to support its critical path initiative for effective and efficient regulatory activities, and adequate funding and other resources, including outstanding staff, are essential to support OBRR's research program and the FDA's critical path initiative.

The critical path, in turn, facilitates the important licensure and regulatory activities of OBRR and, as we all know, that certainly protects the health and safety of Americans, and it is an extremely important funding. Thank you.

I would be glad to take any questions from the committee or supporting other comments that want to be made. Dr. Goodman.

DR. GOODMAN: I would just like to make a few general comments. First of all, I think your efforts were

some time ago and we have thanked you, but I would like to thank you again.

This is very, very important and we take it very seriously. A major goal for FDA is not only to have a science based organization that uses the best science to make our important decisions for the health and safety of the American people, but also, as Dr. Von Eshenbach has said, a science led organization.

So, we recognize that. That said, there are many, many challenges, as you said. I will just make a few general comments.

One is that the positive feedback is very much appreciated and important and, as you said, we need to do a lot more with our partners to be sure people understand what FDA's role is, what FDA science is, how that is science, meets different needs, than academic or NIH science, but how we work together with those partners. So, I agree with you.

I also want to say that it is good to hear that your independent assessment is that there has been progress since 1998, and we also feel within the last couple of years.

I think that has been from input we have gotten as well as from soul searching within the agency. A few comments that, as most people are aware, the federal budget

is quite tight.

We get new very important priorities, such as issues in national defense, pandemic influenza, that end up causing needs for money to flow in those areas at times when total monies might not increase.

So, we are faced with continuing challenges. So, we do need to do a number of the things, and are doing a number of the things that your committee suggests.

There is even increased leveraging, as you said, working with NIH, working with other partners, et cetera, and that can make a big difference.

The outside funding has increased, but an important issue there -- this gets to management of the program -- is that we are sure that that stays with our mission, that we use outside relationships to solve the important issues that are part of our regulatory responsibility, and we are trying to do that.

What else was I going to say? Having you guys look at this program as a whole is part of something that we are very committed to doing and we want to do it regularly, not just from 1998 to 2006, but on a more frequent basis, and we are working out a process for doing that.

One of the things that we have done -- I think you heard some about this -- is we have had a retreat and a

research working group of our scientists come up with ideas and approaches to how to deal with all these challenges and how better to manage our processes.

We have reinvigorated and are reshaping our resource processes within our center, the research priority setting and resource processes.

We can give you more of a report on it another time, but what is important is, the key elements of that are going to be regular stakeholder input -- and that is both external stakeholders such as yourself -- but also internal stakeholders.

We have internal stakeholders. For example, our full time reviewers are stakeholders in the research process.

They have ideas of things that are important from their review activities, and it is also important for them to understand the current science.

So, we sort of empower -- we have a person in each office who is an associate director of research for that office, just like Dr. Carbone is for the whole center.

We have created a new structure that empowers those individuals and they, and the office directors, in each of the offices, are going to basically set research agendas for those offices and prioritize and have resources, limited resources, focused in those kinds of

areas, based on an objective assessment of what the needs are and what the available resources are.

What we are aiming for is to have, in essence, periodic development and reexamination of a research agenda, which we will bring and share with our stakeholders and publicly, and probably including through the BPAC, to again get input, and to then look at how are we making progress on that, what are we leaving out, what are new areas that we need to deal with and, given the limited resources, are we focusing them well.

So, we would like to come and, I think, update you on that. That process is being operationalized right now by those people themselves, not by me. We are going to look at what they come up with and be sure it meets these needs.

The other comment I would make -- and it just occurred to me listening to your presentation, but we had talked about it before when we had received the report.

We are doing this in the other offices, too. So, it is important people realize it is an across the center process.

I already asked our teams in each office to look at the reports they get from the advisory committees and use those in their planning processes.

In other words, they may not be able to accept or

do everything you want, or they may have other reasons to have other views of some things, but we need to address all the things that have been brought up.

I would like to think of a formal way, whether we create a report or just come back, maybe, Kathy and report to you, for each of the offices to say, here is how we are resounding to the suggestions and ideas. Here is where we are with each of these things in detail.

So, I would like to put some time aside at a future advisory committee meeting to do that. One of the things that drives me crazy, that drives committees even crazier, is when people do good work and, because everybody is busy and because there aren't enough resources or whatever, it is sort of the tree falls in the forest but nobody hears it.

Well, we can't guarantee that we can make the forest whole again, but we can hear it and we will very much do our best and value your input.

I think I have said enough, but I really do appreciate -- it is helpful to me to hear where we are making progress.

It is helpful to me to hear other people's ideas of how we ought to be approaching these challenges, and we want to keep you engaged in that, and we very much appreciate your support.

Another comment I would make -- because this hasn't been part of the normal way of doing things -- is in your committee meetings today, if you identify what are essentially scientific issues that aren't being resolved -- and we have colleagues at NIH, we have colleagues in industry and academic -- that can be part of our process.

Identifying and solving those can be important. So, even from a single advisory committee meeting on a single topic, we would not object to hearing, well, gee, if we knew a protective level of X antigen, would we be here today, and how can we get to that point and who would be the right partners and how do we move that forward.

I would just like to say that we are open to scientific input in virtually any way possible, and to use it in solving problems.

The other thing is the critical path initiative. I am working very hard, we all support it. Again, the issue of financial support for it is a challenge, but our view is also that, for some of these areas where the public doesn't immediately think of this kind of research, like transfusion medicine, blood safety, I think it is very important, and you can really help us in articulating that those are important issues for this initiative to address, and we are certainly working on that within the government.

As we talk to people within the congress and

explain what some of the unmet scientific needs are there and how meeting them can help the American people keep safe and accessible blood and blood products.

That was too long, but I think I actually had something to say and I really, again, appreciate your thoughtfulness, both in that report and in sharing your general feelings with us. So, thank you very much.

DR. ALLEN: Thank you, Jack. Dr. Alter?

DR. ALTER: I thought, Jim, you did a superb job of summarizing the process, even though you are just a lame duck at this point. It was very good.

I was on both these reviews over that time period and the change was really palpable. I just want to reemphasize how much more focused it had become and how much better the science had become because of the focusing, I think.

It was just amazing how much had actually been done, given the regulatory work load. I don't know how it was done, but it was. So, very, very good.

DR. HOOFNAGLE: I am Jay Hoofnagle. I am from the National Institutes of Health. I am in charge of funding of liver disease grants.

One of the frustrations I have always felt is that the intramural FDA cannot apply for NIH grants. I think the administrative reason for that is that they are

part of HHS, as we are.

We have other parts of the government that can apply for NIH grants, like the agriculture department. We do fund labs in the agriculture department.

I think this is one potential help that might come to the intramural programs if they could. We actually have funded some FDA investigators indirectly through academic subcontracts to the FDA, and there are certainly outstanding scientists there who could compete in our already tight system.

I think that might be one solution to this problem of shortage of research funding, perhaps more palatable than applying to industry through foundations.

DR. ALLEN: Thank you. I appreciate that comment. Again, those of us around the table should see what can be done with that kind of suggestion as well as the FDA staff, although they may be restricted in terms of how they can hold their hands out to congress. Thank you. I think that is important. Other comments or questions?

MS. BAKER: Thank you for the excellent report. Are the summary recommendations available to the public in any fashion?

DR. ALLEN: I will let Dr. Carbone answer that.

DR. CARBONE: They were publicly presented at the last BPAC. So, they are part of the public record in that

format, and we also plan to put them publicly available in an easier format on the web site. We will include the summary report as well.

MR. JEHN: Actually, the whole report will be posted on the web after this meeting.

DR. ALLEN: Other questions and comments? Okay, our last update will be west nile virus 2006, and I don't know if one would characterize it as a whimper.

Agenda Item: West Nile Virus Update.

DR. RIOS: Good morning. I will be giving you an update on the west nile. The United States is currently experiencing the eighth consecutive epidemic of west nile.

The first human case was actually reported to the CDC earlier this year. There have been close to 20,000 human cases so far reported to the CDC, with close to 800 fatalities.

According to CDC's estimation, for each neuroinvasive disease of west nile viral infection, there are between 150 and 300 infections for each case of neurological disease.

So, it is estimated that the minimum of 1.3 million to 2.5 million of infection has occurred in the past seven years.

In 2003, west nile was begun to be screened for the safety of the blood supply. There have been 1,600

interdicted units, or more than that, which led to the prevention of transfusion of those units and consequently transmission by blood of between 1,600 to over 3,000 cases potentially transmitted by transfusion.

There have been 30 cases definitely confirmed of transmission of west nile by blood transfusion. twenty-three of them were prior to the implementation of NAT screening and six were after implementation under IND in the mini pools of six or 16 which, when we had some changes in the blood industry, changes in the strategy of testing, it declined to one, and last year there were none. There are some inconclusive cases that were due either to the lack of follow up or the lack of a specimen.

The human season for west nile in 1999 was rather short, and it steadily increased over the years. In 2005, it was all year long. The first report was January 2 and the last one to the CDC was December 16.

This year we have already had reports early this year to the CDC. According to the standard reports, there are between eight and 10 cases of blood donors reactive to west nile, either confirmed or to be confirmed.

To give you a brief history of the west nile and the blood safety story, in 2002, it was identified that west nile was a risk for blood safety.

There were initiatives taken by FDA, the office

of blood in CBER, and calls for test development. That led to a strong collaboration, actually before never seen, between government, academia, industry, test kit manufacturers and the blood establishments. Shortly after that the test was developed and implemented nationwide under IND for the summer of 2003.

The platform for these tests were in pools of plasma from donations of six to 16 samples. That surely led to interdiction of reactive units, in 2003, over 1,000 reactive units made by asymptomatic donors, since west nile, most of the infections are asymptomatics.

In the same year, the evaluation for the suitability of mini pool tests of six or 16 for the west nile was performed by the blood centers, and identified that 75 percent of the infected units only were detected by mini pool NAT and another 25 percent were undetected.

So, the approach was that, in 2004 and 2005, during the peak epidemic or between spring and fall, ID NAT was to replace mini pool NAT in the specific areas where there was a high activity of human west nile virus cases, and that obviously led to increased safety of the blood supply.

The status of assays right now, FDA has licensed the first west nile NAT assay for testing volunteer blood donors.

Also, these assays are licensed for organ and tissue. The submission was in January and the approval was in December 2005.

There are INDs currently ongoing on the testing of the blood. The current consideration for assay implementations are as follows:

We recognize that performing NAT assays actually involves a very complex pooling and testing system. So, we are considering recommending the implementation of a licensed assay for west nile within six months from the date of the publication of a notice in the Federal Register announcing the availability of the final guidance.

Our current considerations and tests, as you saw in these slides that I have shown before, the occurrence of west nile activities all year round.

West nile has become endemic in the United States as declared by CDC last year, with the intensity of activity occurring between the spring and fall of each year.

So, in screening volunteer donors for whole blood and blood components for transfusion, we have improved the safety of the nation's blood supply.

So, we are considering to recommend that west nile screening by mini pool NAT should be performed the year round, with implementation of ID NAT in the specific

geographic areas where west nile activity is high.

We are also considering that the criteria to trigger ID NAT in a given geographical area into mini pool NAT should be defined and validated by the centers based on their incidence rates.

We also are considering recommending the confirmation of initial reactive units in the index donation by re-testing the donation, either using the same assay in duplicate or using an alternate NAT with a sensitivity which is comparable to the screening assays. We also encourage the use of antibody testing the index donation.

Regarding donor management, west nile is a communicable agent to the CDC. So, any reasonable attempt should be made to notify deferred donors of their test results.

We encourage additional testing to be performed, either an alternate NAT, an antibody test, actually, alternate NAT and antibody testing, to be performed in the index donation, which may provide information for donor counseling purposes.

We know that in some percentage of cases there are very serious consequences of west nile viral infection and the donors should be attentive to that.

Also, we considered recommending the follow up

testing, which may provide further information on the course and outcome of the infection, and the antibody test may work as a confirmatory tool.

Regarding label, we are considering recommending that the container labeling instruction circular that reflects the results of west nile NAT be consistent with the label of other infectious disease markers upon implementation of licensed NAT.

In the west nile reactive units, it should not be shipped or used except as provided by an FDA approved program and/or research or autologous use only, in such units to be labeled appropriately, with the appropriate warning.

Regrading the current consideration in donor deferral and reentry, unit management and recipient notification, those are to remain as stated in the June 2005 guidance, which can be found at this web site. Thank you.

DR. ALLEN: Thank you, Dr. Rios. Questions about west nile virus?

DR. DI BISCEGLIE: Dr. Rios, you alluded to but didn't say very much about testing in organ donors, deceased organ donors. Can you comment on that at all?

DR. RIOS: The test has been licensed for organ donors, and actually it is another office, tissue and

cellular therapy. That has been evaluated and has bene used for screening of tissue in organ donors.

DR. KUEHNERT: I might just add that we are dealing with some reports of testing. So, it is a challenging situation, because on the one hand there are some compelling reasons to test organ and tissue donors. On the other hand, the sensitivity and specificity in this setting is not well worked out and there are some questions about false positives and what the confirmation algorithm should be.

I think it is a challenging issue that really needs some attention, but I think the organ and tissue community are well aware of the need to consider testing. It is just an implementation issue that really has become a challenge.

DR. ALLEN: Dr. Kuehnert, who is heading up most of those studies?

DR. KUEHNERT: That is the issue. There are no studies. There is no coordinated effort for this. That is really the issue.

I think both government and non-governmental accrediting agencies need to get together, as has happened for blood, to be able to work out the issues.

DR. KATZ: We are starting to take off this season and the cases are starting to accumulate. I just

wanted to express appreciation of the people that are doing the testing for the flexibility that the FDA has shown early on, particularly in the area of the decision making process for triggering ID NAT.

The resources and individual testing facilities, in terms of capacity, vary quite widely and, to date, FDA has not said, this is how thou shalt do it, and it is allowing us to gain experience and figure out what is feasible. It is greatly appreciate that the flexibility has been there.

R. ALLEN: Thank you. Other comments or questions? Thank you very much, Dr. Rios. This concludes our committee updates. We will now move into the presentation discussion of topic one, Food and Drug Administration review of Nabi Biopharmaceuticals Hepatitis B immune globulin intravenous for prevention of recurrent hepatitis B virus disease after orthotopic liver transplantation.

We will start by having an introduction from the Food and Drug Administration presented by Dr. Charles Maplethorpe.

Agenda Item: Topic I: FDA Review of Nabi Biopharmaceuticals' Hepatitis B IGIV for Prevention of Recurrent HBV Disease After Orthotopic Liver Transplantation. Introduction.

DR. MAPLETHORPE: Good morning. My name is Charles Maplethorpe. and I am a medical officer in the office of blood research and review.

Today we are going to talk about Nabi's hepatitis B immune globulin, human. It is a licensed product, and they would like to add a new indication to the label.

The new indication is for intravenous administration of hepatitis B immune globulin intravenous, human, Nabi HB, to prevent HBV recurrence after orthotopic liver transplantation for hepatitis B disease, when given with HBV antiviral therapy.

So, we are going to talk about not the general area of the use of hepatitis B immune globulin for orthotopic liver transplantation for HBV disease, but rather, the ability of the specific submitted data to support this indication.

As we go through our talks, I hope you will keep in mind these three questions, which will stay up during the presentation, so you can consider your answers.

The first question is, please comment on Nabi's post hoc inclusion and exclusion criteria for the classification of subjects as successes or failure following HBIG administration in the setting of OLT, orthotopic liver transplantation.

Question two, given the observational nature of

the information provided, the data limitations, including a priori definitions, and the lack of analysis plan, is inference about the outcomes of Nabi for HBIG administration in this setting appropriate.

Question number three, do the submitted data from retrospective chart reviews and uncontrolled PK assessment and an open label access program demonstrate efficacy of hepatitis B immune globulin -- HBIG Nabi HB -- for the OLT HBV immunoprophylaxis indication.

So, we will first hear from Nabi, and that will be from Dr. Henrik Rasmussen. This will be followed by the FDA presentation of the clinical data by me, and then I will be followed by the FDA statistician, Dr. Jessica Kim. So, Dr. Rasmussen?

Agenda Item: Sponsor Presentation.

DR. RASMUSSEN: I would like to start by thanking Dr. Epstein and the FDA for giving us an opportunity to get in front of the advisory committee and present our case.

The purpose of today's presentation is basically to present evidence that the safety and efficacy data derived from the Nabi HBIV clinical trials should find approval of the BLA for the indication of prevention of hepatitis B clinical disease in hepatitis BsAg positive liver transplant recipients.

It is fair to say that this product has had

somewhat of a regulatory history. We have had numerous discussions with the FDA during the 1990s as to what would be the most appropriate approach for developing a new drug for this indication.

For a number of different reasons that I am going to come back to, it didn't become clear until the BPAC meeting in March 2004 what the exact criteria should actually be.

I do want to emphasize that there are some significant development limitations which we have been faced with in the development of this product.

This is an orphan drug indication in the most true sense of the word. This is a life threatening disease for a very small patient population.

There are approximately 200 hepatitis B positive liver transplant patients in the United States annually performed in more than 100 transplant sites. That obviously does limit the size of any meaningful clinical trials that could be conducted.

In addition to that, hepatitis B immunoglobulin has been the standard of care in the United States post-liver transplant since the early 1990s. As a consequence of that, a placebo controlled trial was obviously not possible.

There have been no approved comparitors. In

addition to that, there has been a continuous evolution of the standard of care with the introduction of antiviral drugs.

However, it is important to emphasize that none of the antiviral drugs had actually been approved for the post liver transplant indication.

We started, as I said, working with the FDA back in the 1990s. However, the criteria for approval were unclear until the BPAC made, in March 2004, and after that meeting we did agree with the FDA to do a retrospective data collection to try to follow BPAC recommendations.

Basically, there are a number of different reasons why we think it is important now that this product be approved.

We are going to show you data from two studies demonstrating efficacy and safety of Nabi HB study 4204 and study 4409.

Nabi HB has been the standard of care for HBV liver transplant in the United States since it was introduced in the U.S. market in 1999.

Since then, approximately 60,000 infusions have been administered to liver transplant patients, establishing an extremely favorable risk benefit profile.

The efficacy of hepatitis B immunoglobulin is very well documented in the literature. It has been the

standard of care in the United States and the rest of the world since the early 1990s, and it is actually approved specifically for prevention of recurrent post-liver transplant within the European Union, as well as in a number of other countries throughout the world.

In addition to that, we have substantial support for the efficacy from the studies we did in the maintenance phase, and I am going to show you briefly those data as well. So, we do believe that we are presenting a very compelling case.

It is also important to emphasize that the lack of guidance in the U.S. label has resulted in numerous examples of recurrence after premature discontinuation of Nabi HB, or hepatitis B immunoglobulin, because there has been no standard guidance.

So, various institutions have experimented with lower doses or premature termination. I am going to show you some examples of patients who, after discontinuation, have rapidly developed recurrent liver disease with sometimes very unfortunate consequences.

We believe that approval would be consistent with a general FDA policy encouraging companies to seek label indications for drugs that are used off label. As you heard earlier today, Nabi HB is already on the market, but only for post-exposure indication. I will talk about the

orphan drug indications as well.

Basically, if you take a closer look at the recommendations from this committee two years ago, there were basically five key points which we got out of the meeting and I am going to address each of them in turn.

The first one is that follow up clinical data should be captured that can be used to guide therapeutic dosing.

We did that from a number of different studies but mostly from study 4204, a pharamacokinetic study done by Roland Dickson at the Mayo Clinic and a number of other sites across the United States.

In that study, 30 new liver transplant patients were enrolled, who all received lamivudine, 100 milligram per day, starting pre-surgery and continued indefinitely thereafter.

Nabi HB was dosed at 20,000 international units on the day of surgery, 10,000 international units from day one to seven, 10,000 international units once daily from week four to week eight, and after week eight, from week 12 to week 36, which was the formal completion of the protocol, 5,000 international units.

Additional doses or modifications were allowed based on trough anti-HBs titer levels. After the 2004 BPAC meeting, we actually extended follow up in the study, went

back to the sites, went back to the patients, and collected data of at least two years follow up, to follow the recommendations made by BPAC.

This is the pharmacokinetic data from the study, which basically show you the number of patients who fall below specific anti-HBs levels.

It is believed that antibody levels in excess of 300 in the early days, 200 thereafter, and 100 on a chronic basis, would protect against recurrence of the disease.

As you can see from this slide, with a dosing regimen used in this study, you can see that, after day five, the vast majority of patients actually had titer levels above the recommended levels.

Based on that study, as well as a couple of other studies we did, as well as the original McGory study, which was the sentinel study for this indication in the United States, we came up with the following recommendation in our label.

The recommended dose should be 10,000 international units anhepatically, and then daily for the first two weeks, followed by 10,000 international units weekly or every two weeks from week two to week 12 and then, beyond week 12, 10,000 international units on a monthly basis.

The target trough levels are generally, as you

saw, achieved with a the dose level suggested, although adjustment based on trough anti-HBs levels may be required in some cases.

BPAC recommended that a historical control could be used for comparison in the pivotal study, recognizing the development limitations of this particular area.

Armed with that information, we went back and looked at the literature. On the left side of the slide here, you will basically see the recurrence rates from the literature in patients who received no, or less than three months, of hepatitis B immune globulin.

As you can see, the recurrence rates are extremely high. In addition to that, not only do these patients recur, but also the severity of the recurrent hepatic disease tends to be more severe than the original disease, presumably because these patients are receiving high dose immune suppressive agents to avid organ rejection.

So, you can see that the recurrence rate rangers in the literature from somewhere from 74 to 100 percent within the initial one year.

As a consequence of that, back in the 1970s and 1980s, liver transplants were contraindicated in patients who were hepatitis B positive, and it was only after the introduction of the hepatitis B immune globulins that

transplant surgeons started transplanting these patients.

We see the change as a consequence of introduction of hepatitis B monotherapy We see that the recurrence rate from 75 to 100 percent was reduced to somewhere from seven percent in the McGory study, to 36 percent in the study by Samuel.

So, there was a dramatic reduction in the recurrence rate as a consequence of HBIG monotherapy. That allows basically transplant of those patients.

Further improvement was reached later in the 1990s with the introduction of lamivudine. On the left side here you can see the results from the literature of lamivudine monotherapy, and the two year recurrence rate, which is consistent which is consistent with what the BPAC committee recommended when you met two years ago.

As you can see from the literature, this is basically the studies which we were using in our meta analysis, which we agreed on with the FDA we could use as a historical control.

The recurrent rate on lamivudine monotherapy from the literature ranges from 30 percent to 67 percent, with an average of 45 percent recurrence rate and confidence intervals ranging from 35 to 54 percent.

So, as a consequence of this meta analysis, we use for comparison, for the historical control, a

recurrence rate of 45 percent.

We also see that, if you look at the literature, the literature is very consistent with the data I am going to show you, that by combination of lamivudine and HBIG, you would actually basically be able to reduce the current rate within two years to less than 10 percent.

Obviously, when one is looking at historical recurrence rates, it is very important to look at the potential changes in patient population.

It is important to emphasize that there is no evidence that baseline risk factors have substantially changed over time from those in the published literature.

However, we did assign what we believe was a conservative estimate of recurrence with the 45 percent, because some of the more recent studies are actually indicating, if anything, a higher recurrence rate on lamivudine because of increased resistance toward the drug.

The pivotal study should start dosing from the time of transplant, and should not be solely based on data from the maintenance phase, as defined by six months or more after transplantation.

In addition to that, if you want to show superiority against lamivudine monotherapy, a minimum of two years follow up would be required. So, those were the guiding principles when we went out and did our

retrospective analysis.

The first study we looked at was Nabi 4204, a prospective study that assessed the pharmacokinetics, efficacy and safety of Nabi HB with concomitant lamivudine in new liver transplant recipients. This was conducted under an investigator held IND and funded by the NIH.

Following the 2004 BPAC meeting, follow up was extended from 30 weeks to greater than two years. We actually had a medium follow up of three years for serology and even longer for clinical follow up.

A couple of assumptions which we agreed with the FDA prior to the analysis, which is important to emphasize, one of them was that the surface antigen can be used as a surrogate marker for efficacy, as it correlates very well with clinical liver disease.

The corollary -- and this was not agreed with the FDA, I might add -- but the corollary of this is obviously that if the patient is clinically well, it is reasonable to assume that he is seronegative, even if there are no measurements of the surface antigen.

Because of this, surface antigen measurements are actually not standard clinical practice in patients who are well.

If the patients have no signs of recurrent liver disease, typically most transplant scientists don't measure

routinely hepatitis B surface antigen.

That is why we don't have as many measurements in some patients as we would have had, had this been a prospectively designed clinical trial.

In addition to that, it was agreed that hepatitis BPNA is not a good marker and should not be used, firstly, because it will always be present if the assay is sufficiently sensitive.

The disease is not going away. The disease is being suppressed but is not going away. So, it will always be positive, and obviously there is no correlation between DNA status and prognosis.

The retrospective analysis plan was submitted to the FDA and, after the March 2004 BPAC meeting, was discussed on a number of occasions.

Patients who would be included in the analysis were surface antigen negative after liver transplant and had a minimum of at least two years follow up data on Nabi HB and lamivudine.

We looked at two different analysis populations, which is part of the briefing document you received. We have patients who have at least two years follow up with serology, and we have patients who have at least two years clinical follow up, which is consistent with clinical practice, as I said, that if patients are clinically well

without signs of liver disease, serology is often not monitored.

If you look at the 30 patients who were enrolled int eh study, we basically excluded the following cases from the analysis:

Two patients who died within 30 days of transplant, two patients had Nabi HB discontinued for economic reasons. The insurance companies stopped reimbursing the patients somewhere between eight and 17 months. So, those patients discontinued, and two patients were followed for less than two years.

So, those six patients were excluded in the Nabi analysis. So, we ended up with 24 patients, in which we had no recurrences within the two year period.

