ADVISORY COMMITTEE ON

BLOOD SAFETY AND AVAILABILITY

Crystal Gateway Marriott

Salon 1 & 2

1700 Jefferson Davis Highway

Arlington, VA

Wednesday, August 30, 2006

The meeting, was held pursuant to notice, on Wednesday, August 30, 2006 at 9:00 a.m., Arthur W.. Bracey, M.D., Chair, presiding.

MEMBERS:

JUDY ANGELBECK, Ph.D.

JULIE BIRKOFER

M. GREGG BLOCHE, M.D., J.D.

WILLIAM DUFFELL, JR., Ph.D.

KAREN SHOOS LIPTON, J.D.

DAVID E. MATYAS, J.D.

JACK McGUIRE

GARGI PAHUJA, M.P.H., J.D.

GLENN PIERCE, M.D., Ph.D.

GLENN RAMSEY, M.D.

SUSAN D. ROSEFF, M.D.

S. GERALD SANDLER, M.D.

MERLYN H. SAYERS., M.B., B.Ch., Ph.D.

LINDA THOMAS

PEARL TOY, M.D.

JOHN W. WALSH

WING YEN WONG, M.D.

NON-VOTING EX OFFICIO MEMBERS:

MATTHEW J. KUEHNERT, M.D.

JAY S. EPSTEIN, M.D.

NON-VOTING EX OFFICIO MEMBERS: (CONTINUED)

HARVEY KLEIN, M.D.

CDR MICHAEL LIBBY

JAMES S. BOWMAN, III, M.D.

P R O C E E D I N G S

(9:00 a.m.)

DR. HOLMBERG: Good morning. In the interest of time, we will get going with the meeting here. I'd call the 30th Meeting of the Advisory Committee for Blood Safety and Availability to order.

I do hope we have a quorum today. I know that when I came down the GW Parkway, there was an accident, which is typical of the Washington, D.C. area, but I was assured that we did have a quorum today and tomorrow.

We do have people that will be leaving tomorrow during the day and going to the International Society for Blood Transfusion in Capetown, South Africa.

Let me go through the roster today, then I have several announcements that I would like to make to the Committee.

Dr. Bracey?

DR. BRACEY: Present.

DR. HOLMBERG: Dr. Angelbeck.

DR. ANGELBECK: Present.

DR. HOLMBERG: Ms. Birkhofer is caught in the traffic. She's one of those people.

Dr. Bloche?

(No response.)

DR. HOLMBERG: Dr. Duffell?

DR. DUFFELL: Present.

DR. HOLMBERG: Ms. Lipton?

(No response.)

DR. HOLMBERG: Mr. Matayas?

(No response.)

DR. HOLMBERG: Mr. McGuire?

(No response.)

DR. HOLMBERG: Ms. Pahuja?

(No response.)

DR. HOLMBERG: Dr. Pierce?

(No response.)

DR. HOLMBERG: Dr. Ramsey?

DR. RAMSEY: Present.

DR. HOLMBERG: Dr. Roseff?

(No response.)

DR. HOLMBERG: Dr. Sandler?

DR. SANDLER: Present.

DR. HOLMBERG: Dr. Sayers?

(No response.)

DR. HOLMBERG: Ms. Thomas?

MS. THOMAS: Present.

DR. HOLMBERG: Dr. Toy is absent.

Mr. Walsh?

MR. WALSH: Present.

DR. HOLMBERG: Mr. Matayas, you're right here.

Government officials, your presence is greatly appreciated.

Dr. Wong is not with us today. This is her last meeting. She regretted that she could not be here.

DR. HOLMBERG: Dr. Kuehnert?

(No response.)

DR. HOLMBERG: Dr. Epstein?

DR. EPSTEIN: Here.

DR. HOLMBERG: Dr. Klein is not with us today.

Commander Libby?

COMMANDER LIBBY: Here.

DR. HOLMBERG: And Dr. Bowman?

DR. BOWMAN: Here.

DR. HOLMBERG: Oh, very good, Ms. Lipton is here. I do want to make several announcements:

First of all, as far as the conflict of interest, if there are any conflicts of interest perceived by the speakers or any other members, please identify that as we go forward.

As the speakers come to the podium, if there's anything to disclose, please do so, and if there are people speaking from the floor, I would appreciate your identifying yourself, so the recorder can get your name, and also your affiliation, and if there is a conflict of interest.

There are several announcements I would like to make concerning upcoming meetings. I would like to inform the Committee that the TSAC meeting will be September 18th and 19th, and the Federal Register Notice has already been posted on that, and it will give you details on that information there. I believe it at the Quality Inn in Gaithersburg.

There will also be a workshop on September

25th and 26th, a workshop on new technologies, that is put on, I believe, by FDA, and also sponsored by Health and Human Services.

Also, I'll let those in the audience know about our upcoming meeting on September 25th and 26th, also. It will be a meeting put on by the Department of Health and Human Services in regards to BioShield.

This is a Congressionally-mandated meeting to inform the stakeholders in Bioshield. You can go to the website and pull that information, also.

Then I would also like to tell you that there will be a meeting that will be published very shortly, and, to give you a heads-up on it, the official Notice will be in the Federal Register. This will be on the 28th of September at the Sheraton Crystal City, the next hotel down.

It will be in regards to ID issues and a request from the Assistant Secretary for Planning and Evaluation, and will take input from the plasma community and the users of bio-ID.

So you can see that there are quite a few

meetings coming up in the month of September. I would also like to tell the Committee members that there will be some adjustments in the way the computer handles the travel claims. If you would like to get paid before November, I would strongly recommend that you get your travel claims in as soon as possible.

We will be converting over to a computerized system. As many of you have experienced with travel, computers are great, but sometimes it takes us a little bit longer to learn computer systems.

We will be converting over to an electronic system, and, they're telling me now that there will be a three-week delay, but I'm thinking that it will be the first of November before any payments can be made, so please get your claims in before the 22nd of September.

With that, I'd like to turn the meeting over to Dr. Bracey.

DR. BRACEY: Thank you. I'd like to welcome everyone to the 30th Meeting of the Advisory

Committee on Blood Safety and Availability.

At this time, I'd like to acknowledge the valuable input by all members of the Board, into the work of this Committee. Some members will be rotating off. They will be specifically recognized for their contributions, but I will do that tomorrow.

While the Committee's efforts have been ongoing for slightly more than ten years, there continues to be work that needs to be done in terms of addressing new threats and old threats, in terms of making the blood supply as safe as possible and eliminating barriers to access to these valuable resources.

At our last meeting, there was a significant departure from what we've done before. We had a significant amount of time, wherein we were able to survey the current status of our blood system and to provide input to the Department for drafting a strategic plan.

The idea was to synchronize this with the Secretary's 5,000- and 500-day plan. The Committee's input has been presented and working groups are being

formed within the Department, and a draft of the strategic plan will be brought back to us for presentation at our next meeting in January.

During the course of the meeting, I was struck by one comment from the public regarding exclusion of public advocates from the Committee's efforts. I would note that this Committee is composed in a manner that fosters the input from a variety of participants, and, during my tenure, I've made sure that we will hear the public voice, the public voice will resonate.

Your needs and perspectives will not be overlooked in these deliberations, and I have no doubt that the collective Committee has the goal of achieving an infrastructure to provide the safest blood products available to all in need.

I think that the agenda we're looking at for the next two days, will bear witness to this. I anticipate a meeting that's rich in important ideas pertaining to the Secretary's intention.

With that, I think we'll go ahead and proceed. The first two subjects that will be

presented, are followups on meetings and task forces that have been formed.

The first will be a update on the FDA Workshop on Malaria and Geographic Deferrals, presented by Dr. Sanjai Kumar. Dr. Kumar has his Ph.D. in Microbiology, and he has been involved in a major way in the study of parasitic diseases, with specific focus on malaria, having spent more than 20 years in this area.

He is a member of the Division of Emerging and Transfusion Transmitted Diseases at the Center for Biologics Evaluation.

DR. HOLMBERG: While the slide presentation is getting prepped, I want to recognize that Dr. Sayers has joined us. Thank you for being here.

(Slide.)

DR. KUMAR: What I'm going to do this morning, is give you an update on the Workshop on Malaria. Then I'm going to talk about the geographic-based policies on malaria.

(Slide.)

DR. KUMAR: Just a brief epidemiology of malaria: It occurs in more than 100 countries, more than 3.2 million people are at risk of contracting malaria, and there are one to two million deaths. The disease is not evenly distributed in these countries, and the impact of the disease is not the same.

For example, more than 90 percent of the deaths from malaria, are in Sub-Saharan Africa. That's an important variable for us.

(Slide.)

DR. KUMAR: So, why do we worry about malaria? You see that in today's interconnected world, no country is immune from the hazards of malaria, and the problem of malaria is rising.

There are more cases today than there were 30 years ago, and there are many factors that can be attributed to the rise. I will not go into that.

(Slide.)

DR. KUMAR: But I'll make case in point here. The case in India, what happened there, there used to be about ten million cases of malaria in the

mid-'50s.

With the implementation of DDT, there's a precipitous drop. And then when the use of DDT was dropped, it came back, up to six million cases. Even though DDT is not there now, these cases have become established.

But the same thing did not happen in Sub-Saharan Africa, so the point I'm trying to make is, in developing countries --

(Slide.)

DR. KUMAR: Malaria in the United States, between a thousand and 1,500 caseS each year, and more than 99 percent of these malaria cases are imported, coming from outside the area.

And, in these cases, those which are undetected, and the people who are the ones responsible, that's what we're talking about here today.

(Slide.)

DR. KUMAR: Who are the people who cause TTM? Travelers with no prior immunity? Residents born in an endemic country, or had malaria and become

carriers of the disease, and the millions of carriers who have been born and lived a long time in endemic countries, and the millions of immigrants who have been prior residents in endemic countries.

Let's talk about TTM. The cases of TTM are at an all-time low here. We get about one case every other year. There is no approved laboratory test in this country that can be used to detect malaria parasites in blood. Blood safety for malaria is maintained through donor deferral based on either residence or travel history.