That is obviously statistically significantly better than the 42 out of 94, 45 percent recurrences, under lamivudine monotherapy. The p value, obviously, is pretty small.

In addition to that, the FDA excluded two patients who died between day 30 and day 730. If we take the FDA's view and we exclude those patients, you would end up with 22 evaluable patients. Again, it doesn't make any difference for the statistical analysis. Zero out of 22 is still statistically significantly better than 42 out of 94.

If you only look at patients who have two year

serology, we will have to exclude an additional six patients, which would take this data base out to 18 patients.

This is actually extremely important because, when you look at the efficacy of the drug, the absolute key is will you agree with the FDA's position that we had eight failures out of 30 patients, or will you agree with our position that we had one failure.

So, I am actually going through the seven disputed patients who represent a difference between the FDA's assessment and Nabi's assessment.

Patient number one was a patient who discontinued Nabi HB on day 252. He was a. surface negative and clinically well at the time. He discontinued for economic reasons, because the insurance stopped paying for Nabi HB, but he continued on lamuvadine monotherapy.

The patient, not surprisingly, developed recurrence of hepatitis B on day 636, that is, one year after discontinuation of Nabi HB.

The FDA counted -- and I don't know why -- but they counted this patient as a failure in their analysis, even though the patient obviously demonstrated a need to continue Nabi HB.

This corresponds to basically excluding somebody who stopped their blood pressure medication. Once you stop

the blood pressure medication, the blood pressure goes up and you count the patient as a failure.

We believe this surely demonstrates the need for continuous treatment with Nabi HB and should not be counted as a failure.

We have three more patients along the same line. This is the second one in the same study, discontinued Nabi HB on day 249, was negative at the time, again, for economic reasons, not for side effects, economic reasons, continued on lamuvadine monotherapy, developed recurrence of hepatitis B on day 906, more than two years after discontinuation of Nabi HB. Again, the FDA counted the patient as a failure. We think he should be excluded.

The third disagreed patient was a patient who died from bacterial sepsis, a direct complication of the liver transplant surgery, on day 56.

He was surface negative at the time of his death. Obviously, we don't believe that his death had anything to do with lack of efficacy of the drug. The FDA counted this patient as a failure.

The last one, which I guess is more debatable from this study, was a patient who had 14 negative measurements of surface antigen, up to and through day 532.

He had one positive value on day 375, but he had a number of negative values before and after the day 375.

We believe that the one value on day 375 represents a lab error and we believe it should be classified as a success. The Fda classified him as a failure.

Moving on to study 4409, this was an expanded access study looking at Nabi HB plus lamivudine, to assess the pharmacokinetic efficacy and safety of Nabi HB, either with concomitant lamivudine in new liver transplantations. We had 32 to start off with, of those, as well as maintenance, we had another 121 liver transplant recipients who fall into that category. We had a median follow up of 4.8 years plus serology.

Starting off with 32 patients, we excluded the following patients from the analysis. Three patients died within 30 days of the transplant.

Two patients were discovered, on the day of transplant, to have been surface antigen negative. Two patients received an HBV positive donor, but were not HBV positive prior to transplant.

One patient only received 10 doses of Nabi HB, with the last dose given within two weeks after the transplant, and we had seven patients who had less than two years of follow up.

So, of the 17 patients who were treated with Nabi HB and lamivudine and had at least 24 months follow up were included in our analysis.

Out of those patients, we had one recurrence, six percent recurrence rate, which is statistically significantly better than the 45 percent recurrence rate on lamivudine.

Again, there are some discontinuation differences between the FDA's failure rate and our failure rate. The first two patients are very similar in course to what I described in the previous study.

The first study received 10 doses of Nabi HB, the last one two weeks after liver transplant. Then he continued on lamivudine monotherapy, developed recurrence on day 548 post-liver transplant, and he died from liver failure on day 852. The FDA counted the patient as a failure. We excluded him from the analysis.

The second patient, same story, discontinued Nabi HB for economic reasons after six months, was negative up until day 534, seroconverted on day 730, 30 months after discontinuation of Nabi HB and, again, the FDA counted the patient as a failure. We believe he should be excluded.

Patient number three was clinically well throughout almost six years. This patient had no surface antigen data recorded.

He had one DNA measure reported at month 10 which, not surprising, was positive. Although we thought we had agreed that DNA should not be used as a prognosis, the

FDA did count this patient as the seventh failure in his analysis. We believe he should be a clinical success. Obviously, without serology we couldn't count him as a serology success.

This is the only patient in whom we agree with the FDA. The patient because HPs positive despite lamivudine and Nabi HB at 146 days.

So, we ended up with one failure out of the 30 patients. The FDA had eight. I think those seven patients are the absolute key to the interpretation of the data base and whether or not we believe that we have demonstrated activity with Nabi HB.

Very quickly, efficacy based on serology, these are the Nabi analysis. In study 4204, 18 cases of available sero recurrence, are statistically significantly superior to lamivudine monotherapy, with a p value of 0.0001.

Similar for Nabi 4409, one out of 11 recurrences, nine percent recurrence rate. If you pool the data, obviously, it could be highly statistically significantly better than lamivudine monotherapy.

The same story, and I won't go into it in detail. These are the clinical data based on clinical measures and you see that we are getting, again, highly statistically significant superiority to the lamivudine monotherapy.

There is a number of additional data emerging

from the literature demonstrating the need for hepatitis B immune globulin on a continuous basis.

That is actually why we believe it is important that label guidance be provided sooner rather than later, because otherwise this stuff is going to continue to happen.

This is from a paper recently submitted to Liver Transplant, an analysis done at the University of California, Irvine Medical Center, where they looked at a total of 20 hep B positive patients who underwent liver transplant between 1994 and 2001.

They all receive Nabi HB or the equivalent. Three died in the immediate post-operative period. One was lost to follow up. So, there were 16 patients who had at least two years of follow up data.

Those patients were followed for a mean of seven years. Ten continued on Nabi HB plus lamivudine for a mean of 80 months. None of those 10 patients developed recurrence of hepatitis B.

Six patients discontinued, one due to side effects, five due to the cost of the treatment or logistics. Of the six patients who discontinued Nabi HB, three out of six developed recurrence of hepatitis B within the observation period.

This obviously gives you a 50 percent recurrence

rate very consistent with data from Nabi's meta analysis from the literature.

This, very briefly, of the three patients who developed recurrence, patient number one received Nabi HB plus lamivudine for 38 months post-liver transplant, had no signs of recurrent hep B, discontinued Nabi HB as he returned to his native country. When he returned to the United States six months later, he had seroconverted and was positive, started high dose Nabi HB, became seronegative and is doing well now on a combination of Nabi HB and antivirals.

Patient number two, same story, was given Nabi HB for 22 months, did well, no signs of hepatitis B, discontinued Nabi HB as the insurance carrier stopped reimbursement.

We are seeing that all the time, due to off label, but continued on lamivudine monotherapy. Twenty-four months later, the patient seroconverted, and he died 62 months post-liver transplant.

The third patient, same story, discontinued Nabi HB and developed recurring liver disease despite lamivudine and developed finally a liver failure.

It is important to emphasize that all these three patients who showed recurrence were non-replicators at the time of transplant, which indicates that it is actually

very difficult to predict patients who are at risk of recurrence.

The number of differences which I am sure the FDA is going to emphasize in their presentation, between their and our approach, basically, the remaining difference, we had a number of agreements outlined out here.

The remaining differences remain death, missing data, as well as how to classify those seven patients, four of whom were patients who discontinued Nabi HB and then developed recurrence.

The FDA excluded all non-HBV related death that occurred in less than two years. However, even if we do agree with the FDA and exclude those four patients from the analysis, which takes the clinical analysis from one out of 41 to one out of 37, or the serology data base from one out of 29 to one out of 25, it actually does not change the overall outcome, relative to lamivudine monotherapy. We are still statistically significantly better than lamivudine monotherapy.

We made every effort, regarding missing data, to follow BPAC's recommendation and collected whatever clinical and serology data were available. However, we do agree that our missing data, that is inescapable, I guess, in retrospective data bases.

The inclusions obviously were clinically stable

in the clinical data base. We agree with the FDA's comment that this could be viewed as reflecting clinical practice rather than rigorous clinical research. However, it is standard of care and we believe is relevant for an indication like this.

It is also important to emphasize that the FDA's comment regarding missing data does not apply to the serology data base.

This is a key, as I have indicated before. The FDA counted patients who seroconverted after discontinuing Nabi HB for economic or logistical reasons as failure. We don't think that is appropriate.

We think excluding those patients, as Nabi did, is the right scientific approach. It is not anti-conservative. These patients, more than anybody else, demonstrated the need for the continued use of the drug.

In summary, we believe that we responded positively to all BPAC's recommendations, that we provided clinical data from the time of transplantation.

Pharmacokinetics should be captured that could be used to guide dosing. We did that from study 4204. Historical control can be used, and you saw the meta analysis we did.

Basically, the two year follow up required for subjects receiving concomitant lamivudine, and we have

follow up data in the transplantations that well exceed the two year recommendation.

We think that this drug has a very favorable risk benefit ratio. As I said, it has been used since 1999. In the FDA post-marketing data base there are 30 adverse events reported in more than 60,000 infusions.

Certainly, it is well characterized from a safety perspective. There is no reported medication failure. Approximately 80 percent of the recurrence rate prior to HBIG is well documented in the literature, a 45 percent recurrence rate with lamivudine, and that compares with what we found in our clinical trials, a three percent failure rate in 41 new transplantations, and a zero failure rate in the 173 maintenance patients who we also gathered data on.

The FDA's questions to the BPAC basically criticizing the post hoc inclusion and exclusion criteria, however, we excluded and included patients based on BPAC's recommendations. The remaining issues, obviously, we have already talked about what we are going to discuss today.

The observational nature of the information, the data limitations and the lack of analysis plan, the clinical data base, while obviously the FDA is correct, that it is observational in nature, it does follow standard of care and we believe it is relevant.

The surface antigen has been accepted as a surrogate by the FDA and by this committee and we therefore believe that the serology data base is not observational and does stand on its own merits. The analysis plan we put together was based on this committee's recommendations from two years ago.

Retrospective data, including data from an expanded access program and PK study, is that sufficient to demonstrate efficacy.

We believe it is. We agreed with the FDA to a retrospective data collection. The efficacy, as you have seen, if you agree with our interpretation of the failure of the patients, which the FDA counted as failure, we have a highly statistically significant superiority of Nabi HB plus lamivudine as compared to lamivudine monotherapy, with a p value less than 0.0001, and we had the same data and even stronger p value in the clinical data base.

We don't believe that the statistical analysis should be invalidated by counting patients who seroconverted as failures.

We did do some sensitivity analysis to try to demonstrate the robustness of the analysis and tried to address some of the issues the FDA raised.

The FDA felt that we should use a recurrence rate of 35 percent following meta analysis, representing the

lower bounds of the confidence interval.

Although we don't think that is appropriate, because that was not the recurrence rate which the meta analysis came up with, but even if you do apply a 35 percent recurrence rate, Nabi's pooled recurrence rate is still highly statistically significantly superior to a lamivudine recurrence rate of 35 percent.

Even if you are assuming the 35 percent recurrence rate on lamivudine and if you exclude patients who died before two years of non-HBV related disease, which the FDA recommended should be excluded, and patients who only received Nabi HB monotherapy, rather than the combination therapy, it is still highly statistically significantly superior to lamivudine alone, with the p values outlined on this slide.

So, we believe that approval of Nabi HB intravenous is warranted and not anti-conservative, given that, firstly, despite the retrospective nature of the data bases, we clearly believe that these two studies demonstrated efficacy.

BPAC's recommendations were followed to the extent that it was possible in a retrospective data analysis. Nabi HB is standard of care and has been so since it was introduced in 1999.

I think it is important to emphasize, as I did

earlier, that this is an orphan drug indicator with an extremely small number of evaluable patients, and that really does limit what you can do in your development program.

As an example, myozyme from Genzyme was recently approved as a treatment for Pompe disease based on an open label study in 19 patients.

For comparison, there are approximately 300 new cases of Pompe disease in the United State per year. So, even more patients than we actually have available for hepatitis B.

FDA stated a desire to bring standard of care, off label uses on the label. That is certainly what we have tried to do with this application.

This is very important, we believe in talking to transplant surgeons. We think it is very important to prevent premature discontinuation.

As you have seen, from our data base, as you saw from the study, when you discontinue hepatitis B immune globulin, there is a very substantial risk that these patients are going to recur within a short period of time.

That is why it is critical for this patient population to provide some label guidance, and that needs to be done sooner rather than later.

The FDA, in their response to us, wanted us to do

a prospective study. The problem we have with that, we have no problems doing it as a post-marketing commitment. We would be very happy to do so.

If we are to go the study as a basis for licensure, it is going to delay the licensure by approximately five years.

The time line is laid out here, half a year for study planning and initiation, one year enrollment, and recognizing the small number of patients available for this indication.

You ask for two years of follow up. Then we need to gather the data, do the analysis and prepare the BLA, and then I think this might actually be optimistic, a one-year FDA review and approval, recognizing that this submission was done back in 2002.

So, the fastest possible scenario we perceive is that it would delay the instruction of this indication on the label by five years.

During this period of time, patients are going to continue to be at significant risk of recurrences and potential death as you have seen for some of these studies, and we don't think that is in anybody's interest.

So, basically, we believe -- I don't want to repeat myself -- we do think that Nabi's data support the following claim, that Nabi HB intravenous is indicated for

the prevention of hepatitis B clinical disease in surface positive liver transplant recipients, and I am very happy to take any questions you may have.

DR. ALLEN: Thank you, Dr. Rasmussen. We will take questions and comments for clarification only at this point.

DR. CRYER: I have got a couple of questions. The first one is, the control group that you used was retrospective. Did it include patients who died early and patients who quit taking their drugs, in other words, some of the same criteria that you used for exclusion?

DR. RASMUSSEN: In our meta analysis we only included patients who had been on lamivudine for two years.

DR. CRYER: And they were all clinical failures that survived at least two years.

DR. RASMUSSEN: Right.

DR. CRYER: The other question I have -- I don't know if you did the analysis -- is the outcome of patients who quite taking the drug in your retrospective study statistically significantly worse than the patients who continued the drug?

DR. RASMUSSEN: We actually didn't do the analysis because numbers were relatively small, but the answer would be yes.

I think we had seven patients who stopped taking

the drug, of whom four developed recurrence. That obviously gives you a very high recurrence rate. Four out of seven -- whether it would have bene statistically significantly different from the one out of 41, I am sure it would be, but we didn't do the specific analysis. I think we answered the question, though.

MR. BORTEY: Enoch Bortey with Nabi Biopharmaceuticals. In addition, we looked at the demographic characteristics of those who were lost to follow up or had inadequate follow up.

Then the question is, are these subjects very different from those with two years of follow up. The baseline characteristics are very similar, comparably. There is no difference.

DR. KATZ: If one of the liver experts sitting at the table can maybe answer this, over the time when the historical controls were accrued and subsequent, the way we do things now, is there any reason to think the way we immunosuppress and the way we maintain these patients, apart from these agents, would impact the risk of recurrence?

DR. DI BISCEGLIE: I think immunosuppressive regimens have been fairly stable for the last eight to 10 years, I think.

DR. ALTER: What I wanted to comment, a critical

assumption of your analysis is that a patient who is well clinically must be surface antigen negative.

DR. RASMUSSEN: Right.

DR. ALTER: I would like to hear your data to support that and, two, hear from Jay and Adrian as to whether that is a valid assumption.

R. RASMUSSEN: Right. We have some back up slides which are specifically addressing that one. So, if you give me back up slide number 49, this is basically showing the correlation from the literature between liver pathology and surface antigen stages.

As you can see, basically these are the various studies which look at it. They correlated clinical outcome as well as liver biopsies to surface antigen positivity or negativity.

As you can see, for patients who are surface antigen negative, this is the number of patients who have significantly abnormal liver pathology based on liver biopsy.

You will see that the average number is close to 100 percent. So, virtually everybody who is surface antigen positive post liver transplant, have significant abnormal liver pathology.

If you compare that to the patients who are surface antigen negative, you will see that the number of

patients with abnormal liver pathology is eery, very small. Indeed, it is less than 10 percent.

These are the data and there have even been a couple of major reviewed papers addressing that. That is the main reason why a number of transplant surgeons don't routinely monitor the surface antigen status.

They monitor the patient clinically and only if they have signs of recurrent liver disease are they then going to monitor or check for their surface antigen status.

So, there is very good evidence in the literature demonstrating the correlation between surface antigen positivity and the patient's clinical status. I don't know if you want to add something, Dr. Hoofnagle.

DR. BISCEGLIE: I guess what exactly is significant liver pathology. I mean, this is a fairly unsophisticated analysis. What are the transaiminases? How much fibrosis is there? How much inflammation is there?

You have a slide on efficacy based on clinical status. What exactly is clinical status? These are things we need to know.

DR. RASMUSSEN: That was defined as no indication of recurrent liver disease. So, normal transaminases, no other sign of recurrent hepatic disease.

DR. BISCEGLIE: What other signs might there be? Normal liver enzymes I heard, but what other signs were

assessed?

DR. RASMUSSEN: This would be something like obviously jaundice or nausea or abdominal pain or a whole range of clinical symptomatology.

I do think it is important to emphasize, though, that you can certainly argue about the clinical definitions, and I think rightly so.

Even if you only focus on the patient in which we have two or more years of serology, we are still statistically significantly superior to lamivudine, if you accept our expectation of the patients who recurred after discontinuation of Nabi HB.

If you exclude those patients, like we did in our analysis, the serology data base does stand on its own and is highly statistically significantly superior to lamivudine monotherapy.

DR. FINNEGAN: You probably don't have the information for this but I am really interested in the economic data. In other words, do you have any idea how much it costs to do the liver transplant and, in those patients for whom the drug was discontinued for insurance reasons, what was the cost to the entire system prior to their death.

Then those patients who received the combination, how many of them returned to the work force and, therefore,

were able to contribute economically.

The second part of that question is, how many of these patients were medicare and medicaid patients.

DR. RASMUSSEN: Your question is a good one. I am afraid I don't have the answer. We do have a number of patients who did recur who did return to the work force.

I think some of the hepatology transplant surgeons in here would be in a better position to address the cost of a transplant. I don't know what it is. It is certainly expensive, but I can't quantify that, unfortunately.

DR. FINNEGAN: The point of my question was, I think a lot of these patients do return to the work force and I think that is an important criteria to look at.

DR. RASMUSSEN: Yes, it is. It is a good point.

DR. DI BISCEGLIE: A follow up to that, you had sort of -- what is the evidence that you have that the treatment discontinuations were due to off label use as opposed to just an insurer not paying.

That is kind of what you are asserting, I think, that treatment discontinuations were related to off label use. What is your evidence for that?

DR. RASMUSSEN: What we do know from a couple of patients in our own data base, as well as patients from the literature -- and you are going to hear about that through

the presentation I believe later today as well -- there are a number of examples where insurance companies, because the drug is off label, have stopped reimbursing after one year or after two years and say, this is off label, there is no indication that it is working, and we don't want to reimburse it.

So, we know that is the case in a number of cases. Some of the other discontinuations were not because of insurance, but it has certainly been because of the lack of guidance and with the emergence of antivirals, there have been a number of different sites across the United States which have tried to simplify the treatment regimens by either terminating Nabi or hepatitis B immune globulin to see where you could make do on antivirals alone, or an alternative, to try to reduce the dose.

The feedback we are getting -- and once again, I would be very interested if there are any transplant surgeons who might be able to address that -- but the feedback we are receiving is that there have been a large number of recurrences and most sites now are going back to using hepatitis B immune globulin on a continuous basis, because the evidence in the literature is mounting that these patients really need it on a chronic basis.

Is that going to continue be so? We don't know. Obviously, as the antiviral drugs are getting better and

more effective, that may well change.

Certainly with present antivirals, there is no indication that you can safely discontinue the use of hepatitis B immune globulin.

Obviously, we can't talk about it because it is off label, and that does make it very difficult for various sites, because there is no standardized guidance.

That is one of the key reasons why we believe it is important to get it into the label, to provide that guidance to the transplant community.

DR. GOLDING: Just a quick comment. There is some information included in this presentation that was not submitted to the FDA, was not reviewed. We would encourage the company that it is important that, if you submit it, if it is based on the abstract, it is the UCI data.

Our presentation is related to the retrospective analysis of two studies, 4204 and 4409. The questions are based on our careful review of those data, and we would ask the committee to answer the questions based on those studies and not on data that we haven't had a chance to look at.

DR. KUEHNERT: I was trying to get a handle on what actually you are trying to get an indication for. So, if this got approved, you would recommend lifelong treatment for these patients; is that right?

DR. RASMUSSEN: Correct.

DR. KUEHNERT: What is the average life span for liver transplant patients? What are we talking about here, 10 years or longer?

DR. RASMUSSEN: This is actually an indication where people are doing relatively well. I don't know what the median is. It certainly could be decades.

Once again, at the moment, the science support a need for continuous administration, which is not surprising, recognizing that the virus doesn't go away. The virus is still there.

As more effective antivirals are coming along, certainly I think that needs to be tested. I am not saying that 20 years down the road people should still get hepatitis B immune globulin, but based on current information, that certainly seems to be what the science is indicating.

DR. KUEHNERT: So, it is basically for life. The other question I had was about, this is for hepatitis B positive recipients only.

So, for a situation where the transplant was -- the donor was hepatitis B positive, whether this was advertent or inadvertent, that is not part of the indication?

DR. RASMUSSEN: That is not part of the

indication. Your question is a good one, and it is actually being used off label in that indication as well.

We have no reason to believe that it would be less efficacious, but the number of patients that we had access to who received an HBV positive liver was so small, I think it had two or three patients across the studies. So, we decided to exclude them rather than to complicate matters.

As a consequence of that, we don't have the data, but that is really something, I guess, which we and others would be interested in for the future. It is used off label in those situations as well.

DR. KULKARNI: I just am curious about your dosing interval, being a pediatric hematologist. I know your recommendation was monthly.

I was wondering whether that played a role in the economic reasons why people dropped off. What is the longest interval that one could go safely without having a recurrence.

DR. RASMUSSEN: Our monthly recommendation is based on measurements of trough anti-HBs titer levels. We know that the half life of the immune globulin is about 20 days or something along those lines.

If you go beyond one month, you certainly start to see lower trough levels. So, the one month period seems

to provide the optimal level of protection, so to speak.

That is not to say that it would not be possible -- I am sure sites have experimented with that, that in certain types of patients it may be possible to only dose in one and a half month intervals or two month intervals.

Certainly the data we have indicates that the optimal regimen, from a pure scientific perspective, not taking cost or inconvenience into consideration, that monthly administration seemed to be the optimal.

DR. HOOFNAGLE: I thought it was a typographical error in this submission. You say that the populations used in the statistical analysis were patients who were enrolled and were surface antigen negative after liver transplant.

Does that mean that people who didn't become surface antigen negative were included and how many such patients were there?

DR. RASMUSSEN: Yes. Well, we obviously wanted to assess the ability of the drug to keep and maintain surface negative status.

So, patients who never converted after the transplant were excluded. I don't know exactly how many we had. We only took patients for the analysis who were surface negative at the time or after the transplant.

DR. HOOFNAGLE Well, you couldn't compare that to the lamivudine studies, then, because they certainly didn't

exclude those patients. In lamivudine, some patients never become surface antigen negative after transplant.

DR. RASMUSSEN: Right, but those patients were -- in the meta analysis, those patients were excluded from lamivudine as well. So, it was a comparison of apples versus apples.

DR. SIEGAL: I have a naive question and that has to do with this slide. You show correlation between hepatitis B surface antigen anemia and liver pathology, but that, on the left hand column, those people, are they antigenemic in spite of the administration of IV gamma globulin that is supposed to put them into antibody excess?

DR. RASMUSSEN: This is just a repeat from the literature. These patients received a variety of different treatment.

DR. SIEGAL: So, these are all historical controls.

DR. RASMUSSEN: Yes.

DR. SIEGAL: You are doing something artificial here which is that you are taking the population of people who are antigenemic and giving them a lot of antibody and putting them into antibody excess.

So, in effect, you are making the antigen go away. The question is, does that correlate with liver pathology, that particular situation.

DR. RASMUSSEN: Yes, it does. That is also -- I think it was part of our submission. That is very well documented in the literature, that you do -- it is significantly correlated.

DR. SIEGAL: Do these patients have progressive successive liver biopsies during this study?

DR. RASMUSSEN: A number of them had, yes, not all of them.

DR. SIEGAL: They cleared their liver pathology? They did not develop liver pathology?

DR. RASMUSSEN: No. Really, the literature is overwhelming in terms of the correlation between normal liver pathology and antigen status or surface antigen status.

DR. ALLEN: An interesting point there. Thank you, Dr. Rasmussen. We do need to move on. We are now going to have two presentations from the Food and Drug Administration, first, an FDA clinical review by Dr. Maplethorpe.

Agenda Item: FDA Clinical Review.

DR. MAPLETHORPE: My presentation will discuss the submitted data to support the following indication, intravenous administration of hepatitis immune globulin, intravenous human HBIG IV Nabi HB intravenous, will present HBV recurrence after orthotopic liver transplantation, OLT,

for hepatitis B disease when given with HBV antiviral therapy.

Nabi's currently licensed hepatitis B immune globulin human product is labeled for intramuscular administration.

The label indications include the following, acute exposure to needle stick to blood containing HBs antigen, sexual exposure to HBs antigen positive persons, perinatal exposure of infants born to hepatitis Bs antigen positive mother, and household exposure to persons with acute HBV infection.

This slide shows the order of my presentation. I will briefly discuss the studies conducted by Nabi. I will then briefly discuss the original attempt to license this product for this indication, using data from another manufacturer's product that were obtained in a non-IND study, and the reasons why this attempt failed.

I will then present a detailed review of Nabi's current attempt to license this indication, using retrospectively collected data from OLT subjects who received the Nabi product.

Over the last 15 years, intravenous administration of hepatitis B immune globulin intramuscular has become standard of care in preventing reinfection of the graft in patients who have undergone orthotopic liver

transplantations for hepatitis B virus disease.

In order to add this indication, Nabi submitted IND 8452 in 1999 -- there was a series of other INDs earlier -- and conducted four studies which are described as follows:

Study 2906 was a pharmacokinetic study in 21 OLT subjects, more than three months after OLT, that is, at the earliest time when PK parameters have stabilized after OLT.

The product was Nabi HB cangene, manufactured by Cangene Corporation. The dose was 180 international units per kilogram intravenous.

Their second study was 4406, which was an open label extension study of 2906 for 10 subjects, conducted in order to provide product to these subjects.

Study 4203 was a pharmacokinetic study in 21 OLT subjects more than six months after OLT, that is, at a time when the PK parameters have stabilized after OLT.

The product was Nabi HB Boca, the current version of the product, manufactured in Boca Raton, Florida. The dose was 10,000 international units IV monthly for three months.

Lastly, study 4409 was an open protocol for use of the product in 153 HBV OLT subjects. Dose schedules and monitoring were not standardized.

FDA recommended that a prospectively designed

study be conducted to demonstrate safety and efficacy, but Nabi did not follow this recommendation.

Instead, Nabi proposed to use the clinical data from a non-IND study conducted at the University of Virginia from 1992 to 1995.

This study used intravenous administration of high doses of an HBIG intramuscular product from another manufacturer to prevent graft reinfection after orthotopic liver transplantation in patients with HBV disease.

This study is sometimes referred to as the McGory study, after the first author. The McGory study was a presentation of the results of subjects transplanted at the University of Virginia from 1992 to 1995.

There is no submitted protocol for this study, however, the publication indicates that there was a treatment plan to use intensive dosing with HBIG during the peritransplant period, followed by monthly dosing with 10,000 international units of HBIG after month three.

Serum anti-HBs levels and serum HBs antigen levels were monitored periodically, but not by specified schedules, and HBIG dosing was adjusted according to rules that were developed and which changed during the study time period.

Because the subjects of the McGory study were apparently all subjects transplanted at the University of

Virginia during 1992 to 1995, the time course of follow up was heterogeneous, and varied from two to 55 months, because there was no specified time period for follow up.

FDA agreed to consider this approach if those data could be shown to demonstrate clinical benefit, and if data could be submitted to show that the same result would be obtained if the Nabi HBIG IV product had been used. In November 2002, Nabi submitted a BLA for this indication, that was based on the McGory study.

The McGory study is a very influential study in the field of HBV related liver transplantation. It is one of the studies that defined dosing practices for this off label indication for HBIG intramuscular.

However, the submitted data for the McGory study were judged not to fulfill the usual FDA requirements for a pivotal study to support product licensure.

Among the deficiencies in the data were the following: There was no submitted control data base. Comparisons were made to literature references.

The analysis was descriptive. No hypothesis was tested in the single center study. There was no prospectively described plan for analysis.

However, these deficiencies were not the major reason for the failure of the McGory study to support this indication.

A major short coming of the McGory study, as support for this indication for the Nabi HBIG IV product, is shown in this slide.

This slide shows the serum levels of anti-HBs that were achieved after dosing in the McGory study, which is the top line, and which is labeled Study 4404 and in the pharmacokinetic study, 4203 of Nabi HB, which is the bottom line.

This comparison is not entirely appropriate because the McGory study did not conduct a rigorous pharmacokinetic study, despite the prominent role that pharmacokinetic considerations play in that publication.

In the McGory study, serum levels of anti-HBs and HBs antigen were measured as non-scheduled time points. So, data for any given subject are sketchy.

However, if the pharmacokinetic data are pooled for all subjects and a population based PK analysis is formed, one can come up with the PK curve that is depicted on this slide.

For both study 2403 and the McGory study shown here, the data are from OLT subjects who are more than six months after the time of transplantation.

Therefore, the high variability in PK parameters in the peritransplant period, and in the immediate post-transplant period, is avoided.

In both study 4203 and in the McGory study, the administered HBIG dose is reported to be 10,000 international units intravenously.

One can see that similar dosing in similar subjects resulted in high dissimilar serum levels of anti-HBs after dosing.

The McGory study achieved higher serum anti-HBs levels almost two-fold higher for the first seven days after dosing.

The McGory publication makes a strong point about the importance of serum anti-HBs levels, and their importance in preventing HBV recurrence.

Therefore, the differences we see depicted on this slide lead us to conclude that Nabi has not fulfilled the second requirement for the use of the McGory data to support this indication, namely that the data must show that a similar result would have been achieved, had the Nabi HBIG IV product been used in place of the product used in the McGory study.

The reasons for the failure of the McGory study to serve as a pivotal trial for licensure were communicated to Nabi in the first complete response letter dated May 27, 2003. These reasons were also discussed with Nabi at a July 9, 2003 meeting.

Nabi has offered explanations to account for the

observed differences and has proposed alternative procedures to address these differences, but Nabi has not proposed to submit clinical data that can address this issue prior to product licensure.

In the summer of 2003, in an effort to find a way to license this product for this indication, FDA considered Nabi's proposal to retrospectively analyze study data and medical records, in order to demonstrate that the Nabi HBIG IV product can maintain HBs antigen seronegativity.

Nabi asserted that a direct demonstration of clinical benefit using their product would be impossible, due to ethical considerations, and that maintenance of HBs antigen seronegativity was the end point that physicians feel is the important goal of treatment.

This issue was brought to the March 2004 BPAC, which voted to accept the end point of maintenance of HBs antigen seronegativity for product licensure for this indication.

The BPAC specified that there should be one year follow up for use of HBIG IV monotherapy, and two years follow up for the use of HBIG IV plus lamivudine combined therapy.

BPAC did not specify any additional details about the analyses that should be performed. As a result, Nabi analyzed their data for its ability to support the end

point of maintenance of HBs antigen seronegativity.

This slide is a graphical depiction of the data base that was submitted by Nabi to support the OLT indication.

I have had copies of this passed out to members of BPAC, if you want to use those to follow. It appears to be very complicated, and I do not expect you to be able to analyze it from this slide, but I would like to point out some features of this graphical depiction of the results that will help us later in analyzing the HPs antigen seropositives.

First, I want to point out that two studies were pooled to form the data base that we will analyze. Study 4204, the top study, was conducted under another IND by another sponsor, Dr. Roland Dickson.

This study was a nine month pharmacokinetic study of the use of Nabi HB in the setting of newly transplanted patients with HBV disease who also received lamivudine at the time of liver transplantation.

The objective of the study was to examine HBIG IV dose requirements in this setting, and it was not designed to support the present indication.

Study 4409, below this red line, these data, I have already discussed. This was an open protocol intended to make HBIG IB generally available in the time period

immediately prior to product licensure.

As such, the subjects and the study procedures were highly heterogeneous. Study 4409 was also not designed to support the present indication.

In order to better understand the features of this graphical depiction of the data, I have selected a subset of subjects, so you can see the features as I described them. The same features, of course, applied to the entire chart. So, here is a subset of some subjects.

In this graphical depiction, you can see that the patient identifiers are listed down the chart on the left side.

Across the top there are the numbers from -1 to +24. These numbers correspond to the 24 months or two years of monitoring that was specified by the March 2004 BPAC for the combination of HBIG IV and lamivudine therapy. Therefore, each one of these little boxes corresponds to a one-month time period.

If there is a number within one of these little boxes, it represents the number of times there were measurements of HBs antigen during that month.

If there were no HBs antigen measurements during the month, the box is blank. You can see that the majority of the boxes are blank, meaning that measurement of HBs antigen was not a routine event.

Next, I want to draw your attention to the boxes with red backgrounds. A red background signifies that at least one HBs antigen measurement was positive during that month.

I also want to point out the box with the X in it, up here. An X signifies that the subject died during that mont.

In this graphical depiction, you can immediately pick out subjects who seroconverted to HBs antigen positive, and you can see their serological status at the time of their death.

The next feature of this chart that I would like to point out are the transitions to shaded background toward the end of the 24-month time period, such as here, a transition to a shaded background.

A shaded background means that there were no additional HBs antigen measurements during the remaining part of the 24 month monitoring period.

In this way, you can immediately see that there is a lot of missing data that would be needed to decide on the HBs antigen serological status at month 24 for many of these subjects.

The last feature of this chart that I would like to point out is the column on the right, that contains comments, including a question mark for many of the

entries.

The comments describe HBs antigen serological status at time points after month 24. A question mark means that there are no additional HBs antigen measurements after month 24 that can inform us of that subject's HBs antigen serological status after month 24.

So, here is the data set again. For study 4204, you can see that HBs antigen was measured regularly during the nine-month course of the study but then only rarely after the study time period was completed.

For the open protocol, study 4409, you can see that measurement of HBs antigen was a sporadic event. I know this has been a lot of information to take in, but at least it gives you some impression of the complicated task of retrospectively analyzing studies that were not conducted to support a given indication. We will return to this method of analysis soon when we describe the HBs antigen seropositives.

In order to compare their outcomes to a control data base, Nabi needed an historical control for the HBS antigen seroconversion rate for OLT subjects in the setting of combined HBIG IV plus lamivudine therapy, or lamivudine monotherapy.

To do this, Nabi examined 36 publications from the time period 1980 to 2005 and came up with five

publications depicted on this slide, as suitable for inclusion into a meta analysis of the results shown on this slide. Dr. Jessica Kim will discuss this meta analysis in detail in her talk.

Nabi states that their meta analysis results in an HBV two-year recurrence rate, 45 percent for lamivudine monotherapy with a lower bound at the 95 percent confidence interval at 35 percent.

The next two slides are taken from the talk of Dr. Anna Locke of the University of Michigan, the talk she gave at the March 2004 BPAC, in which she reviewed the literature of OLT for HBV disease, and the use of HBIG and lamivudine in this setting.

I include these slides to give you other ideas on the response parameters in this setting, and to show that there is no universally accepted fixed rate for outcomes.

In this slide, Dr. Locke told us that for lamivudine monotherapy the HBV recurrence rate at one year is 10 to 30 percent, and this increases to 30 to 40 percent at three years, due to the emergence of resistant mutations.

From this, you can see that Nabi's meta analysis gives a recurrence rate that is at the high end of some estimates.

In this slide, Dr. Locke told us that the HBV

recurrence rate decreases to less than 10 percent when using combination prophylaxis of HBIG plus lamivudine.

When I went into the graphical depiction of the pooled data from studies 420 and 4409, which form the basis for the new pivotal data base, I showed that there were many instances of missing data, namely many time points for which there were no HBS antigen measurements.

The Nabi analysis seeks to rescue these missing data by introducing the argument of clinical stability, which is not clearly defined.

Nabi states that clinicians do not measure HBS antigen if the patient is clinically stable. Nabi states that, if patients are monitored clinically and are judged to be stable, then this clinical stability can be taken to be a sign of HBS antigen seronegativity.

Therefore, Nabi analyzes their pooled data from studies 4204 and 4409 by two approaches. The first analysis is according to clinical stability, and the results are shown on this slide.

Nabi states that there was only one HBS antigen seroconversion among 41 subjects. This analysis considers all subjects for whom there are no data on HBS antigen serological status at the two year time point to be successes.

This slide shows Nabi's analysis when the

analysis is restricted to subjects for whom there are HBS antigen data over the required two year time period. In this case, Nabi states there was only one HBS antigen seroconversion among 29 subjects.

The FDA analysis differed considerably from the Nabi analysis. In the next two slides, I would like to lead you through the process we used to find the set of subjects from studies 4204 and 4409 that could be analyzed for this end point.

So, if we look at this slide, we see that in study 2404 there were 30 subjects originally. Two of these subjects died within 30 days of transplant. So, if we remover those, we are left with 28 subjects.

Two subjects were lost to follow up. So, if we remove those two subjects, there are 26 subjects. Two subjects died in the interval of 30 days to two years and the death was judged not to be HBV related.

Now, there are various ways one can handle deaths in clinical trials, but if we just remove these two non-HBV related deaths from the data base, we get 24 subjects.

Five of these subjects in study 4204 were inadequately monitored for HBS antigen to two years. So, these would be in the group for which there was that long shaded background which represents an absence of information on HBS antigen, serological status, and there

were no data after 24 months that could inform us of the status.

So, if we removed those subjects who did not have data that could inform us, we were left with 19 evaluable subjects from study 4204.

This is the same process for study 4409, which was the open protocol study. Study 4409 had 153 subjects. If we limit it to subjects who received HVIG at the time of transplant, that brings it down to 32 subjects.

So, we start off here with 32 subjects. Of these 32 subjects, 22 subjects were on HBIG monotherapy. They received no lamivudine.

Nabi includes this group in the data base by stating that, had they received lamivudine, they would have done even better.

So, we are always going to have the subset of HBIG monotherapy subjects, as we do this analysis. So, 32 subjects, 22 on HBIG monotherapy.

Three died within 30 days. That brings us to 29 subjects, 19 of which were on HBIG monotherapy, no lamivudine.

Now, we exclude the following four subjects. The first subject, 4409 3013, was discovered to be HBS antigen negative at transplant.

The next two subjects, 4409 10-005 and 10-007,

were not HBV infected, but received an HBV positive liver. So, those two are removed from the data base.

Then subject 4409 28-004 had no evidence of HBS antigen positivity prior to transplant. So, if we remove these four from the data base, we are left with 25 subjects, 15 of which were on HBIG monotherapy.

Now, two subjects died between one month and two years. As I said, there are many ways one could treat deaths on study. We decided here to remove the non-HBV related deaths.

So, if we remove those two, we are left with 23 subjects, 14 of which are on HBIG monotherapy. Now, there were 12 subjects which were excluded for less than two years follow up.

So, once again, these will be subjects who had those shaded bars out to month 24, and no data after month 24 that could inform us what the status at month 24 was, 12 subjects. So, we exclude those. We are left with 11 subjects, three of which are on HBIG monotherapy.

So, really, there are only eight subjects that were actually on combined HBIG and lamivudine therapy from study 4409 that we can include in our data base.

Okay, this slide summarizes the evaluable data base for the pooled data. You can see that there were 19 evaluable subjects from study 4204 and eight evaluable

subjects from study 4409, to give a total of 27 evaluable subjects.

If we include the three evaluable subjects who received only HBIG IV and no lamivudine, the total number of evaluative subjects is 30.

Among the subjects in the evaluable data base, we found eight instances of HBV recurrence as shown by HBS antigen seroconversion or, in one instance, by HBV DNA recurrence.

So, if we take the recurrence rate at eight over 27, you can see that the seroconversion rate is essentially 30 percent and the confidence intervals are 95 percent confidence intervals from 14 percent to 50 percent.

If we include the three subjects who received HBIG monotherapy, then the recurrence rate would be eight over 30, which is 27 percent, and the 95 percent confidence interval would be 12 percent to 46 percent.

In the FDA review of the data base, we found eight subjects who could be classified as treatment failures. This slide shows the HBV recurrences and uses the graphical depiction method shown earlier.

So, if we just go through this, let's look at this first subject, 4204 1-004. This subject died in month two, and the investigator judged the death to be HBV related. So, it is really the only true clinical outcome we

have in this data set, and we have included this as a failure because the investigator said the death was HBV related.

The second subject, 4204 2-003, had a number of negative measurements followed by a positive measurement at month 13, and then subsequently two negative measurements, no measurement from month 19 out to 24, and no subsequent measurements. We considered this a failure due to the positive reading at month 13.

The third subject, 4204 2-005, had negative measurements out to month nine, no additional measurements out to month 24, and a positive measurement at month 37.

Since we can't truly ascribe a time point for the seroconversion, and there is all this missing data here from month 10 out to 24, we have to consider the possibility that it occurred by month 24. So, we called that one a failure, too.

The fourth subject, 4204 15-001, had some negative measurements out through month nine, no measurements out to month 22, which was positive, and then no subsequent measurements, and we considered that one a failure. We took an intent to treat here, in other words, whether or not the product was discontinued or not.

In study 4409 2-003, this is the subject that we both agree on. You see that there were initially negative

measurements out to month three. Month four was positive, as was month eight, as was month 14, and then a negative measurement at month 20, and then positive measurements again after month 24. We both agree that this was a failure.

The sixth subject was 4409 16-010. This subject had one measurement at month 18, no additional measurements out to month 24 but then, immediately thereafter, a positive measurement at month 25 and, given the lack of data in this time period, we have to consider the possibility that they seroconverted by month 24. So, we consider that patient a failure.

Subject 4409 3-002, this is a very interesting subject. This person was HBS antigen positive 200 days prior to transplanted, was transplanted.

There were no additional measurements at all of HBS antigen for more than 1,000 days after transplant, no submitted measurements.

However, there were many measurements of serum anti-HBS levels, and HBV DNA was measured at month 10 and was found to be strongly positive.

Given the total lack of submitted data on HBS antigen measurement, we considered this patient to be a failure. In general, we did not use DNA data, and in this case DNA data is all that we have.

The last one is this subject, 4409 5-007. Every single measurement that was done on this patient was positive, and we considered this one to be a failure. So, those are the eight cases that we considered to be failures.

The next three slides present three ways in which the FDA analysis procedure differed from the Nabi analysis procedure.

The first way that we differed was in the treatment of deaths. As I said earlier, deaths can be handled different ways in different analyses plans.

What we did, FDA removed HBV non-related deaths from the data base. Nabi included HBV non-related deaths in the data base and counted them as successes if the previous HBS antigen measurement was negative. Another way to consider deaths is to count them as failures. We just removed them.

The second way we differed was in the handling of missing data. If HBS antigen measurements were not available to satisfy the requirement for at least two years, HBS antigen monitoring for combined HBIG IV plus lamivudine therapy, Nabi counted subjects as successes if they were monitored clinically for at least two years and judged to be clinically stable.

FDA removed these subjects from the data base due

to missing data. FDA's approach was consistent with Nabi's analysis plan, submitted on September 3, 2003, when we first discussed the use of retrospective data. We used their analysis plan.

The third way we differed had to do with the cases of HBIG IV discontinuation. Seven subjects discontinued HBIG IV therapy prior to two years.

Two of these seven HBS antigen seroconverted. Nabi excluded the two of the seven subjects who were HBS antigen seroconverters and included the five of seven subjects who remained HBS antigen negative.

So, they handled the discontinued -- the subjects who discontinued HBIG differently, depending on whether or not they seroconverted.

FDA used an intent to treat approach and did not exclude any of the seven subjects for the reason of HBIG IV early discontinuation.

This slide shows the point estimates for the failure rate if other, more stringent, rules are used for the classification of outcomes.

Some analysis plans may count all cause mortality as treatment failures, due to uncertainty about the underlying cause for the deaths.

Other very stringent analysis plans may count as failures those subjects for whom there is no information on

the primary end point outcome.

The table in this slide shows various combinations of rules related to death and subjects with missing data, as shown in the table headings.

You can see that the point estimates for the failure rate, using these more stringent rules, go from our present failure rate of eight out of 27, or 30 percent, up to as high as 40 out of 59, or 68 percent, for the most stringent case.

One can see that the FDA approach to the data analysis has been on the less stringent side of all possible approaches.

The next two slides give the reasons for the discrepancies in outcome classifications between FDA analysis and the Nabi analysis.

So, the subject IDs are on this slide, and this slide shows the reasons why FDA included a subject, and over here it gives Nabi's reasons for excluding the same subject.

This subject, 2404 2-003, was positive at month 13. That was our reason for including them. The Nabi reason was that they had less than two years follow up.

Then we have these three subjects, 4204 2-005, 4204 15-001, and 4409 5-007. 2-005 was positive at month 37, day 906, 15-001 was positive at month 22, 5-007 was

positive at all times. Those were our reasons for including them, because they were positive.

Then, Nabi's reasons for excluding these had to do with HIB IV discontinuation, and you can see that they seroconverted at time points quite long after discontinuation, except for this one, which discontinued after 10 doses.

It is really not clear, from the submitted data, whether or not this was a case of the investigator giving up on continuing to give HBIG IV in the case of someone who clearly seroconverted.

This subject I discussed was the one who was HBV DNA positive at month 10, and that was the only data that we had in the submitted data base. There were no HBS antigen measurements for this patient submitted. So, we included that patient. Nabi excluded them because there were no HBS antigen measures.

This is the other side of the coin. It shows the subjects that were excluded by DNA and gives the reason, and then it also gives Nabi's reason for including them.

The first three were HBIG monotherapy subjects. We didn't think it was appropriate to include this subset in the analysis.

It doesn't make a whole lot of difference in the numbers if you include them, but we excluded them and Nabi

accepted HBIG monotherapy. Those subjects were 4409 1-002, 4409 5-010, and 4409 18-001.

Then the last four subjects, we excluded them because they were deaths and they were judged not to be HBV related.

Nabi included these four subjects who died because it appeared that they might be HBS antigen negative prior to death, although there were some with missing data around the time of death. Those subjects were 4204 4-001, 4204 4-003, 4409 3-009, 4409 2-005.

So, this is my last slide, the summary slide. To summarize my talk, there were no prospectively designed clinical trials of Nabi HB to demonstrate safety and efficacy for the HBV immunoprophylaxis indications in patients undergoing OLT for HBV disease.

The attempt to use the McGory data failed because serum ant-HBS levels were not comparable. HB antigen sero-negative end point failed due to unacceptably high HBS antigen seropositive activity rates. So, are there questions?

DR. ALLEN: We are almost an hour behind at this point. Are there questions with regard to clarification only?

DR. SCHREIBER: One thing that strikes me, Dr. Maplethorpe, is the varying follow up periods. It is a

little bit concerning to me that you do an analysis based on a study that they have data that exceeds the cut off point of the study, which is not really very common in, say, a clinical trial situation.

So, when I looked at the HBs AG, there is a lot of missing data, but you know someone out there at 39 months or 50 months or two years or three years. So, can you comment about excluding or including positivity data or results, people in the study, that have results but only far after the trial, the study, has ended?

Ideally, the study or the licensure should be based on a prospectively described study so that we wouldn't have to be doing this.

I really don't know what rules exist and our considered to be appropriate for retrospective data analysis. It is usually something we would not even entertain.

My approach was based on trying to balance the conclusions so that they wouldn't be strongly biased in one way or the other.

For example, if we did have data in the time period immediately after month 24, that could inform us about what the outcome might be at month 24, and we didn't have any data for a year and a half before that, I would take that data so that we could potentially have

informative data on that subject.

DR. EPSTEIN: If I may comment to this point, the advice of the BPAC was really about a minimum monitoring period. You should monitor for at least a year and concurrent therapy with lamivudine at least two years.

It is not that the subsequent evidence of relapse is uninformative. Conversely, we actually inquired with Nabi, we said, well, can you bring the patients back and find out their current status even three years later or four years later.

After all, if they did not relapse at three years or four years, they certainly didn't relapse at two. So, it is not that the subsequent information is not meaningful. It is true that it was not the original intent of the analysis of the retrospective information, but it is not therefore true that subsequent information is uninformative, again, the idea being that these were minimum monitoring periods.

DR. SCHREIBER: We also don't have treatment history or compliance in that time period.

DR. ALTER: Jay, what was the reason for the different minimal period for monotherapy versus combined therapy? If they had both been just a year minimum, a lot of this problem would go away.

DR. EPSTEIN: I think I should let the

hepatologists answer that question, but I think the idea is that the emergence of the lamivudine resistant mutants takes time, and that you therefore don't actually see the additive benefit of the HBIG until you have waited long enough to find out if it suppressed the emergence of the lamivudine resistant mutants. If I have stated that incorrectly, someone should please correct me.

DR. KATZ: The B surface antigen data is very confusing to me, and my thoughts on this are hinging on this clinical whatever.

I need to hear a little bit more about what clinical stability is. Is it normal ALT or is it some composite of stuff? You had to have a definition. What was it?

Dr. MAPLETHORPE: Let me just say there were no submitted data informative on what clinical stability was as a definition, and there were no data to back up this judgement of clinical stability.

DR. KULKARNI: I had this question about this graph. What is the yellow and the blue?

DR. MAPLETHORPE: That is just a visual aid to keep from confusing about where the patient belongs.

DR. KULKARNI: I see. Also, when these protocols were designed, in their analysis, what were they planning to do about the deaths and all? Were they going to include

them, exclude them?

DR. MAPLETHORPE: Nabi only did two studies, and really they were only two studies, the PK studies, only two PK studies, and that was the sole purpose, PK over a three-month time period.

The other two that they did were just open protocols to make the product available. There was no plan to prospectively look at efficacy.

DR. BALLOW: Some of the differences were, I think there were four patients in which the IVIG was discontinued and they subsequently relapsed. Could you just go over your perspective again on those few patients?

DR. MAPLETHORPE: According to the submission on page 20 of the February 22, 2006 submission, that is the basis for our discussion here, Nabi states that there were seven subjects that discontinued hepatitis B immune globulin, and that two subsequently seroconverted. Those two were removed from the data base because they seroconverted. The five that did not seroconvert were included as successes.

Now, there were additional patients here who were here discontinued their HBIG. It is not clear, based on submitted data, whether those were actual treatment failures and the investigator just decided to stop giving this very expensive product to somebody who had already

failed.

According to the February 22, 2006 submission, there were seven that discontinued and two failed, and if you do that ratio, that is around 28 percent. The failure rate, you can see, is very similar to the overall study failure rate.

DR. RASMUSSEN: I just have two very quick points. First of all, we do disagree with Dr. Maplethorpe. We didn't exclude anybody who received or discontinued Nabi HB before two years.

So, we had four patients, as I went through, on a one by one patient basis. None of those patients discontinued because of toxicity. They all discontinued either because the insurance wouldn't reimburse them or the investigator at the time didn't feel that long term treatment was required.