(Slide.)

DR. KUMAR: In the last 15 years, there were 16 cases reported over 15 years. The mortality, if you look at these carefully, most of them were either born in sub-Saharan Africa or lived there a long time. Some of the cases that slipped through the system -- 71 percent of these cases were due to Plasmodium, and in some of those cases it was the failure of the screening process.

(Slide.)

DR. KUMAR: These are our current

guidelines here. Somebody who has clinical malaria is deferred for three years. Prior residents of an endemic country are deferred for three years. A visit to a malaria-endemic area by residents of non-endemic countries we defer for one year.

That's the CDC web site.

(Slide.)

DR. KUMAR: What are the drawbacks? The cases of transmittal of malaria are at an all-time low. This is minimal, but what are the problems here? Donor loss here; it's estimated that 1.2 percent of our donors are deferred. That comes down to about 120,000. And probably this does not take into account self-deferrals. They go much higher. Deferred donors are difficult to re-recruit. Travel deferrals may impact repeat donors, and also certain age populations are disproportionately impacted.

(Slide.)

DR. KUMAR: So what are the considerations? We have considerations for improving TTM. We need to understand that global transmission and micro-endemicity within a country, so we can

identify within the country -- also we can learn about the prevalence and presence of Plasmodium species in an area. Also the implementation of the blood screening test and also parasite biology and natural immunity, which could impact the donors who may have acquired these infections.

(Slide.)

DR. KUMAR: This is, I'm just trying to make the point again, there are more in Africa than the rest of the world at the turn of the century. This is 100 years ago. The world-wide deaths were estimated to be 19.4 percent of deaths from malaria. Now it has gone down. This is the deaths per 10,000, so per 10,000 it used to be 19. But if you look at the deaths in sub-Saharan Africa -- it's pretty mind-boggling -- the deaths have gone up.

(Slide.)

DR. KUMAR: Coming back to America here, where the majority of the cases of malaria reported here, where those are required -- and again the numbers are in Africa close to 70 percent of the infections are coming from there, about 13 percent in

Asia, some in Central America and some South America. So again the majority is from Africa. I'll keep coming back to this again and again.

(Slide.)

DR. KUMAR: Again, the bias of how the different species of malaria are distributed. In Africa and sub-Saharan Africa, it's predominantly falciparum, not viviax. And malariae and ovale are in smaller percentages here. Falciparum is less predominant here, and the predominant species in Asia is vivax.

We have a test for malaria. Malariae is present in Africa and in South America. Ovale is non-existent in Central America and the Caribbean and in South America.

(Slide.)

DR. KUMAR: Once again, the considerations for laboratory tests.

(Slide.)

DR. KUMAR: One of the methods one could use towards defining a laboratory test: the best direct parasite demonstrations, microscopy -- the

method is quite good but not quite enough. DNA tests I'll talk about. Antigen detection, detecting malaria parasite antigens and their indirect demonstration, salivary markers. One could use IFAT and ELISA.

(Slide.)

DR. KUMAR: This is the meeting announcement, the malaria workshop meeting.

(Slide.)

DR. KUMAR: The main object is to seek public discussion of scientific developments that could support donor testing for malaria infections as part of pre-donation, that will be universal testing or follow-up testing to reduce the deferral period for donors deferred for risk of malaria infections they may have acquired.

So that's basically a geographical distribution. Then, what are the risks and benefits of screening the donors for malaria infections. What the screening tests are -- what are available, the tests that could be used to detect malaria. Emerging technologies and the potential effects of donor testing for malarial infections on the safety and availability of the blood supply. Some places the system is working quite adequately, but we also want to have a discussion of universal malaria antibody testing of all blood donors or testing only in a selected population, a population who could have been exposed to malaria. These questions were spread out in four different sessions.

(Slide.)

Some worked on the background, what was the reason. In several European countries and Australia they test deferred at-risk donors using an ELISA that detects antibodies to Falciparum and Vivax.

In the UK, the individuals who have had malaria or a history of prior residence in endemic

countries are deferred indefinitely; in other words, forever. They cannot donate. Everybody else who is there are deferred for one year. But now, with this ELISA in place, people are tested after six months when they return from a malaria endemic area. In France people are allowed to donate if found negative for malarial antibody four months after their return. In the UK, they test six months.

(Slide.)

This is the actual FDA workshop.

(Slide.)

The first session here, some of the talks, I'm going to share some of them here. The global problem of malaria and its impact on the U.S. blood supply.

(Slide.)

Again, the importance of the African continent and the risk of malaria here. So African accounts for only 6 percent of U.S. travel, but 66 percent of malaria infections are acquired there and the deaths that happened here are from malaria acquired in Africa; 93 percent of all malaria deaths

in all U.S. travelers are due to this. On TTM, 16 cases, all but one were acquired in Africa.

(Slide.)

The next session was testing for malaria infections here. We're talking about the developing of a test to screen blood donors and the other tests that could be provided that can be used here.

(Slide.)

So the first talk from Nigel Appleton from Newmarket laboratories, the test that is currently used in the UK, France and Australia. This is the current test. They claim their licensed sensitivity is that they did detect a 94 percent positive for falciparum. The studies only -- then the cross-reactivity, then claim 80 percent and 67 percent PO. These samples are not carefully analyzed. The sample size is too small here. But they do not show -- one cannot do all the impressions here.

They are developing new tests here. They need to include more antigens in their tests and also need to include more sensitivity. With one antigen, they get a sensitivity of close to 70 percent. With

more than one, with four antigens, you get to 99 percent sensitivity. So we are keeping our eye on this development.

(Slide.)

This is the talk I give. The test for malaria infections, SCV and West Nile virus more than for malaria, the problem is sensitivity isn't -- it can detect 2 to 20 parasites per ml or 1000 parasites in the unit of blood, but the problem is not the sensitivity, the problem is the highly infectious nature of the parasites. SU is 10 parasites, it could cause an infection and it's a very difficult problem. It's a technique problem, how does one look? So what we need is a technology that would in some way concentrate the parasite and find the one to two parasites. We're not there yet; I don't know how long it will take there. We're not there right now.

And also the other problem that exists -- we may not need to achieve that sensitivity, but we just don't know what is the minimum parasite burden that could allow us to determine the required assay sensitivity.

(Slide.)

The next one, the actual experiences from the actual users of the EIA in the UK, France and Australia will have speakers from the UK, France and Australia.

(Slide.)

I will summarize some of these talks here for you. Professor Chiodini from the UK worked 2-1/2 years on it and had experience with this test here. They have close to 50,000 cases so far and these are the numbers of repeat reactions here and every time you can perceive what's in the positives. So these are donors who would have been otherwise deferred. So it's about 3 percent positive that had malaria in every country here.

Then I would summarize Garraud from France, so far they say 75,000 cases -- and again, these are exposed individuals, instances of malaria are around. We're finding close to 3 percent of these, 1 percent positive, 1.5 percent indeterminate. In either case, 97 percent of these tests are negative. The safety of these tests -- again, this

is Stramers.

(Slide.)

She sees total malaria deferrals and how many donors are deferred. In five years, more than 33 million presenting donors and the mean donation rate of 1.7. And here's the breakdown. For travel, residents and people who actually had it, there were around 260,000 of these donors were deferred. The percent is around 1.1 percent and the projected loss donor totals is about 454,000, about half a million. Then she projected the use of ELISA in Australia. So it's a nine-month test out of 26,000 donors that they screened, there is a little more than 2 percent came up.

To summarize the data from France and Australia, 2 to 3 percent of reactions, the impact of the ELISA on safety and how they prevented it is very difficult to assess because the rate of transmittals has been so low it will probably take several years to assess that. In the UK in the last 20 years, they had only 36 cases.

(Slide.)

Here's the data from David Leiby. He started his own investigation. He looked at more than 3,000 non-deferred donors. The first part there, 21 people and 11 cases. So when we looked at the history of these donors, these people probably did not transmit directly. But they were born in one of the countries or they traveled to a malarial area, so that probably in some ways points to the sensitivity of the assay. It even goes -- they may have had eventually a lot of different policies.

There was a discussion by panelists and again we posed the questions here what are the desirable characteristics of laboratory tests that we use to detect malaria infections. Were the correct tests used? What are the risks and benefits of donor screening? What are the prospects that one of these tests could be used to screen blood donors? What are the prospects for DNA-based tests in the U.S. in the future? The panelists are here, moderated by Jay Epstein.

(Slide.)

This is the summary here. There is a

broad consensus regarding the deferral of donors who have traveled or were prior residents of Africa. I don't think there was any contention there, and that the policy would be okay, that were deferred because of their travel and residency in Africa. However, there were serious reservations regarding the deferral of travelers who visit the resorts in Mexico or travel to some of the Caribbean countries.

Then parasite detection, I think everybody agrees that the current policy is not suitable. Antibody screening, everybody was impressed from what they saw and those investigators have used the test even though it's based on the serious scientists and professors who used the test were satisfied with the test.

(Slide.)

Antibody testing in the U.S., I did not hear any clear response on universal testing in the U.S. But there was general agreement that careful data analysis is needed to determine geography-based acquisition of infections and area-wise species prevalence to decide what sort of tests should be

done and used in the U.S. and that some members of the blood banking industry expressed concern.

The logistics that we use, the related database configuration, they will need to reconstruct their computer if the test is deployed in a selected population this year. So that's the only thing that we had our discussion on.

(Slide.)

I'm sure the question will be asked here, what are the lessons that we learned from this workshop and how we plan to implement what we've heard and change our current policies, whether those are based on geographic deferrals and whether the implementations were tested. We recognize that antibody testing is becoming increasingly feasible for entry. That's something that could be used, and we are willing to facilitate the development of such a test here. Based on -- the thing here is that probably this test would be real-time testing, on the spot testing, a similar model to that used in Europe. That's the conclusions we have arrived at at this time.

This second thing is that it would be incumbent upon the blood banking industry to find a way, how they would be able to implement this testing. That is not to say that the current test currently evaluated, that is suitable. But we're saying here this time that we are willing to look at it and find a test that would be suitable here.

(Slide.)