I have one very quick comment to Dr. Hoofnagle's question before, because I didn't fully understand it. You were asked by Dr. Hoofnagle, we had some patients, a total of six patients, who didn't seroconvert before the transplant who were positive immediately after the transplant. They were all included in the analysis. So, they are in there. They are included.

DR. BALLOW: Dr. Rasmussen, you said that this patient discontinued the product after I think around 10

doses. Are you saying that that was not discontinued because of a treatment failure?

DR. RASMUSSEN: Yes.

DR. ALLEN: All right, other questions for clarification? If not, we really do need to move on. I am going to declare literally a five minute break for biological reasons, let people stretch, and then Dr. Kim, if you could be prepared to go, I would appreciate that. Thank you.

[Brief recess.]

DR. ALLEN: Jessica Kim will give the statistical review from the FDA's perspective on this study. Dr. Kim.

Agenda Item: FDA Statistical Review.

DR. KIM: Welcome back. My name is Jessica Kim. I am a mathematical statistician at the CBER, FDA. My presentation continues discussing items from Dr. Maplethorpe's presentation, and the title for my presentation is statistical review for the Nabi Biopharmaceuticals Hepatitis B Immune Globulin Intravenous, HBIG IV.

Here is the outline for my presentation. First, I am going to briefly talk about the background of this submission, focusing on statistics related issues.

Then I will revisit the efficacy end point, which was discussed and recommended at the March 2004 BPAC. It

will be followed by a post hoc goal of the analysis based on the recommended efficacy end points.

Then, the issues related to the goal of the post hoc analysis will be stated, and my presentation will be mainly about this issue related to the post hoc analysis. Then I will summarize my presentation to reach a possible conclusion.

In 2002, FDA received a BLA, biologic license application, from Nabi Biopharmaceuticals. The title was Hepatitis B Immune Globulin Intravenous, HBIG IV, for the prevention of recurrent HBV related disease after orthotopic liver transplantation.

Now, in this submission, Nabi included six open label and non-randomized studies. Later, the detail of these studies was discussed in Dr. Maplethorpe's presentation. Later, only two of the studies were included in efficacy data analysis for this submission.

Now, since then, there have been several review and response communications between CBER and Nabi, without conclusive agreement on the definition of the efficacy end point as well as the efficacy data set.

Now, in 2004, issues were brought to the BPAC meeting and the following are the summary of the March 2004 BPAC's recommendations for retrospective data analysis, focusing on the clinical end point.

It was decided that the efficacy should include the following information. One, the first HBIG infusion should be received by the first week from the most recent transplant date, to compare HBIG plus lamivudine versus lamivudine monotherapy, to show the efficacy of the treatment.

Three, the primary end point is defined as HBs antigen recurrence rate within two years following transplantation.

Now, among the six submitted studies, data values from the two studies, 4204, 30 OLT subjects receiving HBIG plus lamivudine, and the study 4409, 10 OLT subjects receiving HBIG IV plus lamuvadine, and 22 OLT subjects receiving HBIG IV monotherapy, were considered.

The total sample of interest is 40 OLT subjects receiving HBIG IV plus lamuvadine, based on BPAC's 2004 recommendation.

Now, a post hoc goal of the analysis becomes HBs antigen recurrence rate of the new treatment, Nabi HBIG with lamuvadine, is less than the HBs antigen recurrence rate of the lamuvadine monotherapy.

Now, to be able to satisfy this post hoc goal of the analysis using the submitted data, the following issues need to be clarified to reach any possible conclusion.

The first one was, what is the HBs antigen

recurrence rate of Nabi HBIG IV, which was discussed in detail in Dr. Maplethorpe's presentation.

Second, what is the scientific method to estimate the historical control, the HBs antigen recurrence rate of lamuvadine monotherapy. Now, slides eight through 15 will discuss detail on that second issue.

Third, what is the scientific method to determine the efficacy of Nabi HBIG IV plus lamuvadine, versus lamuvadine monotherapy. Then slide 16 through 19 of my presentation will discuss that third issue.

Now beginning talking about the second issue, in using lamuvadine monotherapy as a comparator, there are some related problems and concerns.

Mainly it is because there has been no universally accepted information on the clinical benefit of lamuvadine monotherapy. So, we only have a certain percentage to a certain percentage reference number.

Then Nabi proposed to use published studies to estimate the historical control rates. In a literature review, to estimate a historical control rate, due to the inconsistency of the study design, including an exclusion criteria in study populations, non-comparability of selected published studies is questionable.

Also, internal validity and quality of the published studies is questionable. So, keeping those issues

in mind, Nabi proposed to use 30 percent for the HBs antigen recurrence rate of lamuvadine monotherapy, which was chosen arbitrarily, but is claimed that it is conservative, from the range of the observed recurrence rate from the selected published study.

FDA responded to Nabi's proposal as follows. FDA recommended Nabi to apply a scientific method -- for example,a meta analysis -- to estimate the HBs antigen recurrence rate of lamuvadine monotherapy, and specifically requested to find the overall estimate with a confidence interval.

Now, here is the information about the selected studies submitted by Nabi. The first column indicates the author of the study. The second column, it is before 2004 BPAC observed the recurrence rate that Nabi submitted for those studies.

Then, after the 2004 BPAC, Nabi adjusted the observed recurrence rate followed by the BPAC's recommendation.

I want you to notice that the study by Grelier, 75 percent, was not included after BPAC, and study Chen was included after BPAC.

The number for the observed recurrence rate from study Bain is changed to the 50 percent -- adjusted from the 50 percent to the 67 percent. The study Perillo, which

is the second to last row, was changed from 12 out of 37 to 16 out of 39.

This slide shows the confidence interval of HBs antigen recurrence rate of the lamuvadine monotherapy using the information of the submitted information of the study.

As you can see, the range varies widely, study to study, and within study it also has a wide range, the 95 percent confidence interval for the HBs antigen recurrence rate of lamuvadine.

Now, when you see this type of variability between study and also within study, which sometimes is referred to by the terminology, heterogeneity, the question becomes how to account for the heterogeneity in a meta analysis.

One answer can be, such as random effects models can be used that assumes the true effect estimates vary across the studies, and it can include the study as a random effect and estimate the overall recurrence rate using the selected studies.

Now, other than the random effect model, what other method can be applied in the meta analysis? A weighted pool, the point estimate, and appropriate confidence interval also can be used in a meta analysis to estimate overall responses. This, the second one, is the Nabi proposed, and we agreed to accept their proposal.

Now, here is an explanation of the technical method for a meta analysis proposed by Nabi. Nabi would like to use the point estimate, which is defined as a weighted mean, by combining the selected five studies.

Weight is defined in this case as the inverse of the estimated variance of the observed recurrence rate in each study.

Then they concluded a 45 percent rate using the point estimate for HBs antigen positive OLT recipients treated with lamuvadine monotherapy and followed for at least two years.

I want to point out that, at that conclusion, the confidence interval was not considered in Nabi's conclusions.

Now, this slide is to confirm the computational step for estimating the point estimate using the weighted mean approach.

The third column is estimated variance of each study, and the fourth column is the proportion of the weight allocated to each trial, which is the normalized weight.

When you multiply the recurrence rate which is given in the second column by the proportion of the weight to allocate to each trial, the fourth column, you will get the fifth column, weighted recurrence rate.

Then the sum of these weighted recurrence rates from these selected five studies gives you an overall point estimate, which is 0.45.

Now, I want you to notice that the first study, Anselmo, and the third study, Chen, have about the same sample study size, of 20, and also about the same estimated variance, .011 and .011. It looks exactly the same, due to the decimal rounding error.

Again, when you look at the fifth column, weighted recurrence rate, the product of the recurrence rate by proportion of weight for the Anselmo study gives you 0.140, and the product of the recurrence rate of the study Chen, by proportion of the weight, 0.234, givers 0.070, which is a big difference.

The main reason for that result is the Anselmo has a high recurrence rate compared to the recurrence rate of the Chen.

So, this also tells you that selection of the studies will greatly influence the overall estimate, even if we use the meta analysis as a scientifically supported meta analysis.

Now, this slide concludes the second issue that I stated previously about the historical control. Results of retrospective analysis for the historical control.

FDA concluded the point estimate is 45 percent

weighted mean, along with a confidence interval of 27 percent, 62 percent, and Nabi has concluded a point estimate of 45 with a 35 to 54 percent confidence interval.

The difference of those two confidence intervals from FDA and Nabi is due to calculations based on a different formula that was used.

Now, this slide begins with the third issue, how to determine the efficacy of the treatment, efficacy of the Nabi HBIG IV with lamuvadine versus lamuvadine alone.

Now, here are the fundamental problems and concerns of the submitted studies in this submission. A synopsis of two studies of interest, which were selected after the BPAC 2004 recommendation, study 2404 and 2409, both of them are a single arm trial compared to the historical controlled, non-randomized trial.

Efficacy data values were retrospectively collected, which gives you lots of bias. Sample size was not based on study power, and study objective was not statistically hypothesized.

Under this circumstance, only this study can be categorized into the exploratory or observational study, not confirmatory for the license base.

Now, considering HBs antigen, recurrence data from study 4204 and 4409, as per Dr. Maplethorpe's presentation, there were 19 evaluable subjects on combined

HBIG IV plus lamuvadine therapy in study 2404.

There were eight evaluable subjects on combined HBIG IV plus lamuvadine therapy in study 4409, which would give you the final efficacy data set as a total of 27 evaluable subjects on combined HBIG IV plus lamuvadine therapy.

Now, the efficacy of the Nabi HBIG IV with lamuvadine versus lamuvadine alone, the FDA's retrospective analysis result, using the two studies -- the 4204 and the 4409 -- and pooled observed recurrent rate, gives eight failures out of 27 total, which is approximately 30 percent, and the 95 percent confidence interval for the recurrence rate is 14 percent to 50 percent.

Now, here this slide shows including three select HBIG IV monotherapy subjects from study 4409, and pooling these subjects with a retrospective analysis. It gives you about 27 percent recurrence rate and a 95 percent confidence interval, as 12 to 46 percent.

Now, here is my summary about the issues. Regarding the issue of meta analysis and historical control of lamuvadine monotherapy, a point estimate cannot be used as a valid or good -- cannot be explained as a good estimate or a bad estimate without the variability, without the sampling error.

So, in applying a meta analysis, the variability

of a point estimate should be taken into consideration.

Now, regarding the third issue related to the goal of the post hoc analysis, efficacy of Nabi HBIG IV plus lamuvadine versus lamuvadine monotherapy, Nabi proposed HBIG IV efficacy based on previously two arms and recently, later, the submission included a single arm compared to the 45 percent.

FDA would like to assure that the single arm could be considered an analysis for the open label and not randomized studies with the retrospective collected data compared to the historical control.

Now, here is my last slide for my presentation, about the conclusions of this whole process. Regarding the second issue, the HBs antigen recurrence rate of lamuvadine monotherapy, historical, weighted point estimate was 45 percent HBs antigen recurrence rate.

Of course, when you use a different method, a random effect model for this meta analysis, you will get a different point estimate.

A 95 percent confidence interval using the weighted standard deviation is the most conservative method. That gives you 27 percent to 62 percent.

The HBs antigen recurrence rate in HBIG IV with the lamuvadine group, single arm point estimate, eight failures out of 27 total, which is 30 percent HBs antigen

recurrence rate, and a 95 percent confidence interval is 14 to 50 percent.

Now, when you consider this as a testing hypothesis set up, instead of the confidence interval, you will get the same conclusion.

So, the upper limit of the 50 percent does not exclude even the point estimate of 45 percent. So, the recurrence rate is not higher than the HBs antigen recurrence rate of the Nabi HBIG IV plus lamuvadine, is not higher than the lamuvadine -- cannot be shown, even with the testing hypothesis study. Thank you.

DR. ALLEN: Thank you, Dr. Kim. Committee members, specific questions for Dr. Kim on her analysis and interpretation?

DR. DI BISCEGLIE: I guess I would like to question the use of lamuvadine as a historical control. It sounds like the BPAC suggested the use of a historical control, but I am not sure who used that term.

The Samuel paper on use of HBIG was published in 1993. The first paper on the use of lamuvadine was in 1999. Lamuvadine is not FDA approved for use in this indication. Why are we calling it a historical control, and why is this what we are comparing HBIG to?

DR. KIM: That can be answered by someone who can answer about why the lamuvadine was considered as a

historical control.

DR. EPSTEIN: This was discussed at some length at the March 2004 Blood Product Advisory Committee meeting. The bottom line is that the use of lamuvadine, whether on label or off label, has become a standard of care.

The idea of a comparative trial to placebo was considered both unethical and infeasible. So, perforce, one had to consider whether there is an added benefit of HBIG.

It is true, from a truly objective point of view, one could say you could approve it as an independent therapeutic, but in reality current practice would be whether it has an added benefit.

So, whether it is a historical control in the true sense or not, it is, in effect, a control compared to standard of care.

DR. DI BISCEGLIE: Jay, I would argue it is the other way around. HBIG was there first, and then lamuvadine was added to it later. It is not the reverse.

DR. EPSTEIN: Right, I understand. It is just that we are reconsidering the discussion of March 2004, which led to that conclusion. There is another point of view, to be sure, but let me put it this way. What would you propose instead?

DR. DI BISCEGLIE: HBIG, whether it is this product or not, is standard of care. It has been used for

more than a decade.

This product has saved hundreds of lives compared to what we used before, when we let people die without liver transplantation because they got horrible recurrent hepatitis B. That should be the comparison.

Now, it is sort of too late for that, but that is really ultimately what the results of this product should be compared to, I believe.

DR. KATZ: I am not sure that is true. It is easier to take that pill than it is to get these infusions, and a hell of a lot cheaper, and it is really a quandary.

DR. ALLEN: This is really getting into general discussion. I mean, it is an important point, but can we address questions directly to Dr. Kim, and then we need to go on to our open hearing.

DR. KUEHNERT: I just had a question as far as statistical analysis. There was some discussion about exclusion of patients by FDA.

Some of those patients were excluded because they died before the two years were up. I am just wondering, that is sort of, I guess, an intent to treat analysis, but is that the only way that could be looked at? Aren't there other alternatives to that, some sort of survival statistical analysis thing, just excluding them all together?

DR. KIM: I believe there are many possible way when you have retrospective data. As regulatory reviewers, we require all the BLAs to pre-specify an analysis plan, so that we all have the same idea of what to look for.

Here, to discuss all other alternatives, gives a very different conclusion, and I don't think we can determine the value of looking at all kinds of different possibilities when you have retrospective data.

What subjects are excluded and included, that case, as Dr. Maplethorpe presented, was what we need. Other possibilities of the sensitivity analysis, I think it is a matter of, do we include all the subjects with a failure. That is the most conservative approach, as the FDA has been using.

DR. ALLEN: Is BPAC being asked to give input into that? Is FDA flexible on what is included and what is excluded, or have you already determined that is what it is going to be, is eight out of 27.

DR. ALLEN: The FDA has based their determinations using the criteria that they clearly stated. Nabi did the same for the information that they presented. We can comment on any one of those. What the FDA's ultimate decision post the BPAC meeting is, is up to them.

DR. ALTER: This is pretty much on this same point. I think we would probably all agree that this is a

statistically flawed study based on their retrospective analysis, but we were given reasons why the proper study couldn't be done.

I think that, although the statistical analysis is correct, I think it is unduly harsh in the sense of patients who stopped therapy who then recurred after therapy was stopped, considering those as treatment failures is, I think, unduly harsh.

If you take those four or six cases out, your whole analysis changes. If you take them out of the analysis rather than call them failures, then the whole statistical analysis you have fails, and the efficacy of the Nabi product is much better compared to controls. I think that is too harsh a judgement, given the known efficacy of this product in clinical use.

DR. HOOFNAGLE: I actually have a question. When you gave the data on lamivudine alone, was this at two years and was this excluding deaths? You know, the rates will increase with time. Is this the rate of recurrence at two years?

DR. KIM: You are talking about the historical control, the published studies?

DR. HOOFNAGLE: Yes.

DR. KIM: The criteria that Nabi used is two years monitoring and deaths that occur after 30 days, and I

don't remember the third criteria. It is definitely two years of monitoring data. I don't know whether the deaths were included, the early deaths. I think he is asking what is the criteria of the lamuvadine monotherapy from the papers, the selected studies. They can explain the details, how they selected those.

DR. RASMUSSEN: I can answer that one. Certainly deaths which were due to hepatitis B recurrence were included as a failure, similar to our own analysis. Deaths that were due to something else were not included.

DR. ALLEN: Other questions for Dr. Kim for clarification?

DR. GOLDING: I would clarify a few things. The questions from Dr. DiBisceglie, there were three pathways that we discussed with Nabi. One was the PK study. The two other pathways that were discussed at that BPAC in 2004 included one pathway for HBIC monotherapy compared to historical controls with follow up for one year, and the third pathway is the pathway they chose to collect data on and submit to us. So, monotherapy was included as a possibility.

DR. ALLEN: Okay, the presentation session is now closed. We are moving to our open public hearing. I will read a statement.

Agenda Item: Open Public Hearing.

DR. ALLEN: Let me just first indicate that I have three people -- Dr. Imagawa, Lisa Tobin, and Jan Gyn, who have requested to make statements. If there is anyone else who wishes to make a statement during the open public hearing, would you please come now and give your name and affiliation to Dr. Donald Jehn, so that we can get that at this time. We are running seriously behind time. The committee needs time for discussion.

I would ask each of the presenters in the open public hearing to make your statements as brief and concise as possible, and also please follow the instructions that I will now read in terms of identifying yourself and making any disclaimers.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making.

To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, his

product and, if known, its direct competitors.

For example, financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

All right, Dr. Imagawa, University of California, Irvine, is making a presentation that will include statements from three different individuals or organizations. Again, I urge you, please, to be brief. We do have copies of the statement, which we can read also.

Agenda Item: Statement of David Imagawa.

DR. IMAGAWA: Thank you. I am David Imagawa. I am a professor of clinical surgery at the University of California, Irvine, and performed liver transplants up until 2000.

I have been asked, as a consultant to Nabi, to represent the transplant surgeons in regard to our use of hepatitis B immune globulin to prevent recurrent HBV after liver transplant.

I think one of the points that is extremely

important here is that orthotopic liver transplantation remains the curative modality for end stage liver disease from chronic hepatitis B.

What has been briefed upon is that initial attempts at liver transplantation, without immunoprophylaxis -- that is, without either antiviral or immune therapy -- resulted in over 80 percent reinfection of the allograft, followed by accelerated graft failure and death.

In fact, in the late 1980s, this led to a moratorium on liver transplant for hepatitis B. It wasn't until the introduction of hepatitis B immune globulin and the results that came out of the University of Virginia, that transplantation for hepatitis B underwent renewed enthusiasm.

The initial results at that point were done with hepatitis B immune globulin immunoprophylaxis. Subsequently, lamivudine, the antiviral, was added to this regimen, and then attempts were made to wean off hepatitis B immune globulin and look at lamivudine monotherapy.

More accurately I would state, as a transplant surgeon, that the historical control is really the 80 percent recurrence that we saw in individuals who were receiving no additional therapy and what led to, like I said, the moratorium on liver transplants.

Using HBIG immunotherapy, if you review all the domestic and international literature, it reveals really consistent results.

There are low recurrence rates up to five years post-transplant, and the data covers all forms of hepatitis B patients, those that are viremic, serum viremic at the time of transplant, those who have high viral loads, and those who are surface antigen positive and not viremic.

If you look at the larger studies that have been published in the literature again, this is an orphan drug with a relatively small indication, but we see that the recurrence rates, whether they are in Australia or Germany, are in the area of zero to 20 percent at the high, in the smallest study, but really in the single digit recurrence rates if the individuals remain on the immunoprophylaxis, and that is really one of the key things that we have found.

Lamivudine monotherapy is the only really other alternative that has been historically suggested in the literature, although with the advent of newer antivirals such as hep sera(?) and depovir(?), this may be challenged in the future.

However, lamivudine monotherapy is clearly not a viable solution for all patients because there is routine development of escape mutants and drug resistance with

monotherapy.

Historically, we see again, as has been discussed at great length here, 24 to 67 percent recurrence rates across all patients undergoing transplants for hepatitis B with lamivudine monotherapy.

In our particular experience, we have used a combination of hepatitis B immune globulin and lamivudine, and we have followed our patients very carefully with surface antigen and DNA results from 1993 to 2001.

All of them received this combination immunotherapy, and we actually used a modification of the Virginia protocol, 10,000 units of HBIG intravenous followed by 10,000 units for six days.

Administration was then changed to an IM route to maintain titers of 15 international units per liter. Then serologies were checked every two months and doses were adjusted based on these titers.

One of the members of the committee asked what the cost was. The cost at our institution for the induction therapy is $29,000. The cost of maintenance therapy is about $7,000. The cost of the antiviral lamivudine is about $2,500 a year. However, the cost of a transplant is between $75,000 and $150,000 one time cost, and multiple admissions which occur when we have a re-infection with hepatitis B, can range from $50,000 to

$100,000. So, that is the cost that was asked about.

Again, the survival for these patients is comparable or actually better with immune prophylaxis than the other diseases than we have seen, roughly 90 percent one year survival.

Again, the long-term experience, as we have a Kaplan-Meier 10 year survival calculated at 67 percent. So, these patients do extremely well.

In our particular experience, we had six patients that discontinued hepatitis B immune globulin, one of them discontinued for side effects. The other five discontinued for logistical reasons, either insurance reasons, since this was an off label use of the drug, or in one case an individual who went back to the far east and could not receive their immune prophylaxis.

We had recurrence in 50 percent, in three of six of those patients. Again, we have a long follow up of these patients, 36 months to 150 months or almost up to seven years in those cases.

In conclusion, then, the published data strongly support the use of combination therapy with HBIG and a nucleoside analog to present recurrent HPV after liver transplant.

That is the standard of care at the majority of the liver transplant institutes in the United States at

this time.

There are no clear viable alternatives at this time. Again, I think the more appropriate comparison in this particular population is two individuals who received no treatment, and what led to the fulminant recurrence of hepatitis B.

In the interests of time, I have three letters here, but maybe I would best summarize. One of them is to the Blood Products Advisory Committee, and is from Dr. John Fong, who is the chairman of general surgery and the director of the transplantation center at Cleveland Clinic and is co-author, as is Linda Sherer, who is a liver transplant surgeon at the University of Southern California.

Again, they come by the same conclusions that the significantly improved results in liver transplant are the result of hepatitis B immune globulin. Again, they recommend approval so that standardized protocols can be put into place.

The second longer letter is from Dr. Tim Pruitt, who is chief of the division of transplantation at the University of Virginia, and who probably has the largest domestic experience in terms of hepatitis B, and he is actually the lead author on the McGory paper, as has been referred to here.

Again, the experience and the literature cited here, once again, his conclusion is that it would be a -- I will quote -- a hardship to the patients in the United States and incomprehensible to the liver transplant community that the FDA has not recognized the utility of hepatitis B immune globulin for the indications of liver transplantation for hepatitis B induced liver disease.

Citizens of this country have capricious insurance coverage. Medicare coverage and access to care are predicated upon the lack of official designation of efficacy.

In fact, even though medicare approves hepatitis B as an indication for liver transplantation, some recipients risk liver infection from HBV because medicare may not pay for the drug that is given off label for a non-FDA approved indication.

He goes on to again discuss, I wholeheartedly support the approval of Nabi HB for the liver transplant indication.

There is absolutely no doubt in anybody's mind that hepatitis B immune globulin plays a central role in optimizing outcomes in hepatitis B positive liver transplant recipients.

Lastly, I have a letter from the Hepatitis B foundation, again on behalf of the hepatitis B patients,

whose lives have been extended and continue to be dependent upon HBIG post liver transplantation.

We ask that the FDA panel approve HBIG and Nabi HB for liver transplant indications, and this is signed by Timothy M. Bloch, PhD, who is the president of the Hepatitis B Foundation. Thank you for this opportunity to address the committee.

MR. JEHN: Thank you, Dr. Imagawa for your presentation and your brevity. I appreciate that. Our second speaker is Lisa Tobin, advocacy director of the American Liver Foundation.

Agenda Item: Statement of the American Liver Foundation.

MS. TOBIN: Dr. Allen and members of the committee, thank you for giving us the opportunity to submit testimony today.

I am Lisa Tobin and I am advocacy director, as you said, for the American Liver Foundation. The American Liver Foundation, ALF, is the nation's leading non-profit organization promoting liver health and disease prevention.

The foundation provides research, education and advocacy for those affected by liver disease, including hepatitis.

ALF has 25 chapters nationwide with national and chapter leadership composed of scientists, clinicians,

patients and others affected by liver disease, as well as other prominent community and national leaders.

The foundation is honored to represent the interests and concerns of our constituents, and they include friends and family members of patients, volunteers, esteemed members of the medical profession and, of course, the many thousands of Americans who have, or who are at risk for, liver disease.

For the full range of patients represented by ALF, the past 20 years have seen a universe of change. Our physicians tell us stories that convey their frustration when, years ago, they stood beside their patients and watched as their diseases progressed to end stage liver disease and then death.

Today, though, there is renewed hope and life for patients like these, because of the advent of liver transplantation.

Over 6,000 Americans each year receive life saving liver transplants, and we are working to increase that number.

For one of our constituencies, end stage liver disease patients, who have been infected with hepatitis B virus, transplantation has not always been available option.

Because of the exceptionally high rates of HBV

reinfection after transplants, for years many transplant centers abandoned transplantation as an option for patients with chronic hepatitis B infection.

Tragically, this practice was a death sentence for an entire group of patients. However, since the introduction of HBIG, rates of recurrence have been reduced significantly, which has made transplantation once again an option for chronic HBV patients with end stage liver disease.

The American Liver Foundation works with respected physicians around the country, whom we fortunately can call upon for expert medical counsel on a wide variety of topics.

Our expert medical advisors have indicated that this therapy is commonly being used off label to treat HBV patients who have needed transplants.

These professionals attest to the commonplace acceptance within the medical world of the effective use of this therapy in maintaining the long-term success of liver transplantation for HBV patients.

It is really exciting for us to see that these patients now can thrive and meet life with hope. Patients who, a few short decades ago, would have had no recourse at all in the fight against their life threatening disease, now can be good candidates for transplantation.

It is important to note that we are also aware that, without official approval and specific guidance for use of this therapy in the United States, this off label use can result in the therapy's limited availability to patients and increased application by individual clinicians.

This can further result in potential adverse results. For this reason, we urge this committee to recognize this treatment's strong potential for use in HBV infected patients, and we urge you to provide to clinicians clear official guidance for the therapies used in patients in the United States.

While the American Liver Foundation proudly advocates for increased therapies and treatments for the many patients affected by liver disease, we also strongly believe that patient safety is paramount.

For the therapy currently under consideration and for any new treatment or application that is found to increase the options available to our patients, we strongly advocate for clear cut scientific guidance and solid medical oversight. The end result is what we all strive for, which is successful patient outcomes.

In conclusion, on behalf of hepatitis B patients across the countries, the American Liver Foundation urges this committee to take the action needed to ensure that a

life saving therapy will be available to these patients across the United States, and that it will be administered consistently and with optimum safety. Thank you, and please note that we are appearing entirely at our own expense.

MR. JEHN: Thank you. Our third speaker is Jan Gyn. I apologize if I haven't pronounced your name correctly. You may either use one of the microphones there or you may come up to the front. That is your option.

Agenda Item: Statement of Jan Gyn.

MR. GYN: Hello. My name is Jan Gyn. I am here as a guest of Nabi. I live in San Francisco, California. Basically, to cut to the chase, in early 2004 I was diagnosed with hepatitis B through basically just a random drug testing.

In late 2004, by my third sonogram, is when they discovered I had a tumor. I was going to be put on the liver transplant list and then, in 2005, I was discovered to have a second tumor, which effectively put me outside the range of those that are eligible for a liver transplant.

At the same time, the main tumor was growing. So, I had to have a resection in late 2005, and then in 2006, or actually in late 2005, I had a transplant, which would mean that is my second operation.

So, I am now a transplantee, if that is a word, and I am currently taking -- I was currently taking lamivudine after being diagnosed with the first tumor in early 2005, and I have been, since the transplant, they have had me on both HBIG and lamivudine.

I think one of the reasons was, when you did a transplant, you have to take a lot of what they call anti-rejection medication.

Unfortunately, what anti-rejection medication does, it blunts your immune system. Therefore, ironically, I am now -- even though I still have hepatitis B, I am now, in a sense, a little bit more vulnerable to further infection because of the anti-rejection medication.

So, they put me on HBIG, and it was for a one-year period, which will end as of net month. I am just saying that whatever I am -- I am kind of looking forward to living another five or 10 years, or until the next couple world cups, anyway.

I come from being a person who has never in my entire life broken a bone to all of a sudden, in my mid-40s, all of a sudden being faced with a lot of life threatening crises.

I don't know if HBIG -- if the fact that I feel fine now, that it is solely responsible for it, but I know that there has been some problem with other people where

there are either mutations or they become resistant to lamivudine.

I would just like to say, I would like to have more medications that could help those who, like myself, either cancer or with hepatitis B, more of these medications to become more readily accessible by the public.

There are all sorts of ways to test things but, at the same time, there is a group of us who we would sort of like to get our best options as of now.

So, that is pretty much all that I would have to say, and just thank you for the medications that are currently available, and I hope more will be becoming accessible to those who need them. Thank you.

DR. ALLEN: Thank you very much, Mr. Gyn. We appreciate your personal story and testimony. Is there anybody else who wishes to speak in the open public hearing? Okay, I now declare the open public hearing closed. Dr. Epstein, did you want to make a comment?

Agenda Item: Open Committee Discussion.

DR. EPSTEIN: There is an important point that the committee needs to understand. Today's discussion is not a debate about access to a licensed product for an off label use that has become a standard of care.

We don't dispute the literature. We don't dispute

observations that have been made about the historic benefit of HBIG monotherapy.

This is about the standard for an FDA approval of a product indication and it is about whether the data provided by a specific product sponsor for their specific product in a specific use supports a labeling claim.

It may well be -- and many people believe and FDA is not skeptical -- that HBIG works. The question is whether we can approve that indication based on the available data set and what exactly should be our standard for analysis and our standard for approval.

We certainly appreciate the difficulty in the situation of an orphan indication. I mean, that does not escape us, and we do entertain the possibility of small size studies, and we appreciate Dr. Alter's comment about was the level of statistical rigor appropriate to the situation.

I would just highlight for the committee that we have, in fact, even in that context, an unusual situation, which is that this is a totally retrospective analysis without a pre-analytic design that is based on the indication one wished to validate. So, it is an unusual situation and that is why we are here to be advised.

I would like to make a second point which is more specific to the statistical analysis, and this is a

response to Dr. Alter's comment about should the patients who had termination of therapy have been treated as an intent to treat. The question was, you know, is that too harsh.

The alternative would be to exclude the patients. FDA's point of view was that the approach taken by Nabi, which was to selectively exclude the failures and include the successes to date, isn't a valid approach.

Now, the most statistically rigorous approach, of course, is to include them and do intent to treat. The unbiased alternative would be to exclude them.

If you were to take the seven patients in the study who had early termination of therapy, including the two acknowledged treatment failures as stated by Nabi, you would then, by the FDA criteria, have six failures out of 20 instead of eight failures out of 27.

That is the same 30 percent, but with a smaller denominator you would then have an even wider confidence interval.

So, it wouldn't actually change FDA's conclusion, but it leaves open the question of, are the right criteria being applied to the classification of outcomes, as well as the question of the right or the most appropriate -- I don't know about right or wrong but the most appropriate -- criteria being applied to inclusion and exclusion.

So, this is just my effort to put the whole issue into a framework for the committee. Again, we are not in any dispute about standard of care based on an off label use. This is about the criteria, the FDA's criteria for adding an indication to a product label based on data pertinent to a specific biologic product.

DR. ALLEN: Thank you for the explication. I am sorry, we are seriously behind. The committee will have an opportunity to call on you for clarification as appropriate. Dr. Maplethorpe, would you please present the questions to the committee, or if we could have them up on the screen again? Shall I just go ahead and read them?

Our first question is really an open discussion one. What I would suggest, unless the committee would like to have a period of time for discussion first, before we get to the questions, we can do that if you want, or we can move directly to the questions, because the first one is a comment kind of a question. It is not a yes/no vote.

Please comment on Nabi's post-hoc inclusion and exclusion criteria for the classification of subjects as successes or failures following HBIG administration in the setting of OLT. So, the floor is open for discussion by the committee members.

DR. KUEHNERT: I just wanted a clarification on what the indication actually is that is being sought out.

Is it an indication for use of the product with lamivudine or just in general? I am a little bit confused about that.

MR. ALLEN: Let me try to answer your question and if either the FDA or Nabi disagrees, they can clarify. I believe that during his presentation, that Dr. Rasmussen did put up a clinical indication that would be the added approval, label approval.

The FDA, of course, has not stated what the label approval will be but, based on what I understand Nabi is asking for, it would be HBIG is useful in suppression of hepatitis B reactivation in orthotopic liver transplantation.

It is not stating what other therapy would be with it. It is not calling it an adjunct therapy. It is simply there as an indication as part of the total treatment package. Is that an acceptable statement of what the intent is?

DR. KUEHNERT: I understand that 3TC is part of the standard of care currently, but I just wondered whether the indication would mention that or not and, if not --

DR. ALLEN: The point being that you don't want to be too specific because the standards of care will change over time.

DR. KUEHNERT: Absolutely.

DR. ALLEN: And perhaps fairly rapidly.

DR. KUEHNERT: Absolutely. It doesn't have any adjunctive therapy mentioned in it. It is just use of that product.

DR. ALLEN: That is correct, but what the actual FDA labeling if it is approved will be, we are not being asked to discuss that.

DR. KUEHNERT: But it has bearing as far as what we are assessing it for.

DR. GOLDMAN: The problem is the submitted data are in the setting of combined use with lamivudine. Lamivudine does not carry this indication.

This is an example of how flexible we are being in that we are even considering an approval in a setting that, itself, is not approved.

I would imagine that the indication if approved would be more vague and it would say, in conjunction with use of an anti-HBV antiviral agent.

DR. CRYER: Just in terms of the exact question, I find that the post hoc inclusion and exclusion analyses from both presenters problematic.

I don't know about the inclusion criteria, but the thing that was compelling to me was that it is pretty clear to me that if a common sensical approach is used, that there really was probably only one failure in an appropriately treated patient in the group that got both

drugs.

Now, whether you include the ones -- you certainly, in my opinion, shouldn't include somebody who died from something else as a failure.

Whether you include them in the denominator or not is another issue, as I see the same problem for the people who got the immune globulin but didn't get the other drug.

I find the whole thing problematic, but it is pretty compelling to me that there really was only one true failure in the patients that got both drugs.

DR. SIEGEL: I am having a real problem with what we are trying to attain here, what our goal is. Nabi seeks -- this is in black face -- Nabi seeks an additional indication for use of this product as immunoprophylaxis against liver graft re-infection with hepatitis B virus for patients undergoing orthotopic liver transplant.

So, the goal, as stated, is to prevent re-infection. My understanding, as I have learned from this reading, is that you don't really prevent re-infection, because the virus persists after the liver is removed, and it persists because the virus permeates the system and just is there.

So, it is going to be there and it is going to reinfect the liver in any case. What the indication really

should be requested, it seems to me, is for amelioration of clinical disease in the new liver, which is apparently what is being claimed.

Evidently data have been presented that suggest that even liver biopsies and transaminase suppression is achieved.

If that is the case, then we ought to be discussing that. I don't understand what the real question is that we are being asked to approve or disapprove.

DR. ALTER: That is a good point. I especially agree with your analysis that any common sense approach would say that -- well, first of all, I think we are hearing different data about these eight cases and whether or not, when treatment was stopped, there was recurrence, and were they including them all or excluding them all.

In the Nabi presentation it seemed like in those eight cases that the ones who dropped therapy because of cost, et cetera, were excluded but the others were included. So, there is some difference between what the two sides are presenting, but that is not my point.

Jay, it is very helpful to have your clarification. I was a little bit -- I couldn't quite understand the FDA position.

I think there is no doubt that this is an efficacious and a safe drug and a drug that is used, and

that what we are really here about now is not whether a drug is going to be used, or whether it is going to be used with or without a label.

I understand your concerns about applying a label to something where the data supporting that are less than optimal, and clearly they are.

There are reasons why the proper study can't be done at this point. So, then the question is, what are the down sides of labeling it or not labeling it.

Well, if you don't label it, it will continue to be used just as it is now. There are some down sides to that.

One, the use is inconsistent. So, there might be treatment failures by using it at the improper doses. Number two, it has insurance implications so that we force that group to drop out and have recurrence, as was shown in this study.

On the other hand, if you label it, I don't see any down side. You get some consistency, you get a basis for insurance companies to approve payment.

We are not dealing with safety issue. We are not dealing really with even efficacy issues. We are just dealing with the labeling issues.

So, the question is whether FDA can drop its guard a little bit on its criteria for labeling approval

with less than optimal data.

I wouldn't want to be in your position, but from a clinician's position, I think labeling has more benefits than non-labeling.

DR. POLLACH: Louis Pollach from Nabi. I just wanted to clarify that the indication we are asking for is not for prevention of infection or re-infection. The indication is prevention of hepatitis B clinical disease, but not reinfection.

DR. FINNEGAN: I agree with Dr. Cryer entirely. I think that there are problems on both sides. I understand where Dr. Epstein is coming form, but I am wondering if some of the concerns that he has, because the company has stated publicly that they would do a phase IV, could be covered in a phase IV so that you could allow the product to go forward, and yet still collect the data that you need and have some scientific rigor to this proposal.

DR. GOLDING: Just a brief comment regarding Dr. Alter's idea. The question of precedent does bear heavily on us, and we do have to take into consideration other companies and the whole arena of these products, types of products, and make sure that when you make a decision, that we can stand by it and that we can allow other companies to do the same. So, the precedent setting issue does weigh heavily, at least on the FDA.

DR. ALTER: Could I respond to that? I can understand that, but I think it would be very rare that you would be in a situation like this, where you have an orphan drug that has 10 years of experience that has been proved efficacious over and over again.

I just think it would be very rare that somebody else would come to you in that situation where the standard of care really would demand the use of that product.

It is just whether they are going to use it in a better way than they use it now. So, I don't think you would be destroying your credibility.

I do think that, if you add in this phase IV study, then you can bring back the science you want, and make sure that that study is designed exactly the way you want it. I think that is a very good point and, at the end of a year or two years, you will have your credibility back.

DR. ALLEN: That is an interesting statement, Dr. Alter, and I thank you for it. It certainly does speak to the difficulty.

I mean, there clearly are many questions that still remain to be answered in future research. The issue here, I get the sense, over and over from published papers, as well as presentations made here, I clearly get the sense that the immune globulin is much more effective than these

retrospective data are able to show.

I think it is a real shame that we don't have the clinical data necessary in order to make the decisions that need to be done.

You know, I am also impressed that changing or inclusions or exclusions, by only a few cases, statistically alters the significance of the decision one way or another, and that is a real shame in something that, if Dr. Alter is correct, should be much clearer than we are able to tell from these studies.

So, it does put the FDA in a very difficult position, but perhaps we can be of -- Dr. Epstein and then Dr. Katz.

DR. EPSTEIN: I want to comment on the concept of a phase IV study. Phase IV studies are very valuable to answer many questions about product use.

The one thing that FDA cannot do by permitting a phase IV study is to allow the conclusion of efficacy to be drawn in phase IV when it is a prerequisite for product approval.

That is why we want efficacy to be shown at the time of approval, which is usually phase III. What we have here is a request to look at phase II studies that were not designed to show efficacy and we are being asked, can we nevertheless draw a conclusion of efficacy prior to

approval, not in phase IV after approval.

That is why question three -- it is question three because it is the ultimate question. It is, do the data show efficacy.

If the answer is yes, FDA will take that under advisement and we can consider a product approval. What we can't do is approve the product, which means that we have made a finding of safety and efficacy, and then turn to phase IV for the demonstration of efficacy.

DR. KATZ: The irony is that it would have been easier to support approval of this drug for this indication had we never seen the data from Nabi.

A hash was made of this and I think some of it is from BPAC and what was said two years ago and some of it was from the awy that Nabi executed things.

From the standpoint of a clinician who has been taking care of hepatitis B patients for 30 years, there is absolutely not one shred of doubt that this stuff works. We know this, and all of us have taken care of enough patients to say that.

I have a question to FDA and it is probably two parts. Number one, the big problem here is insurance companies, being what insurance companies are, don't want to pay for off label use because they can save a buck and bank it in something else or whatever their rationale is.

Is there an alternate route to ensure reimbursement for this drug without FDA approval?

The second question is, if that was possible, is there any way to get around the dosing utilization problems that we have heard about, and I think not.

Question one, we got a hash of data for a variety of reasons and it has only complicated the issue, in my mind.

DR. ALLEN: Your question about reimbursement, obviously, doesn't take into account Dr. Finnegan's earlier very astute question about the total economic cost. A clinical recurrence may, in fact, cost a lot more than paying for ongoing treatment. Dr. Epstein, did you want to respond to Dr. Katz' question?

DR. EPSTEIN: First, the issue of reimbursement is not primarily an FDA issue. That said, there are other situations in which physician advocates and patient advocates have successfully negotiated with insurers to cover the cost of off label product use.

That tends to be an uphill battle when the product is expensive, but there is that alternative. Then, with respect to the inconsistencies in dosing, physicians often follow the recommendations of professional societies and also follow the published literature.

So, there are other ways in which a standard

practice can be achieved. Again, the important question for FDA is whether the submitted data for the specific product for its intended use established safety and efficacy.

We have not raised safety concerns here. We have focused on the question of whether the available data established efficacy.

I think that what is clear here is that it is a belt line question. You know, no one, including the company, argues that we are looking at a pristine or highly robust data set.

The question is which set of interpretations and which statistical analyses are the most appropriate in this situation and what is the correct conclusion.

DR. GOLDING: Very quickly, I remember at the 2004 BPAC, we did discuss the reimbursement. I am told by colleagues who have better memory than I have, that it was specifically stated at that meeting that in most, if not all, cases patients were reimbursed.

I don't know if there has been some change in the reimbursement policy since then, but my understanding is that, in most cases, patients are reimbursed, but not all.

DR. ALLEN: That is not germane. I am not going to allow further discussion on the reimbursement issue because that is not germane to our question here.

I would ask the committee, it is 12:35, I would

really like to wrap this up in the next 20 minutes if possible. We will go longer if we need to.

I would like to come back to question one. We have had a number of statement,s although they have been scattered throughout, about the inclusion and exclusion criteria. Do other committee members want to comment specifically on those criteria?

DR. ALTER: I don't want to drag this out. I would like to discuss reimbursement of the committee, but that is another issue.

You know, in truth, I think you have to look at these eight cases again, because I am hearing two different things about these eight cases.

The whole analysis hinges on them. If the intention to treat option was dropped and you went to Nabi's way, it would be I think you have shown efficacy, although Jay is disputing that.

It depends on how each of those eight cases go. I don't see how we can make this decision until we have resolved that issue of going case by case and which one should be included and not included in the analysis. I hate to say that at this point, but I don't see how you can get around it.

Dr. DI BISCEGLIE: I would support what Harvey is saying and echo what you said earlier, Jim. It is a shame

that we don't have the clinical data to accompany these cases.

I guess I would ask the sponsor whether this is available but just not submitted. It obviously wasn't submitted.

Then I wonder, Jay Epstein, if the addition of the clinical data might help support a claim of efficacy, because the claim, as Dr. Rasmussen's slide, prevention of hepatitis B clinical disease, but the fact is that no data were presented on hepatitis B clinical disease.

DR. ALLEN: Yes, I think the issue is that the question was specifically brought to this committee or to the former committee back in 2004, and the surrogate end point was agreed upon and that is what has been presented.

DR. BALLOW: Therein lies the real problem. The surrogate end point which was decided by BPAC in 2004 didn't exist in this retrospective study.

I understand at that time why someone didn't draw that to the attention either of the FDA or the BPAC committee or someone to try to come up with a modified outcome measure.

The company has used well being as their outcome measure in lieu of the fact that there weren't data points for the hepatitis B surface antigen.

You are right. We haven't heard the definition of

well being in any kind of parameter to support that. It is very difficult sitting around this table to make any decisions about the data that is presented and about which patients should be excluded, which patients should be included, just based on that one outcome measure of hepatitis B surface antigen, because there is a difference of opinion between the two groups on which patients to exclude and which to include.

DR. RASMUSSEN: In the analysis we submitted, we did specific analysis focusing only on the serology, only on patients who had the surface antigen measures for up to two years.

If you are taking our assessment of those seven cases, we disagree with the FDA. The data are highly statistically significant only looking at serology, and not take the clinical data base into consideration at all. So, those data do exist and they were submitted.

DR. CRYER: I am just going to address number one the way I see it, and that is that BPAC, two years ago, gave some criteria by which this drug could be approved if they fulfilled them.

If you buy the company's interpretation of what the failures are, they have done that, in my opinion. Therefore, I would propose that the answer to number one is that it is fine, that the company has done what BPAC said

they should do, and that is my suggestion.

DR. KUEHNERT: The good news is that since it is a retrospective study, you can just start all over again and look at all these inclusions and exclusions and change them.

I can go through each one, but I agree with the other people on the committee that, you know, depending on how you look at things, both sides are right or both sides are wrong, but there are definitely some extreme positions on both sides.

I don't know if, as a committee, we are supposed to be the ones to work out a compromise or what, but it seems like we could go through each case, but I am having a problem saying Nabi is right or FDA is right. I think there are some issues on both ends, concerning inclusions and exclusions as far as the analysis.

DR. KULKARNI: I totally agree with that. I really have problems calling the termination of the therapy for whatever reason as treatment failure.

At the same time, I have problems with Nabi including cases which really haven't reached their mark. So, I guess both ways I have some issues.

Regrading the efficacy, when I look at the true historic data of no treatment versus treatment, clearly there seems to be advantage to the use of the immune

globulin.

DR. ALLEN: Dr. Alter, would you propose that we go through each case on page 10 of the topic one handout? Is that the listing you would --

DR.ALTER: I don't' know if I am proposing we do it, but I think that it has to be done, that a decision can't be made until -- I mean, if we do it now, then it still has to go back to a real statistical analysis.

So, I think it has to be done off site, but it has to be done with some balance, and not the two sides facing off. So, maybe some of us should be there as mediators. I don't know. I am willing to go through them now.

DR. HOOFNAGLE: I think we first can agree that the data set is very poor. You have to make do with it. I think the FDA has been a bit tough here.

If you look at the criteria they said to use, it was surface antigen positivity. That is the failure. We are talking about eight cases.

Four of them the patients stopped, and there is this argument whether you can include them or not. So, we have four others that are being claimed by the FDA.

I would say in three of those four there really wasn't documentation of surface antigen return. One patient died at five weeks and Nabi has said they were surface

antigen negative when they died.

The FDA called it a case because the PI said it was HBV related. I don't think the PI was thinking when he said that.

Another case was someone who was surface antigen positive on one occasion and had multiple determinations before and after that were negative.

I can tell you, this happens to me all the time, that something like that happens. That just occurs when you do these types of studies and the individual centers are doing the testing. So, you really should have said they had to have two positives.

Then the third case was this patient who really had no follow up at all. They should be just dropped entirely. He had HPB DNA positivity on one occasion. Again, this is a test with very poor reproducibility.

Since the criteria was return of surface antigen, it is not fair to say that that is return of surface antigen. The case should be excluded because there is no data, basically.

That is the trouble with most of these cases. You don't have enough data to say one way or the other. I think the FDA is being a bit tough in that regard.

What we really have is one case that everybody agrees was a breakthrough and then we have four patients

who stopped therapy.

Now you could say, well, that proves the therapy doesn't work but, as pointed out by the FDA, the therapy may have been stopped because it wasn't working. I would say that that is what you would do in clinical practice. If the patient has recurrent hepatitis B antigen, you would stop HBIG. It is not working.

So, without really better clinical information, it is very hard to make these decisions about whether they were recurrence after stopping or before. It is not documented here.

Nabi said it was documented. It is not documented here, when the recurrence occurred in relationship to stopping.

DR. ALLEN: By the same token, if the cessation of therapy was purely for financial or economic reasons and there was subsequent documentation months later of recurrence of surface antigen, I would suggest that is not necessarily a treatment failure because there was no recurrence during the period of time the treatment was in effect.

DR. HOOFNAGLE: Absolutely. I guess one question is why were these patients force to pay for this drug that was being studied under IND. That doesn't make sense either.

Actually, the data for maintenance is much more compelling. The maintenance of HBs AG negativity was gotten by Nabi and now we have this experience with long term therapy, when you stop HBIG five years afterwards, you get recurrence, not just with Nabi products, but with other products as well.

I would say there is one case we all agree on. There are four cases that appear to be breakthrough but the drug was stopped, and that is the crucial issue.

DR. ALTER: As Dr. Rasmussen said, the cases that broke through after the drug stopped, that is really the truth of the matter. >From the Nabi presentation, that is what they are saying. Then this is actually proof of efficacy rather than proof of failure.

At the worst, they should be excluded, but they should not be considered failures. I think if you just reassign those four cases you would now have efficacy but, as Jay says, you could probably reassign seven of the eight cases.

DR. HOOFNAGLE: As Jay Epstein said, if you exclude the ones that stopped, who got reinfected, you have to include the ones who stopped but didn't get reinfected. it is very complex.

DR. ALTER: They are saying they did. That is the difference between the two.

DR. HOOFNAGLE: There are three, I think, that are a bit marginal in calling them recurrence. Those become the important case, don't they.

DR. FINNEGAN: The positive DNA one may as well, because according to Nabi, six years later they are still alive. So, for your Kaplan Meier, that is probably positive, that is probably a success. They say alive at six years.

DR. ALLEN: All right, we have a position sort of stated out. I think Dr. Hoofnagle and Dr. Alter are pretty much in agreement, and we have gotten some other supportive statements from others around the table.

With the position basically that we just have had stated, can we go around quickly and ask for everyone to make a comment? I am not asking for a vote. I am asking for a comment. Dr. Kulkarni, comments on that position.

DR. KULKARNI: I support the position of Dr. Alter and Dr. Hoofnagle.

DR. KUEHNERT: Is that what you want, a supportive position?

DR. ALLEN: Just basically a comment, is that reasonable or do you feel that there are major problems with that, that need further discussion.

DR. KUEHNERT: I think the idea of having arbitration by people who are reasonable about how these

cases should be classified is reasonable.

I could agree or disagree on the minutiae on that, but the major issue here is if the indication is for clinical suppression of disease and you are using antigen as a surrogate marker, fine, look at the surrogate marker.

If they died before they had the surrogate marker, you don't know. You just don't know if they would have had it or not, but you don't want to completely exclude them.

Similarly, if someone isn't on the product, you can't say that the product failed, I think. So, I agree with what was said generally. I would veer more toward Dr. Alter's impression of things in general.

DR. FINNEGAN: I would agree. I think the only thing that should be added is that these criteria were, in fact, given to the company by another group, a third party, which was the old BPAC and that should be entered into the concept.

DR. DI BISCEGLIE: I agree with what I think I am hearing, the concept of reexamining the eight cases. Perhaps because this is retrospective, one can talk about changing the end point that was given by BPAC and maybe think about treatment failures.

That would allow a more appropriate analysis of the cases that Dr. Hoofnagle is referring to. Some of those

are not treatment failures. It is hung up on whether it is surface antigen positive or not, as opposed to treatment failure or not.