We will also be flexible in our consultations so that -- we will not be strict about that. The species, that would include all four species. The last part is for the particular area it's quite feasible now that those particular species on which the test would be used, those tests should not be present in any area in which the test would be.

(Slide.)

Coming to the issue of lessons, I think it's a bit too early for us to decide on this issue. We are internally discussing analyzing the data, how they modify the different characters, including the deferrals for travel. However, our current

consideration is that relaxing a deferral would be premature at this time. I will stop here.

(Slide.)

These are the people helping me put this together and the full workshop transcript and most of the presentations are available on line.

DR. BRACEY: Thank you, Dr. Kumar.

Questions? Dr. Sandler.

DR. SANDLER: I'm not sure what you meant by on the spot re-entry. Does that mean that those are going to hang around at the dose site while some of the tests are being performed or the unit is collected with an R&T and while the unit is potentially viable, testing would be done? What's the concept?

DR. KUMAR: The concept is that it's not going to be feasible in a precondition so that a person that would otherwise be deferred, whether it's going to be three months, four months, six months from there the person will come back and will be allowed to redonate.

DR. EPSTEIN: The concept of on the spot

testing is that if the donor has a risk history, testing will be done on that collection. If negative, the donor doesn't have to be deferred.

What has been recognized here is that it's innovative stratification that we don't really have right now. We have one assembly line. There you have two assembly lines. So the idea is that if we have adequate control systems, we could permit such a stratification.

DR. SANDLER: Thank you very much.

MS. LIPTON: I have a question on the supplies. You lost supplies, but that's donations, isn't it?

DR. KUMAR: 250,000 donors lost. So 267,000 donors were lost. And this was projected total loss donations.

DR. BRACEY: Dr. Sayers?

DR. SAYERS: Thanks. Just a comment about that workshop. It really was an outstanding workshop. My congratulations to everybody who was involved in organizing it.

Another comment about Mexico, you had a

slide which spoke about drawbacks to geographic deferral. One thing I'd like to add is that although programs that are close to Mexico, there really is a disproportionate travel deferral attributable to people vacationing in Mexico -- which, after all, is just a hop, skip and jump away from a state like Texas. And geographic deferrals for vacations in Mexico are a significant source of aggressiveness between those of us that spend time weekending in Monterey, for example. It's not good enough to find out that the donor spent the weekend in Monterey, there happen to be nine different counties in Mexico where Monterey is a city. And I think five of those were permissible destinations and some were not.

On the spot testing is something I think we'll have to come to grips with. On the spot testing might as well be applicable to screening for Chagas disease and also screening for tests for varying activities. On the spot testing I'm sure is something that we need to become pretty efficient at.

DR. KUMAR: We are very cognizant of the difficulties it's causing, but we'd like to proceed cautiously in this direction. We believe maybe that's the answer.

After further analysis of the geographic base, we will come up with something, but it's difficult for us to simply lift the restrictions. I agree with you; this on-the-spot testing, it could be complexity, that we may have a little bit in coming times, the work has to be done in selected populations only.

But I think we have to begin to look at those further.

DR. BRACEY: Dr. Kumar, could you comment -- in the course of the meeting, I think there was pretty clear information to suggest that immigrants represented greater risk, i.e., those with some degree of immunity, then naive travelers, even those in Africa.

Could you comment on that, and whether that might be factored into your assessment?

DR. KUMAR: It certainly is a factor. If

you look at the data carefully, 50 years ago half the cases of transmittal were caused by travelers, and if you look in the last ten years, it's almost exclusively caused by immigrants who were either born in or traveled to certain parts of the world.

All that is coming together, and I think that certainly there are different safety-related tests. For example, if we are talking about sampling, now we will certainly take into account, at least part of the species not present.

So I think those are things which will really guide us, but I would like to say that this is a process that we're going through, and we'll still discussing at this time.

DR. BRACEY: Thank you. Dr. Ramsey?

DR. RAMSEY: I'd like to touch on the issue of information to hospitals, for a second, where the subject of malaria comes up.

As you know, this is perhaps the single most common source of letters to hospitals, according to the FDA statistics. There are a number of reasons touching on the question of donor facilities and

travel and understanding the donor risk, and perhaps their lack of information for travelers, that when they come back, they shouldn't donate.

But, from a hospital standpoint, testing donors would be certainly relevant for exposed patient notices that hospitals get. They will get notices about plasma, which, as far as I know, current issues, short of testing, there are too many notices about plasma.

We get notices about platelets and what is the risk from platelets. If we knew where the donor had been to, we might want to take that into account, in terms of advising our clinicians and physicians about the risk.

So, the test would begin tying that in. I just wanted to comment about that, and, of course, this is a topic for the FDA to consider in terms of notices to how hospitals should handle these notices and what information is relevant to that, in that context, but I wanted to mention that.

DR. BRACEY: Thank you. Dr. Duffell?

DR. DUFFELL: I'd like to ask -- you just

spent a lot of time talking in your presentation about testing. Is there any treatment on the horizon? Filtration products on the horizon, that might equally address this concern, that we should be looking forward to?

DR. KUMAR: Not that I know of. In Africa, where everybody is infacted, transmitted malaria is the least of the problems, but I can't think of anything, a practice that we have in this country at this time, sort of implementing radical chemotherapy for malaria for everybody who gets a blood transfusion, and I don't know that that's the thing.

Dr. Epstein?

DR. EPSTEIN: There has been some demonstration that pathogen reduction technologies could be effective to remove the parasite risks from transfusion, but none of those technologies -- a lot of those technologies have problems, but I think that is a potential solution to this and a host of other things.

DR. BRACEY: In the interest of time, I

think we'd better move on, unless there's a burning question. We certainly look forward to progress in this area.

We recognize that there are many valuable donors whose products cannot be used.

Our next speaker will be Dr. Lou Katz. He will give us an update on pandemic preparedness. Dr. Katz is the Executive Vice President for Medical Affairs for the Mississippi Valley Regional Blood Center, and past President of American Blood Centers, who, over the last year, has done great work in leading the AABB Task Force on Pandemic Preparedness.

DR. KATZ: We can now enter a data-free zone.

(Laughter.)

(Slide.)

DR. KATZ: I want to second what Merlyn said, that the Malaria Workshop was just spectacular, and I actually think that there is movement towards some rational changes in what we do. It's actually quite exciting.

So, I'm the Chair of this group, and this

is herding kittens, not just because we're blood bankers, but because it's the nature of pandemic planning in the United States at this point.

What I want to do is try, in 20 minutes, to go through where we are.

(Slide.)

DR. KATZ: We're very close to delivering the first iteration of our deliverables, which will consist of what you see here in the first three bullets:

A background, to state some of our assumptions; a checklist model on the HHS format, that I'm sure most of you are familiar with; the issues outline will discuss some of the alternatives in planning, that we think are available to transfusion services.

We recognize that, very clearly, what we're dealing with here, is a living document, and I don't know how long the term of the Chair is -- Karen, do you?

And, of critical importance for the Task Force, is continued liaison with the national kind of

public health organizations, and, in addition, the AdvaMed Blood Group, a trade organization of those companies that supply some of our most critical consumables in collection and transfusion.

The deliverables will be available before the 1st of October we believe on the AABB web site right next to the disaster issues.

(Slide.)

DR. KATZ: One of our most important assumptions is seen right there, from the 1918 pandemic. This is London, New York, Paris, and Berlin.

It shows you that the worst-case pandemic, or at least what we think is the worst-case pandemic, based on history, was essentially simultaneously on both sides of Dr. Sayers's pond.

One of the ways we deal with disasters -- natural or manmade -- in blood banking now, that has moved the product from Point A to Point B, or from an unaffected site to an affected site, is the problematic approach in the face of a pandemic.

(Slide.)

DR. KATZ: Dr. Schwartz told you this a year ago, and I think he's correct.

This is our conventional wisdom, and I think I showed you this to remind you, in January when I talked, that I think most of this is true, but we don't have any good numbers. That's the problem.

Finally, I know that there is substantial concern regarding influenza and the transmission of disease, and I'll try and mention it briefly.

(Slide.)

DR. KATZ: Are there valid impact models? The answer is no, so I guess I can quit right now.

There are a number of models in development, some more important than others. I'll show you one, not because I think it's right, but because I think it's further along in development.

There are two things: What can we collect and distribute, collect, process, and distribute, and how much is it going to get used?

I actually think the second is a more important question.

(Slide.)

DR. KATZ: This is a British model. This is from Richard Bedford at the National Blood Service, who provided me this. This is actually a very extensive model.

This looks at a ten-week first wave of 35 percent attack rate, something similar to what we think was going on in 1918. And the bottom line is that with a number of approaches, they've demonstrated approximately 50 percent decrement in their ability to get blood to hospitals, collect, process, and distribute to hospitals.

This is red cells. Like any model, it's all about the assumptions, but I think this just smells right, okay?

I think this is probably somewhere close, and other models give us numbers within ten to 20 percent.

Blood Systems: The American Red Cross and FDA are working on modeling, and as that stuff becomes available, it will need to be incorporated into our planning documents.

(Slide.)

DR. KATZ: So, some planning assumptions: Just parenthetically, one of the nice things about being on this Committee, is that I've had the opportunity to have my preconceived biases about American healthcare confirmed. It's always nice to be right.

But when you look at the UK and Canada and other countries in the EU and Australia, and see their nice, kind of vertically-oriented healthcare systems, and their ability to actually do central planning and get it out to organizations that are working off similar SLPs, it's really nice.

Here, we're very horizontally organized. As past President of AABC, with 76 centers, they know how to do it right. It's very, very difficult to do any central planning. One size does not fit all.

And this winds up being the responsibility of each of the people at the collection facility and the transfusion center and hospitals, to do their own planning. And it makes it a little more difficult, so donors and staff will impacted, like the general population, and donations will fall -- we don't know

how much.

Elective surgical needs will decline -- again, we don't know how much, but when we look at SARS in Toronto, for example, at their epicenter hospitals, their blood needs, primarily elective surgery, but also some for elective medical use, went down 25 percent -- 25 percent during the SARS outbreak in Toronto, so it's not negligible.