DR. CRYER: I think reexamining the eight cases is just going to have the same problems. Everybody will disagree for whatever reason, and it is probably our responsibility to just say, are we convinced by the data supporting the statement of efficacy or aren't we, and I am.

DR. BALLOW: I think I weigh in more on trying to be a little more liberal in interpretation of those eight cases.

This is not a cure. When you stop therapy, we all realize that these patients are going to relapse, and it is remarkable that it took a year or more for some of those patients that came off therapy for economic reasons, to relapse. I think this modality looks very useful to maintain a kind of clinical state of well being, but it is not a cure.

DR. QUIROLO: I agree that the data set is incomplete and it is really pretty difficult for me personally to make any sense out of it.

I think both Nabi and the FDA arbitrarily decided which patients should be in and which patients should be out. It is clearly an efficacious treatment, and that is

what I would go for.

DR. SCHREIBER: I would agree with what is said. I think we need to look at all of the cases, exclusions in and out, since the denominators will also drive the rates. I agree with Dr. Hoofnagle, that there are some ambiguities.

It looks like each side came in with a little bit extreme position. I think that could be modulated and it would show that it is effective.

DR. SIEGAL: As long as the question being asked is changed from what is written here, I would agree that they are probably on the right track and should go forward.

DR. WHITTAKER: Yes, I think the data set needs to be reexamined for conclusions and explanations, as previously stated.

MS. BAKER: I agree with the approaches proposed by Dr. Alter and Dr. Hoofnagle to reexamine.

DR. KATZ: I think reexamination is fine. I would ask that there be some agreement before the reexamination starts about what you are going to look at.

DR. ALLEN: I think that is a reasonable approach and should be done as part of any study design, and I concur with the statements that have been made. Does anybody want to make any further comments or suggestions about question number one?

If not, I will declare that closed and move on to question number two which is, given the observational nature of the information provided, the data limitations including a priori definitions and the lack of analysis plan, is inference about the outcomes of Nabi's HBIG administration in this setting appropriate. Is inference about the outcomes appropriation. Discussion?

DR. FINNEGAN: I didn't flunk statistics, but I came really close. Anyway, the thing that I learned was, the smaller the number, the less reliable your conclusions, and this disease has very small numbers.

I think that observational information is actually probably fairly appropriate and I do think it shows the conclusion that it does work in this setting.

DR. KUEHNERT: I think it depends whether you are talking about HBIG on its own merits or whether you are talking about additive aspects to 3TC.

To me, it is pretty clear that it has beneficial effect. I mean, if you have got less than 10 -- if the N is less than 10, there is not very much you are going to be able to show no matter what you are trying to prove.

Clearly, I think it shows efficacy on its own merit. How much of an additional benefit it adds to 3TC is the question that maybe can't be answered with this data set.

DR. SCHREIBER: Given our discussion on point one, I don't see how we can answer point two. I think we have the data set, we know what the limitations are. We have discussed those.

I am not too troubled by the lack of an analysis plan. This is pretty simplistic analysis. You add a couple, you subtract a couple and you come up with a different rate.

I don't think we can make any inference from the data that we have as we have it. If you believe Nabi's data, you will accept their inference. If you believe the FDA's interpretation, you won't. So, somewhere we are in between and I think we should just not even have to discuss this question.

DR. ALTER: One and two are so integrally related that I don't think we can answer two until we answer one.

DR. ALLEN: Dr. Epstein, are you satisfied with what you have heard, given all the discussion on question one?

DR. EPSTEIN: I think the crux of the matter is whether the committee, assuming there are no further comments on question two, the crux of the matter is, having heard all of this and debated one and two, let's see what the committee thinks about number three, because that is the bottom line.

I am ont so optimistic that just simply telling us to go re-analyze the data -- well, we have analyzed the data, Nabi has analyzed the data. You have heard the basis of the disparity.

We have heard you say that FDA's approach was kind of harsh given the limitations. On the other hand, it couldn't be argued that it is not a standard statistical approach.

I mean, the problem here is missing data. We didn't cause that. Mind you, we didn't preclude the possibility of a prospective study, nor did we dictate that the retrospective study had to be this study.

In other words, it could have been retrospective monotherapy against historic control without HBIG, but this is what FDA has been presented with.

So, the question is, given its blemishes, where does the committee settle out. So, I appreciate the useful feedback, and it will be helpful to us in the context of what you say in question three.

DR. ALLEN: Let's table further discussion on question two at this point and move on to question three. Do the submitted data from retrospective chart reviews and uncontrolled PK pharmacokinetic assessment and an open label access program demonstrate efficacy of hepatitis B immune globulin for the OLT HBV immunoprophylaxis

indication.

DR. CRYER: I will just reiterate what I said before. Given all its blemishes, I think it does.

DR. KUEHNERT: I am not trying to look for a p value here at this point, but given the data, I would say yes. I mean, this doesn't say anything about with 3TC or not. It just says HBIG and the data are pretty compelling if you, I think, take a reasonable approach to inclusion and exclusion criteria.

DR. KATZ: I am trying to take a longer view than two years. After taking care of some of these patients and a lot of AIDS patients over a long period of time, the virus always wins over the drugs eventually.

I think we have learned the lesson that we need something more than one attack, and the real answer to this may play itself out over five, 10, 15 and 20 years.

So, given results before HBIG, results with HBIG, what we have seen in terms of HBIG plus lamuvadine, I am pretty convinced, and I am really searching for a way to ask FDA to give them the indication.

DR. ALLEN: Given the best possible analysis, I suspect that you will find marginal significance statistically.

I think it could have been much stronger based on all that I know and have read, and it is a shame there

isn't unequivocal data to support this.

There are still many unanswered questions and I think there still are many studies that need to be done to answer those questions in the future. It is just a shame that we can't be looking at more definitive data, if that would have been possible. Other comments?

DR. ALTER: I think if we are not going to look at these eight cases in detail together or in a subgroup, namely if we have to answer question three before we answer question one, then we each have to make our own decision as to where we would put those eight people.

I am inclined to put six of the eight into I guess the Nabi side, if you will. I am inclined to say the four who stopped treatment should not be considered failures.

I think that would change the statistics to significance. In addition, I think there are two other cases that either shouldn't be analyzed or would be on the good side.

So, if I am forced to do this, I would really rather see the data again in detail but, if I am forced to, I would vote that efficacy was shown, particularly if you compared it against a different control, namely, no HBIG.

DR. ALLEN: Further comments? We will have a yes/no vote on this question. All right, are you ready for

the question? Okay, Mr. Jehn.

MR. JEHN: Dr. Alter?

DR. ALTER: Yes.

MR. JEHN: Dr. Ballow?

DR. BALLOW: This is really tough. This is not evidence based medicine as we teach it to students, but with the reevaluation of some of the patients in question leaning toward less of a conservative approach, I think the data would probably lean toward a yes vote on the last question.

MR. JEHN: Dr. Cryer?

DR. CRYER: Yes.

MR. JEHN: Dr. DiBisceglie?

DR. DI BISCEGLIE: I guess I would give my vote based on where I think the data re-analysis would end up, and I would vote yes.

MR. JEHN: Dr. Finnegan?

DR. FINNEGAN: Yes.

MR. JEHN: Dr. Kuehnert?

DR. KUEHNERT: Yes.

MR. JEHN: Dr. Kulkarni?

DR. KULKARNI: Yes.

MR. JEHN: Ms. Baker?

MS. BAKER: Yes.

MR. JEHN: Dr. Whittaker?

DR. WHITTAKER: No.

MR. JEHN: Dr. Siegal?

DR. SIEGAL: Yes.

MR. JEHN: Dr. Schreiber?

DR. SCHREIBER: No. I think the FDA analysis raised enough questions that we have to look at it.

MR. JEHN: Dr. Quirolo?

DR. QUIROLO: I am going to abstain because I don't think this data allows you to make a decision on this.

MR. JEHN: Dr. Hoofnagle?

DR. HOOFNAGLE: I thought I was a non-voting member. I think I will abstain as well.

MR. JEHN: Dr. Allen?

DR. ALLEN: Probably so, but I also will abstain on this because we don't have the final analysis in front of us and I think the studies could have been done that would have answered the question definitively and I am disturbed that they were not.

MR. JEHN: Opinion from our industry rep?

DR. KATZ: It doesn't seem to me it should be too hard to get the ALTs. I anticipate that looking at the objective clinical markers would allow me to vote yes.

MR. JEHN: We have nine yeses, two nos and three abstentions.

DR. ALLEN: So, the summary is that the committee has voted in favor of the yes. I think there were a number of reservations and other issues raised, and I hope that is useful to the FDA.

Other comments or questions from the committee at this point or from the Food and Drug Administration? Dr. Epstein, anything further you want to say at this point or ask the committee?

DR. EPSTEIN: Well, just to thank the committee. I think this has been obviously a difficult question to raise and I appreciate the thoughtful deliberation and we will take your advice under consideration.

DR. ALLEN: It is a few minutes after 1:00. At this point, we are well behind where we should be. We will break for lunch. I would like to have the committee back here and ready to go, please, at 10 minutes of 2:00.

[Whereupon, at 1:07 p.m., the meeting was recessed, to reconvene at 2:00 p.m., that same day.]

A F T E R N O O N S E S S I O N (2:09 p.m.)

DR. ALLEN: We are running a few minutes late. I was talking to the center director and that took priority. Why don't we come to order now. We will be going into topic two, which is review of the research programs in the laboratory of bacterial, parasitic and unconventional agents in the division of emerging and transfusion transmitted diseases, OBRR, CBER, FDA.

The site visit was performed May 25 of this year, and I note humbly that other people, including Dr. Mark Ballow and this group have gotten their reports in much more promptly than I managed to do.

We will start with our overview of CBER research by Dr. Carbone, and then we will have a series of presentations by other FDA staff, and then we will go into our open public hearing and report review.

Don, what we got as confidential, is this still a confidential draft? The committee members have seen it but the public has not seen it. Okay. Dr. Carbone?

Agenda Item: TOPIC II. Review of the Research Programs in the Laboratory of Bacterial, Parasitic and Unconventional Agents, Division of Emerging and Transfusion Transmitted Diseases, OBRR, CDER. Overview of CBER Research.

DR. CARBONE: Today I would like to do two things

quickly and hopefully save a little bit for the associate director for research for the office to speaker a little longer.

Briefly, I want to introduce the committee and the attendees to the concept, if they are not aware of it, of critical path research at the FDA, followed by a very brief discussion of research and research management at CBER, and then we will move on to more specifics about the office.

Basically, the critical path is in response to the concept that regulation of products, important medical products in our case, complex biologicals, is not simply a matter of passive rating of different applications, but should be actively supported and facilitated so that effective and safe products get to the people who need them.

The problem is that, despite the large investment in basic biomedical research, there are many cases where this has not translated, and there has been a road block or a build up into an actual medical product, that we have a lot of exciting developmental stages and not nearly enough making it to successful products.

So, the critical path is envisioned as a complement, if you will, to translational medicine, or basic discovery, beginning to be studied and applied to the

human situation, but it is to actively get those products to final form, approval and out in availability.

Nonetheless, as many of you know, who interact with CBER, in terms of critical path involvement in the science, the tools, the knowledge needed to regulate these products, the science of evaluation, if you will, really requires investment and involvement very early in the process.

People in the industry know this quite well. It is sometimes a bit puzzling and sounds a bit oxymoronic, but failure is a good thing if it occurs here and not here, and too many products fail after a lot of investment has been made.

So, the critical path research initiative, which information can be found at this web site is, in short, to identify, focus and manage regulatory and scientific opportunities to improve the product development process and availability.

Many of you who have been involved in this process know that the problems are often the scientific blunders. If only we knew that, we would have a better idea.

Guessing is difficult because the FDA is an extremely data drive organization and, as such, there is never enough data, but we need at least to do a better job

of acquiring it.

The things that we are concerned about, of course, are potency, effectiveness standards, safety, consistency and manufacturing quality, not your typical research endeavors outside of industry. Therefore, we have a good role to play in this niche, if you will, where the FDA can contribute.

Research, of course, applies to policy and guidance based on good science and, as Dr. Goodman said, it is not just a science based, but a science led, FDA.

So, why should FDA play a role here? The most common question I get asked is, you do research at the FDA? The second most common question is, why do you do research at the FDA.

As Dr. Allen so nicely stated in the beginning -- he gave a nice overview of perhaps the significance -- basically the agency has a very unique perspective, in terms of seeing broad categories of products and product development, and hopefully it can intervene and assist in the development on the broad categorical level.

Also, if you will, as the disinterested or non-conflicted party, the FDA can serve a very good convening and coordinating role among industry and all sorts of stakeholders.

I think an example of that, on a critical path

science basis, was this malaria workshop, bringing together multiple partners from industry, scientific, academic arenas, regulatory arenas, to discuss the critical scientific issues that are important in regulation of biological products.

The work done in critical path, though, is not done exclusively, of course, by intramural FDA. FDA collaborates with outside stakeholders and, in fact, hopes to encourage the extramural work in this area sort of to raise it to the consciousness level.

Just a little illustration to show that the scientific information is a clear part of the process. It is not ancillary. The information that supports -- that is reviewed, public input, peer reviewed, et cetera, some of the issues Dr. Allen raised -- it then goes into guidance and standards and only makes it easier for the next one. If you will, the critical path is a figurative path where the pathway is created, expanded and more efficient for product development.

I think this has been covered by Dr. Allen already, but the review in 1998 stated that the model that CBER uses, which is regulatory staff who also work to actively solve problems, if you will, the research regulator model, is fairly unique in FDA, but has worked very successfully for CBER to make more efficient and more

accurate and more predictive product regulation.

So, our people are basically great multi-taskers. Those of you who have been in academia and see patients and teach courses and do research understand that multi-tasking is the secret to becoming a successful research regulator.

The research programs have scientific expertise, obviously, but the administrative responsibility is our product, because that is our mission, but they are fully integrated into the regulatory process, as Dr. Allen stated, and do the full cadre of reviewers.

Now, of course, I don't want to imply that we have also full time regulatory scientific staff, clinical review staff. We are all part of a team, all an essential part of the mission. The research regulatory group provides hopefully some benefit added for that.

The mission relevance of the research programs, I was very happy that it was perhaps a bit clearer to the review this time than in 1998 as to exactly what the application or applicability of the research to the regulatory mission was.

When I came on board, we started collecting this kind of information, specific INDs that were being impacted, guidances that came out of scientific work, et cetera, to be able to get a handle on this information.

The scientists sat down and rewrote their

research progress reports, which were long, sort of scientific based reports, into short, plain language, public health issue, regulatory issue type reports, which are now actually publicly available, along with four year's worth of publications, and that is on the CBER external web site by clicking the research link.

The CBER research in the public domain hopefully supports development of more products and safe and effective, and that are manufacturable.

So, how do we manage research programs at CBER? I will give a very, very brief overview because of the time. Basically, we have moved from sort of the intramural approach of evaluating your achievements in a program, to now evaluating achievements and plans.

So, it is four years of achievements and four years of future plans. We do an external as well as an internal evaluation of those proposals.

The external evaluation is, as Dr. Allen mentioned, done by site visits of the individual investigator plus the laboratory setting. So, the entire laboratory is reviewed at once.

Internal management reviews include the yearly cycle of research reporting, the web based system that we have had developed for us by a very talented fellow, Don Matroon(?).

That includes report of publications, regulatory policy, guidances. We also use this as research QA and QC. We use it for animal protocols, human protocol approvals, et cetera.

The office research site visit, as Dr. Goodman said, is new but something we plan on doing on a continuous basis.

As part of ongoing evaluations of each office, of course, the cross office inter-talk in the office is the next step. In fact, the FDA is planning on doing center-wide reviews, which we should be well prepared for, having done our work at the office level.

It is important within CBER to get cross talk since our research program is fairly stretched in terms of resources and personnel.

So, we have developed a concept of essentially virtual expertise teams across the center. For example, we have a malaria expert who is an expert in malaria vaccines but resides in blood.

Through this virtual team concept, their expertise, of course, applies across the center. It is a matrix, if you will, people with scientific expertise who also have product specific expertise, and something that you rarely find outside the industrial research setting.

The CBER research is, of course, provided with

intramural support but, as Dr. Allen said, in carefully managed select cases, they are going out to get extramural support, the largest of which does come from NIH and select programs that are of importance in product development, for example, cell substrate issues.

I will just I think end here with just some small successes and I will let Dr. Atreya take on more details. For example, it was the ability of scientists here to flex -- and as was mentioned by Dr. Allen in the west nile virus that you heard about, that allowed some innovations in IND evaluation of the NAT testing for the west nile virus.

There are numerous examples, new standards, new assays for patient end points that have been developed at CBER and CBER collaborations for HIV, hepatitis, blood typing, and there is a list here.

We have new safety evaluations, some work in this office working with the hemiglobin based oxygen carriers and characterizing these carefully through novel techniques, mass spectroscopy, et cetera, and have one become industry standards, and careful characterization of products for safety and efficacy.

Of course, a very important area being worked on in multiple international collaborations, also supported in part by NIH funding is prion detection and potential removal.

Of course, there is a future and, as Dr. Goodman said, the plan is to review the office site visit, create responses and document how we will respond and then come back and present that to the BPAC committee.

We also have a research leadership council, as Dr. Goodman mentioned, which is leaders of the research, as well as the regulatory scientist group at CBER, which is meeting to develop the research priorities for the center, for the offices, and develop a new paradigm for evaluating these, as Dr. Allen noted.

So, we will have that information and that paradigm available for you. We are essentially beta testing it right now.

So, I will just end with a thank you very much for your input. I also agree and second Dr. Goodman's notion that if you find scientific quandaries that really need to be answered, we would love to hear them. We can't obviously do everything, but we can always encourage other people to do it, work with NIH to see if we can encourage them to put this on their radar screens, et cetera, and we greatly appreciate your time for the review of the larger office, as well as this particular lab. Questions or later, whatever you would like, Dr. Allen.

Dr. ALLEN: Any questions for Dr. Carbone? Let me go ahead and ask you, I think I could hold this question

until later but, as I was reading through this report, there were several instances in which the scientists were working -- they seemed, at least if I understood it correctly -- to be the only scientists within, or the only science group that is within CBER working on a specific pathogen.

Some of them are working on vaccine constructs, which is not a blood related issue, but it is CBER mission related, even if it isn't OBRR mission related. Is that the way we should interpret it?

DR. CARBONE: I actually was just talking to Dr. Goldsmith about this. I have to compliment blood, because of all the offices, it is probably the best good citizen, if you will, in terms of containing some very unique expertise for the center, which includes malaria, includes parasites and Dr. Atreya, rotavirus even.

I have to compliment Dr. Epstein and his staff for supporting CBER's mission in allowing this unique expertise to function in areas outside specific to blood.

They are always related to blood, there is relevance to blood, and there is work being done relevant to blood, but they serve as the center experts, and I have to compliment this office for their generosity.

DR. ALLEN: I think just as long as the committee is aware of that. I had a few moments where I was

struggling with that myself, if I was applying the OBRR finely focused microscope and I am looking at these and saying, is this really mission related. It certainly is to CBER, although maybe not for OBRR.

DR. CARBONE: I would ask you not to ding Dr. Epstein for supporting something we all use.

DR. ALLEN: That is the reason I wanted the answer from you rather than from those directly involved. Thank you. I think that is an important clarification. Other questions for Dr. Carbone at this point? Okay, we will move on to an overview of OBRR research by Dr. Atreya, associate director for research at OBRR.

Agenda Item: Overview of OBRR Research.

DR. ATREYA: Good afternoon, everybody. My name is C.B. Atreya, and I am acting director for research. As Kathy was telling, it is also called a detail. So, I am actually in the office of vaccines, and now learning about the office of blood and helping them out as an associate director for research.

I will present this overview in two parts, one as the organizational structure and the regulatory responsibilities of the office, and second the regulatory science research programs that the office of blood is currently having.

So, let's first have the organizational structure

and the regulatory responsibilities of the office of blood. As you can see, Jay Epstein is our office director and we have a staff of around approximately 161 employees.

That is being divided into cell one, we have the associate director of policy, and then we have the deputy director, Jonathan Goldsmith, and the associate deputy director, Mark Weinstein, and then I am acting in the capacity as research associate director.

Then we have the associate director for regulatory affairs is also acting. Now, three divisions are there. One is the division of emerging transfusion transmitted diseases.

The second division is the division of blood applications. The third division is the division of hematology. All of these numbers in parenthesis represent the number of staff in each of these divisions.

So, what do we do in OBRR in terms of our regulatory responsibilities? The office of blood is the primary FDA complement that facilitates development, approval and access to safe and effective blood products.

That includes a lot of review work, application reviews, standards development, policy setting and so on and so forth.

Then we also evaluate promising new technologies related to blood safety and retroviral testing. As you can

see now, the office of blood also organizes, from time to time, the workshops that are related to the current topics that we gather information from the public.

Then OBRR is also charged to regulate blood and blood derived products, medical devices used to collect and test processes to store donated blood, and also retroviral diagnostic testing.

So, the regulatory responsibilities are also, you can divide them into product based, and the three divisions have three different product responsibilities.

One is the division of emerging transfusion transmitted diseases. It is responsible primarily for blood donor screening tests for infectious agents and also retroviral diagnostics.

Then the division of hematology carries out a lot of work related to bacterial detection devices, plasma derived products, blood and blood component collection devices and also plasma expanders, including hemoglobin based oxygen carrier solutions.

Then the third division, the division of blood applications, essentially deals with the blood and plasma licenses, the blood establishment software licensing and blood grouping and HIV reagents.

So, let's move on to see what the research programs are in terms of our critical path initiative that

Kathy was talking about.

OBRR research programs, actually our core programs are oriented toward detection and control of infectious agents relevant to blood products, categorization and standardization of blood components, plasma derivatives and related devices.

Occasionally OBRR also engages in hematological studies and methods development, research to enhance product review and surveillance.

OBRR also leads in collaborative investigations within the broader spectrum of CBER's programs of scientific interest, for example, in HIV immunology and development of vaccines for parasitic diseases.

This is exactly the question you were asking. We started with certain expertise and then, as we need, we move around within the offices and centers, but our expertise remains, and then we help out in the regulatory process.

Then what is the vision for research in OBRR? It supports the critical path for product development through focus on scientific questions particular to effective regulation, concentration in the areas where our unique role as regulators is most contributory. Then we also provide an infrastructure for investigation of product failures and limitations.

We also facilitate progress toward the goals and promise of 21st century medicine. That is, for example, genomic and proteomic based medicine and applications of nanotechnology.

So, I will give a few examples and I will not try to give a list of things. Just for example, our research actually accomplishes specific product development. I will give an example.

The blood safety issue, for example, the need for development of technologies and methodologies that can screen blood donors for a large number of pathogens simultaneously.

So, the actions were taken and then developed proof of concept, multiplex NAT nucleic acid basic testing and DNA micro arrays for blood donor screening.

For example, Nakhasi's group has some publications on that. Then the outcomes of that particular action is to identify critical parameters for assay development and the standardization of the panels.

The example that can go on is from the other division, which is the division of hematology. When the safety of smallpox vaccination became an issue, the problem here is that the efficacy of the vaccine immunoglobin as treatment cannot be tested in humans.

So, the actions were developed to produce a SCID

mouse model to test the efficacy. This is from Scott's group's work in the division of hematology.

The outcomes of this work were, we were able to transfer the methodology to the industry and also incorporation of this model helps provide a pathway for licensure of new VIGA products.

So, I can keep on listing several things but, in the interest of time, I will not, but there are a lot of accomplishments from the office of blood.

Specifically I would point out to the last three here, like studies on the decontamination of prions and invention of prototype oligonucleotide micro array pathogen chips, developed from the division of emerging and transfusion transmitted diseases.

The third one is from the implementation of the live attenuated leishmania parasites as potential vaccine candidates.

So, here with these examples I want to impress upon you that actually research is integral to the mission of OBRR and CBER, and the office of blood research and review facilitates product development and is aligned with the FDA's model of the critical path.

I appreciate your time on this and Hira Nakhasi will elaborate more on his division activities. Any questions?

DR. ALLEN: Thank you. Questions? Good. You answered my question very nicely. Thank you. We will move on then to an overview of the division of emerging and transfusion transmitted diseases research program, Dr. Hira Nakhasi, director.

Agenda Item: Overview of the Division of Emerging and Transfusion Transmitted Diseases Research Program.

DR. NAKHASI: Thank you, Dr. Allen. As C.D. and Kathy mentioned to you about the overall mission of the CBER as well as the office, I will focus my remarks to what we, in the division of emerging transfusion transmitted diseases are concerned with.

Our division is organized into three research laboratories, which is the laboratory of bacterial, parasitic and unconventional agents. Dr. David Asher is the head of that, and that is today's site visit discussion.

In addition to that, we have the laboratory of molecular virology headed by Dr. Hubert(?) and hepatitis and related emerging agents headed by Dr. Gerardo Kaplan.

In addition to that, a few years back we set up another laboratory which is the product branch, which is all the staffing that is full time reviewers.

The red lines show you the interconnection between each of those research reviewer laboratories. In

connection to that, we have a product testing laboratory where the lot releases for each product has test kits which we license, they are tested in there.

The mission of the -- obviously you heard -- of the OBRR is here to enhance the product safety, purity and potency in order to override product shortage, and that is our mission, too.

In order to fulfill that mission, how do we do that? Our primary responsibility is to ensure the blood product safety and, as you know, millions of units are transfused annually, and the risk of transmission has gone significantly lower with the introduction of these tests.

This is an example. Some of you must have seen yesterday the slide that, with the introduction of tests over a period of time, the risk of these agents -- for example, HIV, hepatitis, HCV, for the time being, has significantly reduced when there were no tests to when there are now, indeed, tests. The range shows you the events when we had serological, antigen based and non-nucleic acid based tests.