We don't think platelet needs -- or, at least we're going to assume that platelet needs are less elective than red cell needs, and particularly where we're supporting stem cell transplants and hematologic malignancy, they will not fall as much as red cells, with their short shelf life.

That will be a difficult contingency to deal with. While we have always assumed that flu victims will need little blood, we've never really tested a serious pandemic in the face of the availability of ICU care to 21st Century standards.

Those of you who are docs who have done critical care, will recognize with me, that medical patients in ICUs, consume substantial numbers of

blood products, so we need to be a little bit cautious when we talk about how far down need will be driven by the pandemic.

(Slide.)

DR. KATZ: Challenges: I've listed them here, and I'll go through these on further slides.

I think we can deal with the operational continuity. This is really where the planning comes in.

I'll talk a little bit more about it. I think that can be dealt with. I'm not so sure, having been a hospital epidemiologist for some years, to try to get people to wash their hands, how effective we are going to be at implementing and enforcing sound infection control procedures in blood centers.

We'll certainly make the effort. At some point, society needs to understand that blood donation remains a priority during a pandemic, so we need the attention of the national, state, and local public health authorities and EMAs, so that when we start doing social distancing, people don't think

that blood donation is included.

We need to have a discussion about vaccine and antiviral priorities. Are our blood donors and blood center personnel, important priority groups, or should these limited resources go to the guys on the line?

Those are priority decisions to be made on less than great data, but we have them anyhow. And then we need some regulatory flexibility in the worst-case scenario.

I think that in the face of the kind of event that we are actually going to have -- and I'm actually quite confident, based on precedent and then communication --

(Slide.)

DR. KATZ: -- so, operational continuity, it's these sort of things, again, maintenance, prevention of introduction and transmission at collection sites, and communication to our donors and others, of those efforts, is very important, that is a safe place to come.

We need to make our donors and donor

groups and the presidents of companies that support blood drives and whatnot, aware that the blood bank is a safe place to come.

Work rules, I'll talk about a little more. Amended procedures in the face of critical blood or supply shortages, I'm going to show you specific thoughts that we've had.

Triage is really sticky. I was talking to Dr. Sandler about this. Triage is real sticky, and may be the critical aspect of what we have to deal with.

How do we get people to use blood, only when it's absolutely necessary? That's not only a question for pandemic planning; it's a question every day, that we have not come to grips with and need to.

And supply chain integrity -- the bottom two may be sticking points that we're going to have.

(Slide.)

DR. KATZ: This is fairly straightforward. I think the key issue, logistically, is that we're going to need at our doors, check points for both the staff and the donors, to be sure sick people don't

come to work and sick donors don't come to donate.

I think that is the key critical, day number one, most important, no-doubt-about-it thing that we have to do: Keep sick people out of the blood center.

Hand hygiene and cough etiquette are very important, but if you don't let sick people in, it's perhaps a little bit less important. We know that you can shed from the nasopharynx for a day or two prior to the onset of obvious symptoms, so hand hygiene and cough etiquette are right up there with screening.

Personal protective equipment may be more PR than important, but we're going to have to deal with it. My guess is that a lot of us are going to be using a lot of masks, whether it's going to prevent infections, I don't know, but if that's what it takes to make everybody comfortable that the blood center is a safe place to come, that's just fine with me.

Environmental disinfection policies, donor room layout, droplet transmission, we understand

fairly well. If we can keep people a meter or two apart in your collection facilities, if they get sick while they're on the platelet machine, you've gone a long way to protecting the donor in the next chair. We need to think about those sorts of issues.

Vaccine and antiviral priority use is a big topic to talk about afterwards, and then public confidence.

Social distancing. This is when we close the schools, don't put on a ball game because there's flu in the community. Are people going to get scared to come to the donor center? We need to educate our donors and our staff, but our donors in particular, well ahead of a pandemic that when this happens you're excluded. We need the support of public health to make that message. I don't want to say that and then have Jerry make an announcement next week that no, blood centers are unsafe; you shouldn't go there either. We need to be prospective, not just with individual donors but with the corporate sponsors of blood drives, the community sponsors of blood drives, the community sponsors of blood drives, the churches, the school faculties and on and on and on.

Recruitment of recovered donors we think is very important. If you have the pandemic strain, you're not going to have it again, there are some issues of donor viremia and how long that could exist after a serious case of the flu. We need to talk about it with FDA. It's probably not particularly

important. But then explicit messaging from public health, as I mentioned, social distancing in a certain sense excludes blood donor, et cetera, or the mobile blood drive.

(Slide.)

Work rules. They have work rules in Iowa, so it was a little press, it was a big deal. But the most interesting thing, when I put my other hat on as hospital epidemiologist and talking to people who come to work who were symptomatic for months, I said why the hell did you come to work with symptomatic lungs? Because my pay stops if I don't come to work.

The work rules in the hospital involved clearly, by the middle of the year -- people come to work ill because their paycheck stops and they didn't want a short staff to work with. We need to look very, very carefully at our work rules. We need to understand what our employees are willing to do. We need to be surveying blood center employees, in particular, about what they're willing to do in a worst-case scenario and, again, extra staffing, retired employees, volunteers and cross training.

The answer to that is probably yes, we probably can't do it the way we did it 9/11, this has to be very serious cross training so competency is maintained in the inter pandemic period. So if we use cross training in the pandemic, we're using people who know how to do the CCNP work. This is clear. Telecommuting and related interventions for non-critical personnel, labor union input is clearly important.

There may be a surge after the pandemic; we need to think about it. A 20 percent increase in baseline demand and then respite considerations for people at our centers and transfusion services who bust their butts during the pandemic and are working a lot of overtime hours and need to rewind.

(Slide.)

Is influenza a transfusion transmitted disease, never observed, but would we have recognized it. Would we have known it if we had seen it? Viremia does occur, most of it occurs in people who are ill who will not be eligible donors. It's purely characterized for the strains that have been studied

and it's obviously not been studied for future pandemic strains. Whether animal models are relevant for people, it depends. I don't know how to answer that. But whether animal models are relevant, I don't know.

Deferral for contact is very problematic in collection. If we are in the middle of a pandemic, somewhere between the Asian/Hong Kong experience in 1918, we can be looking at huge percentages of our donors who may have been in contact with the flu, and if we have to defer for a contact a bunch of well people, it may be a big problem. This is a topic of ongoing discussion at the agency about how to deal with that.

At any rate, we believe at this point, based on the data available that the FDA should remain silent on those issues until there are direct data or we're there. That's actually more my opinion than the explicit opinion of the task force. So I wanted to say that.

(Slide.)

Amended procedures. Well what things

could we do differently that would qualify more donors if we were in trouble. This is not a complete list at all, but it's what comes to mind actually in a bar in Bethesda when I was talking to some other people -- Roger not included, with the Red Cross. We could relax the hemoglobin deferral during a pandemic. We could change travel deferrals during a pandemic. We could change weight limits, vital signs, interdonation intervals.

What's magic about the 56 day deferral for red cells if the donor comes in in half that and has a hemoglobin of 13 grams? For example, do we need to do West Nile virus NAT, HIV NAT when supplies run out or personnel run out? We're looking at very, very rare events, so could that be relaxed.

We do a lot of QC testing, we do a lot of audits, we have reporting requirements of X number of days, could that stuff be relaxed during a pandemic, the hepatitis deferrals? Cross training we mentioned. I think there's an excellent precedent that kind of answers the question, as we do some of these things, that's website use.

There's a guidance document from FDA that came out, I believe, the day that the towers and the Pentagon were hit. That gave us parameters under which we were allowed to change things that are carved in stone. So those who think that the FDA cannot be flexible and move quickly need to read that document and pay attention. I think it sets a precedent for being reasonable to base a bad case or a worst case scenario.

(Slide.)

Triage, big big problem. We're going to recommend this. This is what we're going to tell transfusion services and collection facilities. Prospectively plan medical staff and administration and patient advocates about who gets blood if there ain't much on the shelf. Prospective planning and collection facilities for rationing is what we're trying to avoid.

As a reasonable blood center medical director, if I got half of my blood supply, I don't want to be in a position where I just say to my 57 hospitals we have half our blood supply, you get half

your order and I don't care how you use it. I would like to have the sense that my hospitals have done enough planning for the people whose lives are going to be saved when they get the blood, that that means hospital X gets more and hospital Y gets less. That's fine with me. But I don't want to be sitting in my office making decisions that may affect the lives of patients that I've never laid hands on as a clinician, as opposed to a pathologist.

What is the role of professional organizations in providing guidelines for the use? This is a controversy at the agency right now. The transfusion medicine committee, for reasons I think that are apparent to all of us, are a bit reluctant to start saying well don't transfuse at 7 grams but go ahead with 6.9, we're in a pandemic. We'll fight that out in some further iteration of this living document.

I advocate that we put in some rather explicit suggestions for medically stable non-bleeding patients in the transfusion. We're not there yet but I think we will in fact get there. In

the end, triage is about altering physician behavior, and I don't have to say anything more about altering physician behavior. This is not a pandemic issue, this is a global issue in transfusion medicine.

(Slide.)

Supply chain integrity. This may be one of our biggest hurdles in the worst case scenario. In a just-in- time economy, we take delivery twice a month of our critical supplies at my blood center, which means we have 13 or 14 days supplies on the shelf. We need to engage the major vendors in this planning exercise, there may be transportation or border issues for stuff coming from outside the United States. We have to deal with all that.

The bottom line is their planning -- I don't mean to exclude them and say they're not part of the blood community, they are. But our major critical suppliers need to tell us how far they're willing to go in terms of expanding the pipeline products, which I'll get into.

(Slide.)

There are mixed messages on stockpiling

critical supplies. HHS a year ago said six to eight week stockpile of med-surg supplies, Homeland Security in May says two to three weeks. Which is which, you know.

The American Heart Association, the Association for health care resource and materials management says don't stockpile. We need to get this one straight. VHA, military hospitals of American, surveyed their hospitals and 60 percent keep less than a seven day supply, if a pandemic wave is 12 weeks, where does seven days of supplies get you?