Now, having said that, we are constantly undercut with emerging pathogens, such as HIV drug resistance, mutants for HBV, and the question is how do our tests, currently licensed tests, detect those agents. So, we have to be always on guard on that.

In addition to that, we also have the responsibility to make sure that the new and emerging pathogens such as west nile, SARS, corona virus, influenza virus and other things, are threatening the blood supply. So, we need to be cognizant of that fact.

In addition to that, the old agents, such as parasitic agents, which are always there -- malaria, you heard a lot about it yesterday, and chagas, over the years, you have heard quite a bit, and leishmania is unfolding in Iraq and Afghanistan, which I mentioned some time back that a lot of people are traveling to that, especially the U.S. army where people have come down with infection. So, how does it threaten the blood supply. They are all blood borne pathogens.

Then the other area is the TSE agents, and we again, in those areas, we don't have tests and we defer donors based on exposure, and there is a significant donor loss. So, it is not only the blood safety, it is also the issue of blood availability.

Now, how we achieve our mission is to by proactively ensuring the safety of the blood supply through regulation, regulation of these blood screening and diagnostic tests for all of these agents which I mentioned, evaluation of new technologies for rapid and flexible screening of the blood supply, developing FDA guidances for

use of screening for those agents, and then implementation.

Then we also maintain the lot release testing for approval of these tests before they are sent for approval. We develop reference materials for validation of these tests.

We have inspections of the facilities where these tests are manufactured. We consult with other agencies in the government to provide advice on how the test implementation is to be done, and we discuss these issues, just like in advisory committees just like today, and keep the public abreast of what is happening.

So, in order to do that, as both Kathy and C.D. mentioned, we have a research plan along with it to support the mission.

The basic plan for this research is very much integrated in how to understand the pathogenesis of these blood borne pathogen infections, so as to know what is the period when the person is asymptomatic, is the viremia there, how do we detect these things.

So, we have to understand how these agents are functioning, are causing the disease. Then, in addition to that, we also have significant research programs in developing the panels, trying to see new technologies, how they are improved.

In order to do that, we also have, in addition to

that, again to answer your question, because that pertains particularly to my research program, is having a unique expertise in the whole center to see how we can interact with the rest of the center to provide the unique expertise which a particular group has, such as in the case of parasitic agents and vaccine development. Not only that, we also are involved in the blood area.

So, in summary, our mission in relevant research in viral, parasitic, PSE agents, improves our OBRR CBER's ability to evaluate the safety and efficacy of blood and blood products, as well as the vaccine, which is the CBER mission. Thank you very much for your attention.

DR. ALLEN: Thank you, Dr. Nakhasi. Questions?

DR. FINNEGAN: We talked earlier about creative funding for some of your research. In your malaria and leishmaniasis, is it possible to go to somebody like the Gates Foundation, who has expressed great interest in this and get some funding from them? Is there a pathway to do that?

DR. NAKHASI: Yes, actually maybe Dr. Carbone, who is our fearless leader of our getting the funding should maybe tell you about that.

DR. CARBONE: There is good news and bad news about Gates. I agree. I think that our regulatory mission relevant research is a wonderful match for foundations like

that.

Right now we have limited legal mechanisms for obtaining funding. One of those is the CRADA, the cooperative research agreement.

There has been some reluctance on the part of some groups to use that mechanism for essentially giving money for granting situations, since that is not a cooperative research.

Now, in one case, in the case of glycoprotein vaccines, we actually with a third party, PATH, to make sure the funding is available in a WHO international collaboration.

So, that pathway is most definitely not closed. It is somewhat difficult from a legal standpoint, but we are working on that.

Actually, Dr. Goodman has been in contact with that group. I don't know if you want to speak further on that, or enough said.

DR. FINNEGAN: One additional question would be, the CDC has set up a foundation to help with some of these legal issues. Has the FDA or CBER thought about something similar?

DR. CARBONE: Funny you should ask. The CDC and NIH both have foundations which required acts of congress to set up.

We did an analysis of several different mechanisms by which the FDA could ethically and legally accept funding for specific projects that were of public health importance.

One of those options that we provided the analysis for was an FDA foundation. We forwarded that up the chain and they are considering that document.

It was very helpful that we have a lawyer on my staff, Danno Murphy, who was able to cite the legislation, the language, et cetera.

So, we are definitely trying to work with the commissioner's office to explore that. That is a long-term plan but still, starting now would be better.

DR. NAKHASI: If I may add a little bit to that, to answer your question, there is some collaboration between CDC and FDA on like the national vaccine program, and some of these initiatives for malaria or something like that, they are helping from time to time for funding.

DR. ALLEN: Thank you. Our next presentation will be by Dr. David Asher, who is chief of the laboratory of bacterial, parasitic and unconventional agents, and he will give us an overview of the research in his laboratory.

Agenda Item: Overview of Laboratory of Bacterial, Parasitic and Unconventional Agents Scientific Program.

DR. ASHER: Thank you. I would like to elide the next two talks, first to introduce the laboratory of bacterial, parasitic and unconventional agents, and then my own projects in that laboratory, trying to summarize in just a very few minutes two longer presentations at the 25th of May site visit.

The laboratory was formed in 1999 when four investigators from the office of vaccines -- all of us working in spongiform encephalopathies -- joined the office of blood and existing staff that was made up of a malariologist and a bacteriologist, both gone on now to other positions.

As you probably understood from Hira's talk, our primary responsibility is to conduct research having to do with FDA regulated product development and safety, leishmania, chagas disease, malaria, spongiform encephalopathies having to do with candidate blood donor tests, developing some, evaluating others.

As Dr. Carbone explained, there is a reason why we are also involved in vaccine related research on all of those diseases, including a major project on spongiform encephalopathies as related to vaccine safety.

We conduct other regulatory relevant research, pathogenesis at both cellular and molecular levels on the parasitic diseases and the spongiform encephalopathies.

The pathogenesis research not only provides material and information of regulatory relevance, it includes our reviewers' insight into regulatory issues, for instance, a better understanding of what happens during window periods, eclipse periods, sanctuaries in non-blood tissues in which agents may be residing.

It also -- the activity also helps to maintain our scientific expertise and it increases the level of enthusiasm and commitment to the regulatory mission.

Not to be crass, but some of this research is not only self supporting, but it also supplements the more directly regulatory relevant research.

The program is divided into two major areas, the parasitic and bacterial diseases, which joined us in the following couple of years after the laboratory was founded. We have a total of 18 total staff last count, five principal investigators, and each one will be presenting today, as well as two of our other scientists. Each of the presenters will present his own program. So, I don't need to review those.

In our section on transmissible spongiform encephalopathies, Pedro Piccardo is primarily concerned with pathogenesis and the safety of source material and Pedro's talk will follow my own section's concern with the safety of manufacturing facilities, including evaluations

of blood donor screening assays, which we both are concerned with that.

Let me move on now to the spongiform encephalopathies themselves. I don't need to tell any of you that the spongiform encephalopathy is named because of the most striking histopathological change seen in the disease, terrible infections that lead to incurable, invariably fatal diseases.

These infections have been transmitted, albeit relatively rarely, by products of classes regulated by the various centers in the Food and Drug Administration.

Of greatest concern to the office of blood has been the recent recognition in the United Kingdom that three transmissions of variant Creutzfelt Jakob's disease, the kind that arises from exposure to the agent of bovine spongiform encephalopathy, BSE, that there have been three infections presumptively transmitted by blood that produced clinical disease. One of them the patient died during what must have been the pre-clinical period, of an unrelated illness.

That is from a very small number of people who were exposed to the non-leuko-reduced red blood cell concentrates that were implicated.

It remains to be seen -- we are holding our breath -- about whether any of the other component

derivative products will turn out to be responsible for accidental transmissions of the infection.

Dr. Piccardo will talk with you about his work, particularly directed at the so-called abnormal prion protein forms that appear to be associated with infectivity and other forms that are not.

In describing my own section, I am going to review for you briefly three active projects and one project that we have been trying to get launched for the last several years.

The first one will be a method to evaluate -- not to develop, but to evaluate various clean up and disinfection methods that have been recommended by the World Health Organization and generally accepted by the CDC for treating facilities and equipment potentially contaminated with TSE agents.

The second will be to look at a computerized morphometric method that attempts to increase the objectivity of routine regulatory decisions based on immunohistochemical examinations of infected or potentially infected tissue, in support of product safety, not only in the center for biologics, but also in the center for devices. That is very concerned with what to do with surgical instruments that have been exposed or potentially exposed to these agents.

Then I will review for you a study evaluating the susceptibility of biologic cell substrates -- that is, the cell cultures actually used to manufacture biologics, mainly vaccines, but other biological products.

Finally, I will close by describing a proposal that we have made for setting up a U.S. biological reference material collection.

We already have brain material from the NIH, but there is a need for blood based material which we don't have, and frankly nobody else, including the World Health Organization, has them at this point.

It is hard to understand research on spongiform encephalopathy without understanding at least a little bit about the abnormal prion protein, which has been designed as scrapie type prion protein or protease K resistant prion protein.

Because of considerable confusion in the various types of abnormal protein and what is an appropriate nomenclature, the World Health Organization has recently suggested calling all the abnormal forms as PRPTSE, and I will do that. It is not clear that the name will stick but, if it does, it will help to simplify it for ordinary human beings talking about this protein.

It is derived from ubiquitous normal precursor proteins that all of us have. Regardless of what it

ultimately turns out to be in terms of infection, it is clearly a very useful marker of TSE infections, and even for classical animal infectivity assays.

Most of us now use this test to confirm that an assay animal did, in fact, have a spongiform encephalopathy. It was first detected by electromicroscopy, and it is also readily detected by immunostaining, by immunohistochemistry, by ELISA tests, and very frequently by western blot, where it is discriminated from normal prion protein because normal prion proteins are completely digested by the enzyme proteinase K, whereas the abnormal prion protein has its N terminus cleaved off, but the basic protein remains.

These proteins are an abnormally folded cleavage product of the normal cellular protein, relatively insoluble in detergent salt solutions in which most of them are precipitated, and relatively resistant to digestion with the enzyme proteinase K, and it is the last two properties that are used ordinarily in testing to discriminate between ubiquitous normal protein and the abnormal protein.

The normal protein is a 253 amino acid protein encoded by a gene on chromosome 20. It is linked to a series that, in familial cases -- which comprise about 10 percent in most series of Creutzfelt-Jakob disease cases,

it is associated with one of about 30 mutations now that have been described in the prion protein encoding gene.

Mice lacking expression of that gene cannot be infected with a TSE agent. So, it is clearly responsible for susceptibility to infection, and it may, or the protein itself may, or may not, be a component of the infectious agent or even the whole infectious agent, as the prion hypothesis predicts.

Coordinated by Kitty Pomeroy in our laboratory, and supported by the office of science at the FDA, we have conducted a study attempting to set up a method for evaluating the effect of various decontamination regimens on the infectivity of these agents when they are dried onto surfaces.

These should be relevant both to manufacturing facilities and to potentially contaminated equipment. In the first method, hamster adapted scrapie agent is dried onto cover slips, which can then be exposed to disinfectants or autoclaving or combined treatments.

Afterwards, disinfectant is rinsed off, the cover slip is ground to a powder in diluent. The glass promptly settles out and infectivity enters the supernatant fluid, which then can be assayed for infectivity by injecting hamsters intracerebrally.

In a second model, infectivity in the form of a

hamster brain paste is dried onto steel needles, which can be conveniently arrayed in the familiar 96 well format, which they can be dipped into conventional cell culture trays.

After exposure to various contaminants, the needles are inserted into anesthetized hamsters. For both of these models, if any hamster than dies of scrapie, you can conclude that the method was not successful in freeing the object of all its infectivity, although it may have dropped titer.

I won't present the data, but when we looked at the WHO recommended methods, which are mainly combinations of either sodium hydroxide or sodium hydrochloride -- that is chlorine bleach -- either with or followed by autoclaving.

We found that these methods were quite effective in removing substantial amounts of infectivity, but we did have an occasional hamster that died with scrapie. So, they didn't seem to be 100 percent effectively, although they were clearly quite effective.

That is not the way that decontamination in hospital and manufacturing settings are done. In the real setting these are combined -- one hopes they are combined with effective cleaning methods.

So, what we tried to do was model what was done

in a more realistic setting, and we began by seeing how much infectivity would come off if we did an ultrasonic cleaning in hot alkaline detergent.

We found that a great deal of infectivity was removed in both models. At least 100,000 lethal doses were removed, but there was still a significant amount of infectivity that was left adhering to the glass or to the steel needles.

However, when we did this and followed them by WHO type decontamination procedures, we found that all the hamsters tested were protected against infection.

This might explain why so few surgically acquired infections have been documented over the past 60-some years, only five well documented surgically transmitted CJD cases in that time, and some other WHO methods we found to be effective, if they were used in combination with preliminary ultrasonic cleaning in hot detergent.

I think WHO -- Matt -- has left the room, but I think WHO would be pleased to see that the methods they have bene recommending for the past number of years, at least in this limited study, was effective down to the limit of detection.

You have to keep that in mind. We can't be sure that, below the limit of detection, there might not have been a little bit of infectivity left but, to the limit of

detection, we were able to keep these hamsters that would have otherwise died in 90 days or less alive for 550 days.

The next project I want to summarize for you attempts to use computerized morphometric analysis to make possible more objective evaluations of immunostained prion protein in brain tissue.

In regulatory agencies we have had the problem of getting conflicting readings, sometimes from the same pathologists, for brains that are considered to be ambiguous for the diagnosis of spongiform encephalopathies.

This can make a major difference in regulatory decision. Does the center for devices tell someone that they have to destroy a whole set, or quarantine a whole set, of instruments, or is it okay for them to go ahead and clean them well and use them again.

We don't necessarily have to be right, but we feel we have an obligation to be consistent in the kinds of regulatory decisions that we make.

So, we, under the leadership of Olga Maximiva, have looked at a commercial computerized morphometric analytical method for evaluating the amounts of abnormal prion protein seen in brain tissue.

In the first stage of this study we compared the morphometric scores, total area stained or total optical density, with scores assigned to the same sections by

conventional histopathological evaluation by Pedro Piccaro and Dr. Maximiva.

We found that there was a pretty good correlation between the visual scores assigned and the total area stained or the total optical density.

I won't show the data, but we then went on to use this method for a pathogenesis study of scrapie in hamsters, and found that it was very useful for describing the sizes and shape of the aggregates of prion protein, as well as the total area stained.

Later this summer we plan to put it to a more severe test, by having blinded examinations of ambiguous areas as well as the diagnostic areas selected from the brains of patients with known Cruezfelt Jakob disease, other neurological diseases and no neurological disease to see if this method will, in fact, make a contribution to reaching decisions about whether a brain with ambiguous visual scores, in fact, has Creutzfelt Jakob disease.

The last project I want to summarize looks at the susceptibility of real biologic cell culture substrates to infections with the BSE agent, the agent of variant Creutzfelt Jakob disease, and sporadic Creutzfelt Jakob disease, compared with an artificial worst case culture, in which a human cell line expression neuronal and glial properties, is engineered to over-express prion protein,

one variant of which bears the most common mutation that is seen in families with familial Creutzfelt Jakob disease.

The basic protocol is to expose these to high doses of infectivity, and then carry the cultures for 30 passages, assaying them at intervals for accumulation of abnormal prion protein and, at the end of the 30 passages, for infectivity.

The cell cultures that we are looking at are viro cells, Chinese hamster ovary cells, HEK293, which is a model for a commonly used proprietary cell line that we couldn't get the sponsor to send us, and WI38 human diploid cells.

We have also added, since the study began, Madden Darby canine kidney, because that has been selected to make an experimental influenza vaccine.

To make a long story short, this is where that study stands with sporadic CJD. We have completed the 30 passage for a number of the cultures for BSE.

We have completed -- that is cultures exposed to the BSE agent. We have completed it and we have just begun looking at variant CJD.

On this project which is -- let me add, I should have before -- this is a joint project between Dr. Piccardo's part of the program and mine, together with Dr. Lorissa Chervinikova of the American Red Cross, and

investigators at the Bioqual Corporation.

So, all these studies for abnormal prion protein have been negative so far. We also have initiated infectivity assays in transgenic mice for BSE, and conventional mice -- for conventional mice as well as transgenic mice which are susceptible to BSE infection.

With BSE we have done a limited number of experiments using squirrel monkeys, because nobody has ever compared the sensitivity of various strains of mouse to monkeys, which are known, from work in the old literature, a very useful assay for all the spongiform encephalopathies.

This work is generously supported by the NIH, by NIAID, and we expect that support to continue for the next couple of years.

Let me close by discussing a proposed study that we think, from a regulatory point of view, is very important, and that is setting up a collection of blood derived biological reference materials.

There ar a number of sources beginning with rodents, which should be easily done, through larger animals -- sheep, monkeys.

We have a chimpanzee blood that is supposed to be infected with an agent derived from a patient with Gaersman-Stroisler-Shinker(?) syndrome, which is

essentially a variant of familiar Creutzfelt Jakob disease. We have no access at the moment to human materials.

We think that those are very important for the following reason. We had, at the last TSE advisory committee, an evaluation of two devices in development that may have the ability to remove TSE infectivity from blood and other biologic materials that are contaminated.

At the World Health Organization in September, six potential developers of tests that are showing some promise for identifying animals and even people infected with TSEs, reviewed their progress, and we are hoping that some of those tests will, within the near future, be well enough developed to consider review looking toward implementation.

We are at the moment not able to assist the sponsors in developing those tests, nor do we have the ability to evaluate their performance independently, and we think that would be a very useful activity for the agency to be able to do and to help manufacturers to do.

We three times presented this proposal to various U.S. government agencies. It has been greeted with considerable enthusiasm, but not yet with any funding, and we did want you to know that we have this in mind and we are not giving up.

At that point, I will close and either take

questions now or after the whole session is completed. Thank you.

DR. ALLEN: Thank you very much. That is certainly an exciting area and one that there is a lot of interest in. Our next presentation following up on that will be by Dr. Pedro Piccardo.

Agenda Item: Pedro Piccardo.

DR. PICCARDO: The rationale for the work that I am going to present is two-fold. Human TSE is also known as prion disease, and may be underreported, due to their similarity to more common diseases, such as Alzheimer's disease or Parkinson's disease or many other very common disorders.

o, the aim, number one, of our work is to characterize atypical forms of TSEs or prion diseases. Once again, why? Because we need to make sure that they are not misdiagnosed as something else.

As Dr. Asher already mentioned, the prion hypothesis, which is the prevailing hypothesis, indicates that the PRP is the infectious agent. So, in short, a protein that is infectious.

So, this led to the following question. If the PRP molecule not associated with infectivity can accumulate during the disease, it is important to define them, since PRP accumulation is commonly assumed to indicate the

presence os infectivity in animals and humans.

So, the second aim of my work is to try to answer the following question. Is abnormal PRP always associated with infectivity.

So, coming back to the first part, which is what happened with atypical forms of prion diseases, I had the opportunity to study basically -- this is the summary of a lot of work -- I had the opportunity to study two patients.

One had a typical form of TSE which, in the brain, shows these vacuoles. So, this is spongiform development. Usually when people have these they have dementia, and this was the case here.

When we take a piece of brain and we run it on a western blot, what we see is usually this. This is the prion protein, and when we treat it with proteases, we get these abnormal fragments.

When we don't know for sure, we get this very simple pattern of one band of abnormal PRP, and this is usually used for diagnosis.

The question here is what happened with this. As you can see, this patient has a pathology that is strikingly different from the typical form.

There are no vacuoles here. This patient had a very long duration. So, it was very problematic for the clinical to make the diagnosis.

My hypothesis was, well, if this is so different, there must be a molecular marker that will indicate when we run, for example, western blots, that we are in the presence of an abnormal prion disease of TSE.

What happened is this. As you can see, the pattern of western blot in the atypical case is very different from the pattern of western blot in the case of typical TSE or prion disease.

I want to draw your attention to this low molecular weight band. When we have treated with proteases and when we remove sugars, we still have a very complex pattern and the presence of this prominent, low molecular weight band.

So, the question was the following: with these low molecular weight peptides, if there is infectivity associated with the presence of these low molecular weight peptides, meaning in patients that are very atypical.

So, once again, having the opportunity to study these two patients, this is typical with the tropic dementia and with this abnormal pattern of prion protein on western blot with a low molecular weight, and this atypical case with no spongiform degeneration and, as you can see, a low molecular weight band protein has cleared the system of AKD.

So, once again, to try to answer the question of

was infectivity associated, this case was used as a control, meaning taking a piece of frozen tissue from this patient which shows this abnormal prion protein of 21 KD, and this was inoculated into transgenic mice, transgenic mice that are highly sensitive to these disorders.

In a very short period of time -- short for these diseases, meaning 290 days -- what happened is that these animals reproduced the disorders in the patient.

This is the brain of the mouse. This is the brain of the patient. There was spongiform degeneration. There was accumulation of abnormal PRP.

So, in short, there was a very efficient transmission of disease. Now, the question that I asked, my question was the following, what happens here.

So, when brain homogenate was taken from this patient that has this low molecular weight band of abnormal PFP, and this was inoculated into transgenic mice, the results were strikingly different.

I mean, this is a mouse after 600 days. I never though that a mouse could live so long. They live very long, up to 800 days. So, we have to wait to have the final results, this amount of time.

These mice did not develop spongiform encephalopathy. it was not possible to detect prion protein using the conventional methods. So, there was a very

inefficient transmission of disease.

Now, what was very striking was that, in selected parts of the brain of this mouse, meaning the area where we inoculated the tissue from the patient, there was accumulation of abnormal PRP in the form of plaques. So, we were able to detect abnormal PRP but associated infectivity in this highly experimental model.

So, we concluded there is inefficient transmission of disease, and that we were able to detect abnormal PRP in the apparent absence of infectivity.

So, the next question that I am trying to tackle is, if amino formation could be a protective mechanism in these cases.

The collaboration is a collaboration with Washington University in St. Louis, Indiana University and, more important, with the institute for animal health, neuropathogenesis unit in Edinbrough, Scotland, which has this highly sensitive transgenic model. Thank you.

DR. ALLEN: Thank you very much, Dr. Piccardo. Questions?

DR. DI BISCEGLIE: The detection of the protein in tissue and in western blot, I am not sure what the antibody is directed to.

This is a normal protein that is abnormally folded; am I understanding right? So, is the antibody

detecting the conformational change, it detects abnormal protein. The epitope is not present in the normal protein.

DR. PICCARDO: There are many antibodies that have been made against this protein. In most cases the protein will not detect antibodies. So, we will not be able to differentiate the normal against the abnormal protein.

However, we know that is the abnormal protein because usually we treat it with protein SK before running the western blot.

So, if it is protein SK resistant, then we are selecting for the abnormal protein and then we use the antibody.

However, there are a few instances -- only two after so many years of research -- in which the researchers claim that they were able to make an antibody against a confirmational epitope that is an abnormal epitope. That has very, very recently been used for amino precipitation of the abnormal component.

DR. ALLEN: Other questions? Thank you very much. Dr. Nakhasi will discuss his -- he wears different hats at different levels. This will be your section level research program.

Agenda Item: Hira Nakhasi.

DR. NAKHASI: As Jesse and Kathy said, we wear several hats. I am the real proof of wearing several hats.

So, my job here is to give you a little bit of an overview of the parasitology program, which Dr. Asher told you that this laboratory of bacterial, parasitic and unconventional agents is doing.

My job is to give you an overview of a little bit of the parasitology program, and then there will be individual investigators who will be talking about this program.

My personal program, my laboratory program, is divided into three presentations. That is my presentation, Dr. Duncan's presentation, and Dr. Selvapandiyan's presentation.

I will be talking about -- then there will be a presentation by Dr. Debrabant and also DR. Sanjai Kumar who is going to be talking about the malaria program.

My laboratory program will be divided into two programs. One, I will be talking about the vaccine, our efforts of vaccine that you heard, development of a live, attenuated vaccine, potential candidate. Following, my talk, and Dr. Duncan, will be talking about how we can use that as a biosafety -- issues about the safety of these vaccine candidate, and Dr. Selvapandiyan will be talking about how efforts on developing diagnostics for detection for the leishmania pathogen in blood screening.

So, without further ado, before I dive into my

program, I just want to give you a snapshot of the impact o the visceral leishmaniasis, which is the topic of discussion today.

As you see, this disease is throughout the world in the tropical and subtropical areas. There are 350 million cases at risk world wide, one or two million cases each year.

An estimated 50 million die of this disease, and there are drug treatments which are very unsatisfactory, painful and, over a period of time, develop resistance to that.

Then also after treatment what is happening is that you get this post kala-szar dermal leishmaniasis, and this disease is emerging in the HIV patients who have the hidden disease.

Again, the important point is its transmission through transfusion and there also has been shown to be congenital transmission through mother to child transmission.

Now, why are we interested in it? Its relevance to U.S. public health is, again, as I said, millions of American travelers and thousands of U.S. troops are deployed in the malaria endemic -- malaria, chagas and leishmania endemic -- areas.

The increasing rate of immigration raises the

concern about the potential for transmission through blood. There are known cases of visceral leishmania transmission through transfusion.

A significant number of potential donors are deferred based on exposure, and there are no donor screening assays available for this disease, as there are no vaccines available.

So, my goal here is to give you our efforts as to what we have been doing in the vaccine arena. Again, another important thing I just want to emphasize here is, as Kathy mentioned to you earlier, sitting in a place like FDA, we see the successes and failures in what is happening out there.

To know that knowledge, we are trying to develop proofs of concepts. They are not developing vaccines, but trying to develop proofs of concept which could then be utilized in a real world situation.

So, before I go to that, I just want to give you, for those non-leishmaniacs, the life cycle of the leishmania parasite.

It is a digenic. That means that the parasite lives in two stages of life. One is insect stage and one is in a vertebrate host.

The vertebrate host is the one where it is infectious and the invertebrate, which is the sand fly,

takes a -- it is the female sand fly which causes disease -- is the one that takes a blood meal from the vertebrate host, injects these pro mastigote(?) forms of the parasite into the vertebrate host.