(Slide.)

We looked at our blood center -- let's say we wanted to get out to six to eight weeks of supplies, a lot of our critical suppliers require environmental control. We certainly don't have it on-site. We cannot, in our community, find warehouse space that meets the regulatory requirements. So we have to work on that. That is not to say it's insoluble, but we have to think very carefully about that.

(Slide.)

I'm a democrat, by the way.

(Laughter.)

DR. KATZ: My boss is not a democrat. And this is his and L.D. Moria -- who's on the task force with several other people, thinks this is the equation that runs the economy right now. Preparedness in this case, public health equals excess capacity equals waste. This is not a criticism of that, it's just a question of is that the way we should look at it, isn't that preparedness waste?

Well, it is if nothing happens. I suppose you should ask people in New Orleans whether preparedness is waste. But this is the hurdle we're trying to get over. I'm not being cynical or nihilistic in asking for it, we can't think this way if we intend to be ready. This is -- somebody in the blood sector asked me, when they started having this conversation in the late winter.

(Slide.)

I think this is the crux of the matter in the supply chain. One company that makes bags has

three weeks in the pipeline. One company that makes reagents has six weeks in the pipeline, another has 12, on and on. It's all over the board. And the question they want an answer from me is you want us to change our business model? The facile answer is yes, of course. They say are you willing to pay? I say well, of course not, because preparedness equals waste.

So this is probably -- the availability and storage of supplies.

(Slide.)

The checklist includes these elements. Operational risk planning, which is basically all those work rules and that sort of thing, the donor issues, recruiting and recovery, making available for committed platelet donors vaccine when it becomes available or antivirals -- they prevented antivirals from becoming available for stockpiles, staff issues in many ways similar, plus the issue of burnout, safety and availability covers a lot of bases, but I think mainly our questions are about how much do we need to think about flu as a transfusion-transmitting

disease, my answer is not very much.

Supply chain I've touched on. Local and state public health at the level of the collection facility or a transfusion service, it's local and state health. The task force is trying to have the appropriate discussions with national authorities and I think everybody's hearing each other.

Then communication planning in terms of externals -- these will all be in the checklist with a fair amount of details and I'll answer questions, if there are any.

DR. BRACEY: Ms. Lipton.

MS. LIPTON: Not a question. I just want to publicly thank you. There are a lot of questions that are unanswered, but we're moving forward in a major way in terms of preparedness. Thank you.

DR. BRACEY: Dr. Sayers, then Dr. Sandler.

DR. SAYERS: You spoke about recurring the recovered donor. Are you assuming that's recovery based on serological evidence?

DR. KATZ: No. I think in the middle of a pandemic of the kind that would affect us seriously,

that we can take the donor's word in the middle of an epidemic that they had the flu. And I have defined recovered as they passed screen when they come in the center.

DR. BRACEY: Dr. Sandler?

DR. SANDLER: I'm the representative of the American Hospital Association on the committee and I'd like to address this issue from that perspective. First, by commending you Dr. Katz. The initiative that the AABB has taken is totally appropriate, that AABB be in this. Hospitals are going to look to a professional organization for guidelines. Exactly what you say, the practice of medicine, the FDA has got an enormous responsibility in this that relates to the product.

But what you're talking about is central. That is, what are the hospitals going to do in a given community when there isn't enough to go around and there's going to be a need for guidelines. The direction you're going is perfect.

There is a pool in this community, for example, of goodwill by the people who have given the

blood. We have to use it equitably amongst all of the hospitals for donations that are there. We need guidelines just like you're proposing for practitioners and I would really like to see those go forward at this time.

DR. BRACEY: I've got one question for Dr. Katz. In terms of the ability for the blood organizations to have the impact at the hospital level, there's been some discussion of the idea that some of the transfusion medicine experts and blood centers, if you will, stay somewhat distant from clinical practice, and I'd like to hear your ideas on how we can improve that and make this work better so that we can have these guidelines.

DR. KATZ: It's a really good question, Dr. Bracey. I was a critical care infectious disease doctor until 11 months ago. When I go back into the hospital now, the clinicians say who are you? Eleven months after 30 years. Credibility is very very important. It's not just about pandemic planning, I think all of us need to spend more time with the docs that are writing orders for transfusions.

That's pretty tough. My blood region is from St. Louis to southwestern Wisconsin, from near Des Moines, Iowa to halfway to Chicago on the Mississippi River and there's 57 hospitals and how much time can I spend getting to know the transfusion clinicians. This is really an issue of champions on the ground in every hospital and I think in recent years, you know, it's probably come back somewhat. But I think we're very much behind the eight ball in terms of getting our message to the docs. It's not pandemic planning, this is just transfusion medicine, this is what we should be doing. It's just kind of a foot in the door.

DR. BRACEY: Thank you.

Additional questions or comments? Dr. Epstein?

DR. EPSTEIN: Just a brief comment. You focused a little bit on the question of the risk of pandemic flu, it's been reported in people who had it.

On the other hand, there is an uncertainty whether there could be a brief period of enforcement,

and there's also an uncertainty whether there could be any circulating virus in convalescence. We just don't know. The question of whether we can answer it scientifically has been the subject of great debate. That's been why there are sort of well directed initiative coming forward. People are very skeptical with studies in animal models and non-human primates would be informative.

So what I can say is that the issue has not gone on unrecognized. There's a small amount of federal funding that has gone toward setting up limited experimentation and the most potentially relevant animal models and, although we don't have a directed effort to develop a screening test to be used in the blood setting, we do detect that spin-off from diagnostic development for rapid diagnostics, which is ongoing as part of epidemic control, could potentially be helpful if it turns out there is an increased risk. The issue is not unrecognized, but I would not say we're progressing terribly fast because of all the skepticism about whether that's a worthwhile investment compared to say developing a

vaccine. Of course, a lot of effort is going in that direction.

DR. KATZ: I think in the blood sector we're just paranoid, and I think you understand that as much as anybody. The nice part about this committee is it's about safety and availability. When we talk about a 1918-like event our best judgment based on not good data is availability may be more critical than any theoretical risk of influenza. What about an Asian or a Hong Kong event? It may be a totally different thing. There are no sharp, bright lines in any of these discussions. It's inherently difficult. I think everybody's negotiating on the use of the term.

DR. BRACEY: Thank you.

Before we move on to the public comments, I'd like to ask the committee if there are any questions from these two presentations that we've heard today that you think we need to address for the department, any specific questions on the malaria issue or pandemic preparedness.

DR. EPSTEIN: I have a question for Dr. Kumar. You explained to us quite carefully that the ideal test for reentering donors involved testing for the different species of malaria. What do you think are the prospects for developing such an assay, and is there any role or assistance from government funding?

DR. KUMAR: After I came to work with the transmission/transfusion issue, I realized the problem of handling malaria and the transfusion issue, is no different than handling malaria globally.

And the industry is not doing it. It will have a handsome return, so government investment will be very critical.

As we know, we only utilize what is available to us. We can definitely solve this problem.

The technology is there, as far as investment and research, and it could be of great benefit. Once the problem is solved, it's solved forever.

DR. BRACEY: One question that comes to mind: To me, having experienced some blood shortages recently, it is the issue of a proactive approach towards resource-sharing at the level of hospitals.

It seems to me that the AABB test, in terms of getting people to think about managing crises, however, we're at the beginning. I think, as Dr. Sandler mentioned, this is a resource that the donors provide to support a given region or the nation.

I just think it would be important to signal that this is an important issue that needs to be addressed, so that we don't end up having an inequitable distribution.

I can tell you that in some regional settings, inequities do, in fact, exist today.

With that, we will then move on to other comments. Sorry. Dr. Sandler?

DR. SANDLER: I'd like to just raise one question, if I could. Looking back on the HIV epidemic, afterwards, we all agreed that there was a

lack of one voice to speak for all of the issues, whether it was statements from the AABB, the FDA, which took certain initiatives, the United States Public Health Service, my understanding was that the Assistant Secretary of Health is going to be the point person on blood in the future.

We got to 9/11, and the FDA was right there, and they had their web page, as was pointed out. We had a supply problem and FDA took care of it.

Going forward, I have a feeling that practitioners dealing with a shortage, may be getting some direction from over there, and if there's a supply problem or something, do we know who the czar is? Do we know if there's going to be one person and one boss that's going to speak for the United States about this issue? Or, are we going to go to five web pages and get it?

DR. BRACEY: Secretary Holmberg?

DR. HOLMBERG: It's a very good question. I would like you raise that question tomorrow.

The Secretary is planning to be here

tomorrow morning. I've briefed him. He's been in the office since January, and he's extremely aware of his responsibility on the issues.

I think that one of the greatest things for him to realize, is the history of blood banking, all the way from pre-World War II, through the '50s and '60s, thruogh the evolution of the national blood policy, to the evolution of the creation of the national or the American Blood Commission, and to the demise of the American Blood Commission, to the ION report.

He hears that message very loud and clear, and I would be very surprised if he doesn't preempt you on that statement, as far as his responsibility to the country.

As far as having one location, I think that's something that we need to work on very diligently, especially as our strategic planning goes forward, that we have a central location where information can go one place, and maybe move on to other locations, so that it's all consolidated.

I think that what you've seen in the last

month, even, has been a great step forward. We'll have a little bit of a briefing on that today -- tomorrow, I should say -- and that is in regard to the West Nile surveys and the migration of the information there onto the AABB website.

I think that what you're saying, is very important, and I take that very seriously. I will take that back, as far as consolidating the information.

DR. BRACEY: Thank you. We will then move on to the public comments. We have a comment coming from the Immune Deficiency Foundation, that will be presented by Marsha Boyle, President and Co-founder of the IDF.

MS. BOYLE: Thank you very much, Dr. Bracey and Committee members. I'm very grateful for you allowing me to update this Committee on the problems our nation is encountering with IV/IG.

There's a continuing need for action to resolve the situation. We thank you for your history of involvement and in encouraging solutions to this issue, which is very much greatly appreciated by our

whole community.

Although I'm speaking on behalf of the primary immune deficiency community, the issue of access to IV/IG and many other disorders that depend on IV/IG, including on-legal and off-legal uses, and are supported by strong medical evidence. As many of you know, the previous testimony from the last year and a half, with a new ASP plus-six percent formula, went into effect in January of 2005 in the physician office setting under Medicare/Medicaid.

IDF, the Foundation, started hearing from hundreds of Medicare patients and physicians, who no longer receive or administer IV/IG, because physicians could not afford to continue treating at the reduced Medicare rates.

During 2005, an IDF survey, which we presented here, documented that many of the Medicare patients were shifted to hospitals, away from their physicians, trained nurses, and their usual brand of IV/IG.

Many suffered serious reactions to different brands. Some were hospitalized, and then

you had infections.

Some patients were not successfully transferred to hospitals, or were denied access to IV/IG altogether.

Working with other concerned groups, we strongly advocated that Congress and CMS not reduce the reimbursement rate for hospitals, to allow physicians to use it in an outpatient setting, because that would be the last major site of care.

However, on January 1st, 2006, the hospitals were also switched from the AWV to the ASP plus-six formula. Since then, we've heard that some hospital outpatient clinics have stopped providing IV/IG to patients, because reimbursement is inadequate.

Patients in some states have been particularly hard-hit, particularly Texas, Nebraska, and Florida hospitals. The impact of that Medicare reimbursement, doesn't stop with Medicare patients.

In recent months, since, again, January, we've been hearing from more private insurance carriers, reducing their rates to those of Medicare.

We're hearing of more patients who have been taking IV/IG for years, now being denied, and having physician supporters overruled.

Medicare reimbursement does provide a standard for private insurance. We have been working closely with the American Academy of Allergy and Immunology, to provide resources to physicians who are facing denials for patients they have been treating for years.

In May of 2005, IDF and representatives of other patient communities, testified in front of this Committee about the devastation that the new reimbursement formula was having on patient health and access to care.

We thank the Committee for recommending that the Secretary declare a public health emergency to restore access to IV/IG. I think that many of you have heard, very sadly, that one of the patients who testified at that hearing, Pam Waye, has passed away as a result of the situation with access to IV/IG.

In September of 2005, this Committee once again recommended that the Secretary declare a public

health emergency. In response to the two recommendations by this Committee, last Fall, 28 members of Congress sent a letter to Secretary Levitt, requesting that he declare a public health emergency.

Two months ago, 58 members of Congress sent a letter to Secretary Levitt, requesting that he declare a public health emergency. To date, we have not heard of progress toward establishing adequate reimbursement to provide for covering the cost of purchasing IV/IG.

CMS did act to establish a temporary, one-year, pre-administration payment for physician services, to help cover the service portion of the costs.

While this was appreciated and a positive step, it did not make up for the inadequate product purchase reimbursement. We have quite a bit of evidence that it doesn't cover the administration, as well.

At IDF, we've done everything possible to advocate for our patients. In May 2005, we conducted

a national survey of Medicare patients.

As you know, the survey found that nearly two out of five, or 39 percent, primary immunodeficient patients being treated with IV/IG, experienced a wide variety of IV/IG treatment problems, most commonly, changes in locations for infusion, 12 percent; and postponed infusion, 16 percent.

They also reporteded problems on getting on IV/IG in the past 12 months had negative effects on patients experiencing these problems.

And we also document the policy received in 2005 which I'll be sharing with the Committee.

In 2005, we added an action alert on our website, that allows patients to automatically send letters to members of Congress and to the 1185 activists, sending messages to their Congressmen, Senators, and CMS.

We're currently involved in administering three surveys to better understand the impact of access to care among primary immunodeficient patients, as well as the cost utilization and

availability of IV/IG.

These include a mail-based patient survey, based on a random sampling of our national database. We did a Medicare sample, as well.

The survey is in the field, and when we have the results, we'll be happy to share them. A web-based physician survey is being administered by the American Academy of Allergy, Asthma, and Immunology, which has been pre-tested and is now being administered.

We are working with outside agencies on a telephone survey for our national sample of hospital pharmacists, trying to assess the usability of the survey.

I certainly understand that the issue of IV/IG reimbursement is complex, and that many people are studying it.

However, from our experience, it's clear that the reimbursement under the ASP-plus-six percent formula, is not sufficient for most hospitals, home healthcare companies, or physician offices, to adequately purchase or administer this lifesaving

product.

The health of patients who depend on IV/IG, has been put at risk. Earlier in August, CMS published two proposed rules for 2007 -- the hospital outpatient respective payments system proposed rule, and the Part B physician fee schedule.

CMS proposes reducing the payments for covered therapies in hospital settings, to ASP-plus-five percent, which would make the IV/IG situation even worse. In addition, the temporary pre-administration payment for physician services, is not renewed in 2007.

This would result in a significant decrease for physician. While CMS makes up some of the lost pre-administration payments in the hospital setting, which is a good thing, there's no understandable reason for a large disparity between the physician and the hospital setting, making the physician setting less accessible.

While the physician communities and this Committee were asking for positive action to address the current shortfalls, these proposed rules would

make the current shortfalls, even worse. Unless CMS takes separate action to address the urgent concerns of patient access to IV/IG, due to reimbursement, I respectfully request that this Committee reinforce its urgent need to Secretary Levitt and CMS to find interim solutions that will restore IV/IG access to patients.

Thank you again for allowing me to update you on these access issues.

DR. BRACEY: Thank you, Ms. Boyle. Comments from the Committee? Mr. Walsh?

MR. WALSH: Thank you, Marsha, for your comments. The meeting referenced earlier by the Executive Secretary, in September, on the IV/IG issue, are you satisfied that all the stakeholders will be there and give an adequate representation?

MS. BOYLE: We're certainly going to try. Certainly, the whole primary immunodeficiency community will have statements. We just hope that what we have to say, will be listened to.

We know this Committee has listened to us, but, certainly, particularly with the new proposed

rules, we're not convinced that we're being listened to at CMS.

DR. BRACEY: Other comments from the Committee? Yes, Ms. Thomas?

MS. THOMAS: I would like to know how many individuals are affected.

MS. BOYLE: If I'm speaking for the primary immunodeficiency community, about 20 percent or our patients are on Medicare. We figure that about 50,000 patients are receiving IV/IG, but we are a primary immunodeficiency community.

Seventy percent of IV/IG utilization is off-label; it's not on-label, so we certainly, although we have no other product, and we are on the label indication, we certainly don't represent a majority of patients who depend on this product.

MS. THOMAS: Thank you.

DR. BRACEY: Any additional questions?

(No response.)

DR. BRACEY: If not, we thank you, and we certainly will be following the issue, particularly paying great attention to the meeting that's upcoming

on the 28th.

MS. BOYLE: Thank you very much for your vigilance.

DR. BRACEY: With that, we will take a break for 15 minutes. We'll reconvene at about five of.

(Recess.)

DR. BRACEY: We would like to reconvene. We do have two additional public commenters. I'm going to give you a chance to take care of all those matters and to communicate with one another.

The next presenter will be Courtney Yohe. I hope I'm pronouncing that right. Courtney is the grassroots coordinator for Public Health Pharmacy Coalition, an organization of about 350 disproportionate share hospitals throughout the nation. She will speak to us on the topic of the Public Hospital Pharmacy Coalition.

MS. YOHE: I'd like to join Marsha in thanking the Committee for their time and attention to this important matter.

(Slide.)

MS. YOHE: I am speaking on behalf of the Hospital Pharmacy Coalition, a group of hospitals that participate in the Public Health Service Drug Discount Program. For those of you who are not familiar with the program, the last hospital serve a disproportionate share of low-income patients and other covered entities to obtain pharmaceuticals to

use in outpatient settings. Prices are statutorily defined and are similar to discounts available to the Medicaid Program and the Veterans Administration. The Hospital Pharmacy Coalition believes that the current state of the IV/IG market and factors affecting product availability are a subject of considerable debate. Certain aspects of the market are quite clear. One, the price IV/IG products are rising each year; two, the limited availability of the product is causing concern to providers and patients alike and three, hospitals that participate in the federal 340B Drug Discount Program are particularly disadvantaged in obtaining IV/IGs at discounted prices and are not getting it to the patients at all.

(Slide.)

MS. YOHE: In late February 2006, THCP distributed to its members a survey designed to show how much IV/IG products they were able to obtain over the course of a three-month period to meet the demands of their patients. Several of the survey respondents were asked to identify whether the

products were available for purchase at 340B pricing. Hospital reported they were unable to obtain IV/IG products at 340B prices and there were a variety of reasons given by their wholesalers or related manufacturers for the lack of 340B pricing. Sixty-eight percent of respondent hospitals indicated that they could obtain some amount of IV/IG products through their regular wholesaler distribution channels from November 2005 through February 2006.

Thirty-two percent of respondent hospitals could not obtain any IV/IG products from their regular wholesalers. Approximately 79 percent reported that the IV/IG products that they obtained were neither available nor purchased at 340B prices. The remaining 21 percent of respondents reported that they could obtain a relatively small amount of IV/IG products at the 340B price from their regular wholesalers.

(Slide.)

MS. YOHE: Only 51 percent of respondents needed to purchase an adequate amount of IV/IG products to meet their patients needs. Many of these

hospitals also reported that the inadequate IV/IG supply forced them to delay or cancel important IV/IG infusions for patients. Several hospitals indicated they had to ration IV/IG products for the use of strict priority protocols that reserves IV/IG products for patients most in need.

Seventy-four hospitals indicated that their IV/IG hospital treatment was not available. Another IV/IG product had been substituted to avoid cancellation. As we referred earlier, the substitution of products can also lead to medical problems. THCP and its members are not only concerned about hospitals inability to purchase IV/IG at 340B prices, but also about the hospitals' procurement of IV/IG in general, which has become increasingly difficult and expensive. Most of all, IV/IG, almost all of IV/IG manufacturers have product on allocation, meaning that providers are only providing IV/IG that is pre-allocated to them. These are based on historical purchases of IV/IG going back a number of years. In many cases this means that IV/IG products are not being delivered to facilities

that need them most. This is exacerbated by the reimbursement policy that does not meet the needs of healthcare providers. As a result of the changes, including the Medicare Prescription Drug Improvement and Modernization Act of 2003, in 2005 the rate of reimbursement for IV/IG administered in physicians' offices became 106 percent of average sales price.