They are taken up by the macrophages. Inside the macrophages, they develop, multiply and then cause the disease.

To make a long story short, as I said, we see the successes and failures of the vaccine development. As I said in the beginning, there are no vaccines available at this time.

Various attempts have been made to develop the vaccines. I don't want to go into detail. To make a long story short, of all these studies over many, many years, the conclusion is that parasite persistence may be required to maintain the immunological memory to prevent infections, and how can that be achieved.

Now the idea circulating among the scientists is that could it be achieved by the live attenuated parasite immunization that could process indefinitely without inducing the disease. This was recently published by my group in a review article.

The aim of my study is the three major things. One is to develop attenuated lines, which can be genetically manipulated, then look for the immunogenicity

of those leishmania attenuated lines, and then identify biomarkers for the safety of these vaccines.

So, how did we achieve that? We achieved that by removing a gene which I don't want to go into detail because we have provided you lots of information background on what we have done to achieve this genetically modified parasite.

For example, here we have removed one of the essential genes for parasite growth called centron gene, by knocking out both alleles of this parasite and have shown, by a series of experiments that the parasite which has lost the gene cannot grow as an infectious form of the parasite, which is the a. mastigote form.

The defect is that it cannot divide, and also the defect is basically a molecular defect because the basal body, which is important for the duplication is not -- there is a defect in that, and by showing in vitro that these parasites, the wild type can multiply in the macrophage and the knockout cannot multiply.

It is shown here, that if you look at a certain period of time after infection, the wild type survives very well and the parasite which has a deleted gene does not survive.

Therefore, what is shown in this study gave us an idea that these null mutants will be important for vaccine

candidates.

The second goal of our study is to really see the immunogenicity. When we took these null mutants and put them into the animals, we showed that it elicits an immune response, which is more production of interferon gamma, less of IL4, which is a protector type of response.

Lastly, the biomarker response is how we wanted to identify the biomarkers in these attenuated parasites. What we did was, we took these parasites, analyzed them on a micro array, which has the parasite genes, which you will hear a little bit more from Dr. Duncan's presentation.

Using that micro array, we put the -- we take the RNA from wild type and the attenuated parasite and asked the question, can we see the differences.

This is an example of one of the genes.What we found is, this gene called caltane, like cysteine peptase, is absent in the knockout, but it is present in this wild type parasite.

When you add back that gene to the knockout parasite, this expression comes back again. So, we can monitor, when we take these parasites and inject them into animals, we can monitor the stability of this parasite by looking at the expression of the gene. Therefore, it becomes a viable biomarker.

So, in conclusion, we have shown that we have

developed cell lines which can be attenuated. We have shown there is an immunogenicity. We have also shown that we can identify biomarkers and, therefore, what we need to do is, over a period of time, show in the larger study how, when we inject into animals, can that response be -- can that immune response be protective.

I would like to acknowledge, at this point, various colleagues of mine, such as Dr. Selvapandiyan and Robert Duncan and other colleagues, Dr. Debrabant, Dr. Streenivas and Nancy Lee, and the collaborations from different groups all over the world.

Here, our collaboration with India, various centers in the ICMR, which is the Indian Council of Medical Research in India, Center for Drug Research Institute in India, National Center for Cell Sciences, Pune, India, our collaboration with the University of California San Francisco, and Mayo Clinic, Rochester, Minnesota. Thank you very much for your attention.

DR. ALLEN: Thank you, Dr. Nakhasi. Questions? I guess we don't have any leishmaniacs in the group. Okay, Dr. Duncan?

Agenda Item: Robert Duncan.

DR. DUNCAN: While he is getting my slides up there, I just want to put everybody's mind at east. My broken bones have nothing to do with the stringency of the

site visit. It was a completely unrelated incident.

I want to talk about two projects that I am supervising in my laboratory. The first Dr. Nakhasi has mentioned a little bit, the biomarkers on the live attenuated parasite. The second is the application of micro array technology to detecting pathogens in blood.

So, the kind of central point of this search for biomarkers in the attenuated parasite is to harvest the benefits of the gnomic era.

For the genomic era, for the leishmania parasite, that means that the complete genome has been sequenced, open reading frames, meaning the protein coding sequence in the genome have been identified, about 8,000.

What is really instructive or sort of demonstrative is that only 307 of those 8,000 have been experimentally characterized.

So, there is a vast array of genetic information that needs to be mined to better understand this parasite, understand its pathology and various methods.

So, the method that I have developed is a genomic micro array which I am using to harvest new gene information.

My goals are to find, in a broad sense, genetic mechanisms of leishmania pathogenesis, but more specifically to look to do genetic characterization of live

attenuated vaccine candidates that we are developing in our laboratory.

Along the way, there is also the possibility of harvesting that genomic information to make better diagnostics, and also that they will identify biomarkers of vaccine safety.

I want to present a little bit of the rationale of using this technology to focus on the centron deleted cell line, which is our current best candidate as a live attenuated vaccine.

First of all, Dr. Nakhasi has pretty much given the background of the importance of a vaccine, but I wanted to emphasize that, in the approach of a live attenuated pathogen vaccine is genetic stability.

If that organism, whether it be virus, bacteria or parasite, can mutate, can change in the process back to a virulent organism, that is exactly what we want to avoid. That would be a lack of safety.

So, we want to be able to genetically monitor to avoid any possibility of reversion. In this case, I am looking at global gene expression as a monitor of that genetic stability.

I am just going to show you two examples that, through the micro array analysis, we have looked at thousands of genes and honed down to two that have very

good promise as biomarkers.

What you are seeing here is northern blots done with a gene that was identified on the micro array. This is a gene that has a lot of homology with a known enzyme in other mammalian species, and the pattern of expression is fairly clear on the northern blot, where it is not expressed in the knockout parasite, but it is expressed in these other normal parasites.

This is just a graphic that shows the pathway that this enzyme sits on, and it has been identified as an important drug target by other researchers. That just sort of highlights the point that placement on a critical metabolic pathway and the reproducible pattern of expression make this enzyme a potential biomarker of attenuation, where it should be continually at a low level if the parasite is non-virulent.

Another one that I have identified has a very striking pattern of expression. As you can see, it is very low in the knockout parasite, abundantly expressed in other wild type forms.

What you are seeing there is the probe that came from the micro array. I went back, made a more careful analysis, cloned out the open reading frame, the protein coding sequence, and showed that it has the exact same expression pattern. So, this is, in fact, the gene that we

are looking at.

Unfortunately, that gene has no homology with any known proteins. So, we have very little guide as to what the function might be.

What is most instructive, it is highly conserved among the three pathogenic protozoan parasites that are closely related and not found in any other species.

So, that makes it, as I summarize here, the restriction to the trypanosomatid family, as well as the high level of conservation, suggests a critical function that may be unique to flagellated parasites. Furthermore, the reproducible pattern of expression suggests a potential biomarker of attenuation.

So, I just summarize. I have identified differentially expressed genes and validated their expression on other means besides the micro array, taken selected genes with potential as biomarkers of attenuation for further characterization.

Characterization of these genes reveals physiological correlates of central deletion, and characterization of these newly described gene functions may lead to better understanding of leishmania pathogenesis. We are looking for broader interpretations with this research.

Then I would like to move to the second project,

and here I would like to directly meet the challenge of blood safety, harvesting the benefits of these new technologies.

As has been shown already, the transfusion blood safety has been dramatically improved with pathogen testing, but with an increasing number of potential infectious agents and emerging threats, the burden of testing is becoming quite extensive, with so many different tests or every unit of blood.

So, there is an urgent need for methods that will streamline this kind of testing and consolidate it, either through nucleic acid tests, real time PCR, micro arrays, or nanotechnology, i we can harvest this technology to develop multiplex testing so that multiple pathogens can be tested in a single one.

I am looking at a proof of concept with the micro array as a means of that kind of multiplex testing. I am just very briefly showing you what we have been able to do.

This is a lay out of the micro array that we have developed and have been testing. At this stage, the multiplex is very easy.

It is easy to print a micro array with a lot of different pathogens on it. The choke point in this process is the limit of detection PCR basis of the assay.

We have been able to put together as many as four

different targets in the same assay, and I show you some results here, of application of this micro array, where we used one assay, the same one assay, and were able to detect three different pathogens as well as an internal human control at a very sensitive level, 50 cells per ml, and that is a good start.

We are working together the future now of focusing more. This work was originally funded by counter-bioterrorism funding. We are working now with some additional funding to push toward multiplexing more of the common blood borne pathogens. With that, I will close, if there are any questions.

DR. ALLEN: Thank you, fascinating work. I assume one of the problems with the micro array in combining viral and parasitic agents is that the sensitivity for the parasitic assays is probably orders of magnitude different than for the viral agents. Is that a safe assumption?

DR. DUNCAN: Well, the sensitivity is a combination of sample preparation as well as the PCR aspects. On the level of the ability to amplify the target by PCR, the parasitological assays can actually be made much more sensitive, because there are a number of genetic targets within the parasite that have many, many, many copies. So, that is to our advantage.

What is to our disadvantage is the infectious

dose of a parasite can be very, very low in a unit of blood. So, we have some ongoing work that is focusing in that area -- I haven't talked about any here -- to improve the sample preparation technology that can, in some way, concentrate the pathogens that may be present in a very low number, and that is another reason to do it.

DR. ALLEN: Other questions for Dr. Duncan? Okay, thank you very much. Our next presentation is by Dr. Selvapandiyan.

Agenda Item: Angamuthu Selvapandiyan.

DR. SELVAPANDIYAN: I would like to jump on to the second aspect of my research, which is detection of some of the blood borne pathogens from blood using a fluorescence based PCR technique.

I would not like to go into detail of the background, but there is an urgent need for methods to streamline and consolidate testing.

So, my interest in that regard is design a method that can detect rapidly for many pathogens simultaneously using multiplex fluorescence based PCR, using a portable instrument, a SmartCycler.

So, these are some of the blood borne pathogens that we showed an interest in screening in the blood. Two of them are bacteria and two are parasitic organisms.

Bacillus anthraces, as you know, causes anthrax

disease. Yersinia pestis causes plague. Leishmania and trypanosoma cause leishmania and trypanosomiasis diseases respectively.

In the assay segregation we used some of the vaccine candidate lines. For example, for bacillus anthraces, the vaccine strain was used, and yersinia pseudotuberculosis was used to address yersinia species. Leishmania donovani was used for the leishmania species.

These are some of the PCR markers that we have addressed. All of these are seen as multiple copies in the genome.

In order to have an internal control, human 18S rRNA gene was also included. So, in the multiplex reactions we have four sets of oligos.

The fluorescent molecule used in the PCR is SYBR green. SYBR green fluorescence is very utile when it is in the free form during the denaturization state. Then, during the extension step, in every PCR cycle, when the molecule goes into the double standard structure, then that increases the level of the fluorescence.

The reason for the assay is to have the molecular analysis. The sample, after the final PCR cycle is heated from 60 to 95 degrees celsius, at which point the systems are made to peak, depending on the DM value or the melting temperature of the amplified product. That is by way of

release of SYBR green.

In a sense, depending on the number of amplified products, you will have those many numbers of peaks, provided all the amplicons have their own DM values.

This is a typical multiplex assay, with all the four genomic DNA, and then as you can see, the readout shows four separated peaks.

Each of them has its own melting temperature, like 82 for bacillus, 86 for leishmania, 87 for yersinia and 89 for human.

What you see here is the temperature of the amplified products, and this shows a clean amplification of all the four amplicons, and not showing any non-specifically amplified primers or primer dimers.

This way of checking on the gel are not intended to be used in the actual screening procedures. We just will go with a melt peak readout.

So, this outlines the development of a multiplex PCR for the simultaneous detection of the bacterial as well as parasitic pathogens.

So, once we have achieved that, we would like to know what is the minimal detection level for each of these pathogens.

For example, for bacillus anthraces, where a known number of cells has been spiked, as you see here, in

each internal molecular blood, and the DNA was extracted and then an assay was performed.

A bead corresponding to bacillus was seen in all the cases by the cells that had been spiked. Interestingly, what you observe here is the gradual reduction in the height of the peak of the bacillus, depending on the number of cells we spiked. So, the more number of bacillus cells you have the larger in the peak height and the lesser number of pathogen cells, the shorter the height of the peak.

So, we have used this varying peak height as a novel way to quantify the pathogen cells. So, what you see to the right is the human control, which is a uniform height.

The peak height seems as a novel measure to quantitate pathogens in blood. In addition, what we also see is that we could detect as low as 10 cells per 200 microliters of blood. That means 50 cells per ml.

The varying peak height was used as a standard curve for bacillus, as you can see here, and a similar experiment was also conducted for the other two organisms, leishmania as well as yersinia.

So, for all the pathogens, we could detect as low as 50 cells per ml of blood. So, once we had a standardized multiplex assay, we wanted to validate this assay by using

some of the clinical samples.

So, 11 samples coming from patients infected with leishmaniasis, all of them show positively for the parasite, and the approximate cell number is given here.

Three samples coming from post-treated leishmaniasis patients, none of them show the presence of the parasite.

In addition, we also got in vivo samples from mice infected with bacillus anthraces vaccine strain. Blood samples were obtained after 24, 36, 48 hour time period after infection.

They show positive for the bacterium, with an increasing rate after infection, like 25, 66, 100 percent of the samples show positive for the bacteria, and the approximate cell number is mentioned here.

So, the assay correctly detected pathogens in the samples from leishmaniasis patients, as well as mice infected with bacillus anthraces.

In summary, this study outlines the development and evaluation of a single tube, multiplex real-time PCR for the simultaneous detection of bacterial as well as parasitic pathogens.

For all the three pathogens,we could detect as low as 50 cells per ml. Leishmania primers recognized the DNA sequences from other species as well. Similarly,

yersinia primers could identify sequences from yersinia enterocolitica.

The assay accurately detected pathogens in the blood samples from leishmaniasis patients, as well as mice infected with anthrax.

This assay takes less than one-and-a-half hours, and hence could be useful for rapid identification purposes. Thanks.

DR. ALLEN: Thank you. Questions for Dr. Selvapandiyan?

DR. KUEHNERT: Thank you. This is very interesting. I wonder if you thought about trying to apply this not only for blood and blood donors, but also for tissue? I think this could really have some application, particularly considering it is real time.

DR. SELVAPANDIYAN: Absolutely. This is just a proof of concept and the slide here, as you see, is the blood, and it can be applied to any tissue material, certainly.

DR. KUEHNERT: That is good to pursue. I think it would be very important for that field.

DR. ALLEN: Other questions? Okay, thank you again. Our next speaker is Alain Debrabant.

Agenda Item: Alain Debrabant.

DR. DEBRABANT: Good afternoon. So, I am an

investigator, a researcher, reviewer in the laboratory. What I would like to do in the next five minutes or so is give you an overview of my research program that focuses on the role of the programmed cell death pathway, in trypanosomatid parasites.

The primary parasite model that we are using in the lab is leishmania. I will not go back into the description of that model, since it has been described in the previous talks.

I would like to emphasize that during the two -- inside the two hosts, either inside the insect vector or inside the mammalian host, the parasite undergoes a series of differentiation and multiplication inside the host.

This multiplication leads to a heavy parasite burden, in the case of leishmania, delivered in the liver and the spleen, which is directly correlated to the pathogenesis of the disease.

However, the mechanisms involved in the control of this parasite amplification or multiplication inside the host are not very well understood.

My contribution to this question is to try to address -- ask the question, is a program similar to apoptosis being involved in the process. So, is the programmed cell death pathway involved in the replication of the parasite inside the host.

As you are probably familiar with, apoptosis, as described in mammalian cells, is a pathway that a cell utilizes in response to some very specific signals, some death signal.

The pathway leads to the self destruction of those cells. The molecules involved in these pathways, in the case of apoptosis, are known and most of them have been described.

The major players are caspaces or proteases or nucleases. A few years ago, we described a similar process in the leishmania parasites, and other labs since then have described similar processes in other unicellular organisms.

However, what we do not know is the pathway, the molecular component in this pathway. Now that the leishmania genome is known, we have looked for homologs of caspaces, nucleases and other regulatory molecules involved in apoptosis, and we cannot find them in the leishmania genome.

So, the pathway theoretically exists. However, it has to be very different to the one described for apoptosis. So, the major goal of my research is to try to understand what are the molecular components of this pathway. So, to identify the effector molecules of the leishmania programmed cell death pathways.

The outcomes of such research is to try to better

understand the parasite growth and pathogenesis and the more applied outcome is that these targets will be very different.

So, this molecule represents new targets for drug that could be used to trigger the cell death of the parasite inside the host.

So, as I mentioned, we described the pathway in leishmania. The leishmania is able to respond to some death signals, and there are very specific events that are happening at the level of the mitochondria, the plasma membrane.

There is activation of proteases, nucleases, that degrades the DNA in the nucleus, and that leads to the cell death of the parasite.

I just wanted to, in the next couple of minutes, describe our work on proteases and nucleases that we identified as being part of this pathway.

Let me start with the protease. We have identified a protease called metacaspace, in the leishmania genome. These are caspace related enzymes.

I was telling you earlier, caspaces are the major players of apoptosis. We cannot find them in the leishmania genome, but we can find metacaspaces.

So, they were good candidates to try to investigate to ask the question, are these metacaspaces

involved in leishmania PCD.

We cloned these molecules and showed that they have protease activity. However, unlike caspaces, they are unable to cleave caspace substrates. They behave like serine proteases, and are able to cleave tripcine substrates.

We developed an antibody against the metacaspace and showed that they were localized in a very specific compartment called acidocathizone, but I don't have time to go into that.

We have shown that they are likely to be involved in the pathway, since in a parasite, if you trigger the pathway in a parasite, there was a significant increase of metacaspace activity in those parasites undergoing PCD.

I would like to move on to a brief description of a nuclease that we have identified called endonuclease-G. This endonuclease-G exists as a single copy gene in the parasite.

The way we went about investigating was to over-express this protein into the parasites. First of all, the parasites localized as expected in the mitochondria.

I forgot to mention that endonuclease-G has recently been described as part of the programmed cell death pathway in mammalian cells as well, and have been shown to be involved in a caspace independent pathway. It

was localized in mammalian cells in mitochondria. The same thing for the parasites.

In cells over-expressing this molecule, they are very susceptible to undergo programmed cell death, as shown in this top panel, as seen by DNA degradation in that tunnel assay.

If you do the opposite experiment, you reduce the level of expression of endonuclease-G in the parasite. We see the opposite effect.

The technique we used to do this experiment is called RNA interference, where we blocked the transcription of the endonuclease-G gene.

The reason is that the parasites, with reduced expression of antigen, are more resistent to undergo PCD, demonstrating that these nucleases are involved in the leishmania PCD pathway.

So, just to sum up again, the goal was to identify the effector molecules of the leishmania PCD pathway. I give you two results that we have got so far, that I have shown you some information about metacaspace and endonuclease-G, that are probably two effector molecules of that pathway.

We are now investigating the role of these two molecules and overall the role of programmed cell death pathway in leishmania pathogenesis using an animal model,

using mice as an animal model for leishmaniasis.

Again, the outcomes of such research is to better understand the parasite's growth and parasite pathogenesis, and the effector molecules that we characterized are potential new targets for drugs that could be used to trigger programmed cell death or self destruction of the parasite into an infected host.

With that, I would like to thank my members in the lab and my collaborators at the University of Illinois and the NIH in the LPD, and I thank you for your attention.

DR. ALLEN: Thank you very much. Questions? All right, our final presentation in this section will be by Dr. Sanjai Kumar.

Agenda Item: Sanjai Kumar.

DR. KUMAR: Good afternoon. In the next few minutes I am going to summarize the malaria program. So, our mandate is two-fold, blood safety from transfusion transmitted malaria. You have heard some of this through the malaria workshop this morning. In that direction, we have developed DNA antibody tests for blood donor screening.

Then we provide expertise for the review of malaria vaccine INDs. It is not a theoretical concept. I am in the office of vaccines, but I am the only malaria expert in terms of active malarial program, and that is not

only in CBER but the entire FDA, actually.

So, I am actually called upon to help them set the standards for the malaria vaccines, since that question was raised.

This is my immediate malaria program, myself, two masters level biologists and then a post-doctoral fellow. So, you heard -- I will be very quick with this, you heard some of this, this morning.

So, there are no laboratory tests to screen for malaria. The donor demographics has changed now. So, we know where the infection is coming from. We do blood safety by donor deferral policies. In the process, we lose about 150,000 donors.

So, what can we do about it? The best that we have is screening tests. So, this is data from my own lab. So, DNA tests -- actually, since this slide was made a few months ago, we are doing better than this now in DNA testing.

It is still, as you heard again and again, it still leaves enough parasites there that could be potentially dangerous and also, as I said this morning, we don't know what the sensitivity should be.

I would like to remind you of one thing. The sensitivity limit we have agreed is the best in the malaria field. So, we are on par with the field and maybe doing

better in some senses.

For the antibody test, we have a fairly specific ELISA that recognizes all four species of malaria parasites. Where this will go and end up, I just don't know yet, but at least we are keeping up with the field.

Coming with the program with malaria vaccines, malaria vaccines are a very complex business. As you know, it involves work with the pathogenesis, with immunology.

So, talking about the recombinant malaria vaccines, the first malaria vaccine was produced and clinically tested in 1987 by SmithKline, the R32 peptide.

The R32 amino acids that were represented the four amino acid specific types of malaria surface protein. The other 32 amino acids were from tetracycline genes from e. coli that were out of frame. How that happened, I don't know.

That vaccine, I was told at that time, was when they were starting the first recombinant protein tested in any model.

The paper was published in 1987, Protective Efficacy and Safety of Malaria Vaccine, although there was zero efficacy there.

Twenty years later, the best recombinant vaccine we have is RDSS. It was only in production for a short time. That is the data, in naive users and in the field

there.

So, people in the malaria community already started to look for the alternatives there. So, recombinant protein helps synthetic vaccine.

The parasite itself showed the way. People have known a long time that naturally limiting reducing response to repeated infections in the field.

So, what people are trying to do now is to go back to the original vaccines, plus producing genetic attenuation, the sort of approach that you heard in leishmania.

By reading the literature and by knowing the field personally, that is the way the field is heading. Why we got involved in this business? By simply standing on the sidelines, we would not be able to have enough expertise to deal with these vaccine INDs.

It is going to be way too complex. The vaccines are complex by itself, but now the complexity that is present in terms of profiles, we have to get involved in the field.

So, we have programs to identify molecules associated with parasite growth and survival. Then we are using those identified molecules and targeted deletion to produce live vaccines.

A lot has come out of this program. I will not

present that. I will just give you some snapshot. Then also, the only awy we can use the virulence profiles and long-term safety of these vaccines is by identifying the markers that are associated with the virulence and efficacy.

So, here is the approach here, the sort of thing that you heard in leishmania. So, this is for falciparum. This is in the mouse model. So, we do genetic deletions.

They have large genomes. So, it is a little easier, but the efficacy is lower here. Then we do genetic profiling here.

So, we are somewhere in this stage now and the progress is quite good and hopefully in the next few months something will begin to show up.

It has been my long interest to identify the markers of virulence. This work was started about five years ago when I was not even at FDA.

So, this is a mouse model that gives us the way to do this, in both a lethal and non-lethal way. So, we did very extensive micro array profiling here and at least two sets of genes came out.

So, one thing people note in the field, physicians in the field for a long time, is the metabolic acidosis resulting from the accumulation of lactate is an important prognosis indicator of severity of malaria.

So, especially with falciparum malaria, they have metabolic acidosis, and thus the accumulation of lactate. How that happens? That happens in the up-regulation of the enzymes involved in the metabolic pathway.

Really, one thing that came out of all this work was, in the non-lethal model there were self-resolved infection, there was transient increase very early on in the metabolic pathway. The glycolytic pathway, all the enzymes are downregulated. That is not in the case of malaria. They are upregulated. This is known in the field for a long time. So, that was very pleasing.

So, I will just quickly summarize here. In summary, I will tell you how we are doing, which direction we are going. A lot of this work is published now.

To summarize here, in a nested PCR, we can detect two parasites in an ml of blood and we have an ELISA that detects all four species of the parasite.

What we are doing, we are trying to define the markers both on the parasite and in the host. We have identified falciparum associated biological pathway induced by response to febrile assay.

This is work that has gone very well. Also, we are doing work in identifying virulent and non-virulent, and also we are doing work on non-recombinant vaccines so that we can predict the host marker for infectivity.

This is going to be our future direction here. Some work is published here, some is in the process, and some are still data. I will just stop here and take questions, if any.

DR. ALLEN: Thank you. questions? It is fascinating to learn about updates on malaria. My great-grandfather, more than 100 years ago, almost died from black water fever.

DR. KUMAR: The black water fever is pretty well eliminated now because that responded to the use of quinine, and quinine used to cause very active hemolysis of infected rat cells. Quinine is very rarely used in crude form now.

DR. KULKARNI: I was just wondering if you can detect this -- I know it is for transfusion transmitted, but how about in other body fluids, like cerebral spinal fluid and things like that?

DR. KUMAR: Parasites are usually shown to stay in the circulation and then go unwind in the deeper endothelial vasculature, for example, the brain and the liver.

I guess it is possible, but I would say this. By the time you need to detect parasites in the cerebral spinal fluid, it is too late for the patient anyway. He will not need diagnosis by then.

DR. ALLEN: Thank you very much, Dr. Kumar. Any other questions from any of our speakers from this afternoon? Okay.

Agenda Item: Open Public Session.

DR. ALLEN: We will move to our next phase, which is an open public hearing. We do not have any listed speakers. Are there any speakers who wish to make a statement during the open public hearing? The open public hearing is closed.

We now will ask the FDA staff to please clear the room and any other people to please clear the room for our closed session.

[Whereupon, at 4:02 p.m., the open session was adjourned.]