Prior to 2005, however, the price for reimbursement costs by IV/IG physicians at a rate 95 percent of the drug's average wholesale price. According to some sources, this reimbursement made it impossible for physicians to provide the patients IV/IG treatments without financial loss. As a result, many of the services that were once provided in physician's offices were shifted to hospital settings presumably because the physician no longer regarded IV/IG administration as a financial viable part of their practice.

Hospitals would see more Medicare and Medicaid and uninsured patients than non-DISH hospitals have seen more patients requiring IV/IG because other physicians can no longer see them. The

increased demand for IV/IG treatment at hospitals requires them to refer higher volumes of IV/IG products than before. Difficult because of the limited market supply and rendered virtually impossible by manufacturer allocation.

Furthermore, if the DISH hospital was able to give IV/IG for purchase, the survey shows most were unable to obtain the product at 340B prices since these initial physician reimbursements changes hospitals have also seen a change in reimbursement rates to bring them in line with other physician reimbursement rates. Without intervention, physicians not affiliated with hospitals are not able to accept patients with IV/IG. This year concerns were expressed by providers and beneficiaries. There was some effort to ameliorate the situation by providing IV/IG patients -- the Public Hospital Coalition strongly urges further investigation by both private and governmental entities into the recurring IV/IG distribution structure. Existing demand for IV/IG products, the cause of IV/IG shortage for hospitals and a minimal availability of

IV/IG products that is statutorily mandated. Although we appreciate the effort of government agencies to analyze IV/IG by allocation issues, we are concerned that the analysis will not be complete unless these studies include hospitals.

Finally, THCP urges the Office of Pharmacy Affairs to take affirmative steps to assure that 340B providers are able to purchase IV/IG products for patients at 340B prices to which those providers are entitled and the pharmaceutical manufacturers industry leaders are not allowed to circumvent the 340B program. The results of the survey will be issued in a report that should be made available in the coming weeks and can be found on our website. If you have any questions, you can contact me.

DR. BRACEY: Thank you. Questions from the Committee.

(No response.)

DR. BRACEY: If not, we look forward to the report.

Our next speaker -- questions from the floor.

MS. STARKEY: Jen Starkey with the American Blood Center. I just had a question about the definition of "need" in the survey. Did you distinguish between labeled and off-labeled use?

MS. YOHE: That's a very good question. I am not sure. I think the hospitals were left to define "need." We'd have to go back and check. I can follow-up on that question.

DR. BRACEY: Dr. Holmberg?

DR. HOLMBERG: I think that most of us around the table here and probably most people in hospitals, and also in government, do not fully understand the 340B and I would just really encourage you to press that at the meeting at the end of September to be able to enlighten some of the people there as far as the role of 340B. We have worked very closely with the HRSA agency regarding the problems that 340B facilities are facing. Some people on the Committee may not realize about 340B is really part of the Public Health Service Act. It is a provision to be able to provide the IV/IGs at a reasonable rate to non-profit organizations and

hospitals. So I would just really encourage you to come to that meeting and to be able to present and clarify for many of the people there the role of the 340B.

MS. YOHE: Thank you.

MR. MATYAS: In your study does it explain why some of the participating hospitals are saying why they can't purchase through the 340B program?

MS. YOHE: The prices, the 340B prices are not being made available by industry leaders, but they can sell the drugs elsewhere at a higher price.

MR. MATYAS: Exclusively to the 340B facilities?

MS. YOHE: I would tend to say that it's a product of the shortage that is not necessarily out of malice that they do that. But if there is something to sell, they can sell it some place else for more money.

DR. BRACEY: All right. Thank you.

And additional question? Ms. Birkhofer?

MS. BIRKHOFER: I need to make a comment for clarification regarding Ms. Yohe's use of the

word "shortage." TBTA maintains an industry-wide data gathering problem based on storage data to third parties. Based on our aggregate industry-wide data there is no shortage of IV/IG contrary to the fact supply distribution is at record high levels. So there is no shortage of IV/IG.

DR. BRACEY: Thank you.

Dr. Sayers?

DR. SAYERS: How do we reconcile those opinions then? There is a shortage. There is no shortage.

DR. HOLMBERG: Dr. Sayers, I think you really hit on a really good question. One of the things that you have to be aware of -- I don't want to speak for Ms. Yohe, but I think what I got of the presentation there was that actually it's the shortage of product available in the 340B channel. It may not be an overall shortage across the nation, but it's a shortage in the allocation. I think that's one of the problems from my point of view that I've seen. I think that what has been brought up here is the allocation issue of the different

channels.

DR. BRACEY: We'll move on to the comments. Thank you, Ms. Yohe.

Melissa Schweitzer? Ms. Schweitzer represents the IV/IG Access Coalition.

MS. SCHWEITZER: Thank you for giving me this opportunity to address your important committee. I would like to first say a special thank you to Dr. Jerry Holmberg for his hard work and dedication to restoring access to IV/IG. Dr. Holmberg has spent countless hours working with patients, physicians, pharmacists and other members of the IV/IG community trying to help patients receive their IV/IG. We are grateful for his commitment to the community.

On August 28, 2006, a meeting was held in Washington, D.C. to form the IV/IG Access Coalition. This was the first meeting of its kind that brought together several organizations that represent various patient communities that rely on IV/IG as a life-saving therapy. It also brought together professional medical societies representing the providers who treat these patients as well as

congressional staffers from the House Ways and Means Committee, the House Energy and Commerce Committee and Senate Finance Committee and also representatives from the Department of Health and Human Services, Office of the Assistant Secretary Evaluation and Planning who is doing a study on the access to IV/IG products, and of course, Dr. Jerry Holmberg.

The participants from the patient and medical communities included the American Auto Immune Related Disease Association, the Guillain-Barre Syndrome and CIDC Association International, the Immune Deficiency Foundation, the Myositis Association, Disorder Support Association, the American Academy of Allergy, Asthma and Immunology, the American Academy of Neurology, the American Society of Clinical Oncology, the American Society of Hematology, the Community Oncology Alliance, the Infectious Diseases Society of America and the Public Hospital Pharmacy Coalition.

The participants share the common goal of trying to restore access to IV/IG for those patients who have experienced problems due to inadequate

reimbursement of product by Medicare as well as private payers, availability of product and the lack of access to sites of care. As a patient with a primary immune deficiency, common variable immune deficiency or CVID, I know first-hand how vital IV/IG therapy is to my well-being. By replacing my antibiotics and thus reducing the number of infections I experience it has allowed me to lead a relatively normal and rewarding life. Because of IV/IG I've enjoyed a successful career as a genetic counselor and patient advocate working to help educate and support other individuals affected by rare genetic and chronic diseases.

Because of IV/IG I've had the immense fortune of becoming wife to a wonderful and supportive husband and a mother to not just one, but two beautiful children after once wondering if I would ever have the opportunity of becoming a mother at all. Because of IV/IG, I feel that it is my personal and professional mission to help work towards as solution that will restore access to my fellow patients who are not getting this life-saying

therapy. With IV/IG, they too, can have the hope of enjoying at least a fraction of the good fortune I've experienced. I always thought that if I had to be born with a rare and chronic condition, at least I was lucky to be born with one for which there an effective therapy. I am sure that this is what many of my fellow patients thought when they were finally diagnosed with their respective conditions, prescribed IV/IG therapy, began the recovery and started to live their lives again. I can surmise that they did not envision the horrible day when they would be told their IV/IG product was not available or they could no longer receive it in their trusted physician's office because the doctor cannot afford to treat them any longer.

What parent should have to imagine that his or her child can no longer receive one therapy that has saved them from succumbing to life-threatening illnesses? What patient should have to imagine that she will again lose her ability to walk because of lack of access to these life-saving products? The last time I testified in front of this

Committee was in May 2005. At that time I had the opportunity to meet another patient, Pam, who was mentioned earlier. She had shared her tragic story of IV/IG access problems in front of the Committee. I vividly remember Pam who had a diagnosis of chronic inflammatory demyelinating polyneuropathy and myositis, and was at that time confined to a wheelchair because she was unable to get her IV/IG on a regular basis due to lack of access to her site of care. I remember her tears as she begged the Committee to help her find a solution to the IV/IG problem that would save her and the patients affected by this crisis.

I remember the tears we shared together when we met each other after the testimony, and I remember the tears I shed when I heard of her death this past Spring. As a patient and a professional patient advocate, I feel that I'm in a unique position to help effect change. While I am part of the Primary Immune Deficient community, I identify with all patients who rely on IV/IG therapy to maintain their good quality of life. I see the

creation of the IV/IG Access Coalition as an effective step in seeking to restore access to IV/IG to all patients who truly rely on this therapy.

While these various patient organizations represent different constituencies, they also have the common goal of saving lives of the patients in need. To accomplish this goal, they come together to speak with one voice loud and clear from the patient community. We should not have to lose one more patient or watch the health of existing patients decline because of a lack of access to their therapy.

On behalf of patients I thank the Committee for its strong leadership and for its past recommendations to Secretary Leavitt to declare a public health emergency in order to restore access to IV/IG. Unfortunately, as you heard, access has not been restored and I request that the Committee continue to work with the communities most affected by this crisis in finding solutions to restore access. Thank you very much.

DR. BRACEY: Thank you, Ms. Schweitzer. Comments or questions for the Committee, for Ms.

Schweitzer?

Ms. Birkhofer?

MS. BIRKHOFER: Thank you for your time. I just, for the record, would make a point of clarification. When you listed the consumer organizations, are all those consumer organizations participating in your IV/IG Access Coalition, for the record?

MS. SCHWEITZER: For the record, at this point they have not, but the majority have. We are working on a formal structure. As I mentioned, this is the first meeting of its kind. We're working on that, but we have heard from a number of organizations very interested in working with this coalition.

DR. BRACEY: I'd like to ask the executive secretary to give us a follow-up in the meeting that's upcoming on the further progress to tell us what's happening in this area. Thank you.

With that, we will then move to a major topic for the next two days. That is biovigilance. In our May meeting, Executive Secretary Holmberg

presented the concept of an Eastern philosophy of oneness in the same direction the upcoming surveys surveyed one safety activity, both in the U.S. and elsewhere, the aim is to consider the potential of aligning many groups into a parallel course to achieve the optimal safety and to assess the role in U.S. Government. While a broad array of initiatives were discussed in the Strategic Planning session, one area -- I'll call it biovigilance -- stood out as an activity in need of prioritized focus. In preparation for this meeting and discussions along the lines of biovigilance, they have been initiated by the CDC and the executive secretary. It is clear that while we have many pieces of vigilance operating the U.S. a comprehensive system has yet to be developed as pointed out by the Committee in May. We are a huge nation with a particular set of challenges related to decentralized structure of our healthcare.

Nevertheless, I believe that partnership between industry, consumers and government can create the necessary development of a comprehensive system to assess not only the adverse outcomes of

transfusions, but also the positive outcomes so we can use it more efficiently. That said, we have a set of questions for the Committee's consideration that we developed. I'd like to share those questions with you now.

If I could have the next slide.

(Pause.)

(Slide.)

DR. BRACEY: I'll just present the questions so we, through the deliberations over the next day, you can keep these in mind. One, on the one broad area is definition. That is, what are the essential components, basic elements of a biovigilance system. Should biovigilance be considered a part of a comprehensive quality standard as expressed in CGMP, CGTP or CLIA? What are the characteristics of a biovigilance system that are already in place in the United States?

(Slide.)

DR. BRACEY: Then under "Impact" does the U.S. need a biovigilance system to ensure blood safety and availability? What would the strengths,

weaknesses, opportunity, threats? What would be the SWOT analysis of the biovigilance system? How would a biovigilance system contribute to and integrate with the transformation of the healthcare system in the United States under the lead of the strategic plan of the secretary and should a biovigilance system integrate with international systems, either planned or currently in existence? There is much activity that's taken place on the international level for the above question, what does integration mean to the Committee? Standardized definitions, standardized data elements, platforms, data sharing, analysis or a forum to discuss analysis?

(Slide.)

DR. BRACEY: Finally, under "Responsibility," what is the role of the federal government and the private sector in a biovigilance system and what recommendation or recommendations would we have in regard to the government's role and function in the development, operation and support of a national biovigilance system? These are sort of the frameworks that we would like you to keep in mind

as we go through the presentations and will ultimately come up with a set of recommendations for the secretary.

That said, our first presenter will be Dr. Kuehnert. He's going to review some of the discussions we had along this line from our last meeting.

Matt?

(Pause.)

DR. KUEHNERT: Great. Thanks. What I wanted to do is to review the discussion from the last meeting and I also added some slides to facilitate discussion of the concepts. Also, in addition to that, I have a couple of slides on hemovigilance and some of the things that AABB has done, which will be discussed more tomorrow, just to integrate with some of these concepts.

I finally want to briefly introduce organ and tissue safety to the Committee so that the concept of biovigilance is rounded out in addition to hemovigilance.

(Slide.)

DR. KUEHNERT: First, the agency disclaimer on the presentation. And now to go back to the review.

(Slide.)

DR. KUEHNERT: On May 9th of this year we discussed developing a blood safety and availability strategic plan under four themes of the secretary's plan -- transform the healthcare system, modernize Medicare and Medicaid, advance medical research and secure the homeland, along with others. We were asked to focus on biovigilance mostly. Onto the first, transfer the healthcare system, but as you see there was also synergy with some of the other concepts. We noted that in the slides.

(Slide.)

DR. KUEHNERT: This was the list of the biovigilance discussion group. These were most of the group that was present.

(Slide.)

DR. KUEHNERT: So under "Transform the healthcare system," we were asked specifically in the working group to discuss surveillance of adverse

events related to blood donations and transfusions, and error prevention in blood collection centers, transfusion services and clinical transfusion settings.

(Slide.)

DR. KUEHNERT: We thought the first task would be to define "biovigilance" because it's a new word to most people and it's a compound word. We thought we'd start with the first part of it, which is "bio" and what that means. I thought it should be a comprehensive interpretation of biological products, including blood, plasma derivatives, immunogobulins, albumin, also organs, other tissues, which is a wide array of allografts, including musculo-skeletal tissue, heart valves, skin, eyes, dura stem cells. This is just a sampling of the tissues that are available. But we also were thinking even more broadly about where biologic products may also go and also where synthetics and recombinant products will need to replace biologic products. That really probably needs to be lined up front. When thinking about a surveillance system,

what is really being encompassed?

(Slide.)

DR. KUEHNERT: The second part is the word "vigilance." That's where we spent most of our time, what that really means. It really means different things probably to different people. You'll see some of the illustrations of projects exactly what that means. For instance, to some there's donor surveillance and the data referring to deferral laboratory testing and donors. Then there's recipient surveillance for adverse events. Then unrelated to either donor or recipient events there is emerging infectious disease monitoring. I'll discuss that briefly as to what that means. Then there is the issues concerning error detection and response to product quality assurance.

Finally, which is really surveillance unto itself, is the issue concerning the denominator and what other products are used and the availability of those products.

(Slide.)

DR. KUEHNERT: So just turn for now to the

recipient surveillance of this, the discussion group thought the best thing to do ideally would be to define things prospectively as much as possible. The idea of a data dump is attractive in some ways as far as being easy for everyone to put whatever data they have, but it leads to a real problem when you get to analysis. So it's something that we thought, as a group, should really be thought through. For instance, infectious, non-infectious events, the severity of the events, the root cause of the events and also included in the surveillance there's a trigger to the intervention. Really, thinking of all these we thought the focus should be on outcome and that's something that really was emphasized throughout the discussion and also includes errors, which overlaps some with adverse events but isn't exactly the same thing so it may not result in an adverse event or a poor outcome but still maybe significant.

(Slide.)

DR. KUEHNERT: We talked a little bit about the systems currently in place for blood

tissues. They're different. They have some sorts of systems, but most are passive with multiple pathways. For instance, blood has a regulatory pathway extending into the hospital, but there are some weak links concerning how the clinician or recipient triggers an adverse event report, which is certainly not guaranteed in the current structure. Organs, for instance, in transplantation only requires outcome reporting and other aspects that are present for blood and tissue regulations concerning FDA extend only to the hospital donor who gets the tissue. It's usually the surgeon and not beyond.

A joint commission has new standards that start from that point to the recipient, perhaps we'll hear more about that later on in the day. But the regulations only extend to that point. So all these really have to be looked at when we're talking about a system.

(Slide.)

DR. KUEHNERT: Really what we're talking about in surveillance we'll hear more about from Dr. Pinner. There's really two needs and so two models

probably needed. The first is a comprehensive reporting model for common, well-defined events and outcomes. These are the sorts of things that can be benchmarked or seen as events that occur on a frequent enough basis that you can use a selective site methodology and some sort of sampling and you can develop rates for these sorts of things.

Then secondly, there is sort of the zebras, the rare events that you really want to know about that are unusual and perhaps a passive surveillance approach can be used, a methodology that has to be national because the events are too rare so that you think you're capturing a good sample. But for either model, you need to determine what the intervention threshold is going to be and what the action should be when you reach a certain point. This is something that came up again and again in the discussion group. If you're going to collect data, you need to do something with it. You can't just sit there. That really is not useful.

(Slide.)

DR. KUEHNERT: Just to illustrate this

concept again, you have these two outer columns where you have unusual events or sentinel events where you have a cascade of certain things happening and a certain way of measuring. Then you have common events, which as I said, really lends itself to benchmarking, a national surveillance template called national surveillance, but is really selective centers that can be sampled nationally to create a system. But for both you need a denominator which requires so-called "universal data" that would be more useful to the outcome driven. So you really can figure out what the rate of events are. And again that would facilitate actually having useful interventions.

(Slide.)

DR. KUEHNERT: The third rail is what I call it, the EIDs. You've got this problem where it's something you're not detecting in donors. You don't have recipient adverse outcomes to guide you on the threat, so there's some hypothesis that there's some risk there. Pandemic flu is one example. It's plausible but you just don't know. What do you do

with that? You really need to devise a whole other system I think to address that. We thought there, there was synergy with the research agenda group on this. Once you have a hypothesis, how do you test it and perhaps repositories reflecting current donors would be the best way to do that. We thought this was sort of a third problem that needs to be separate from the other two.

(Slide.)

DR. KUEHNERT: Then moving on from surveillance to error prevention, the group agreed errors need to be defined, manufacturing versus bedside. Again, these may be independent of an adverse recipient outcome, but still may be important. The error investigation should not be punitive, but should result in intervention and efferent or feedback on biovigilance is important here.

(Slide.)

DR. KUEHNERT: Just to illustrate the point then, and this is one example for healthcare associated infections. This could be any event that

you have infections that are caused by medical errors and those that are not caused by error and those that are in this box are considered preventable. If you detect those, you have improving quality of care.

(Slide.)

DR. KUEHNERT: So you have a cycle of success where you're using your surveillance to compare local rates of benchmark. You see there are outliers. You see what the root cause is through discussion. You try to effect a change through education, feedback and decision support. Then you see if the changes work through the surveillance. So it's a cycle for success that then can be used.

(Slide.)

DR. KUEHNERT: Finally, on the discussion of the points we've come to, availability and use surveillance, if you don't know, if you don't have data about the use of the product, it's very, very difficult to try to put the events in perspective. So you need a system to track, as you'll see with organs and tissues, which I'll briefly touch on. It seems like that's a good way to start. You need to

be able to track products that are used. It also creates its own system concerning unmet needs, what's the impact of those needs, what are inequities, unavailability, and trying to increase donation and increase availability and there are models for this in the organ world. OPTN is really very focused on availability and maintaining equity of distribution. But also in blood there's a basis for HHS and the blood registries that can be used as a model for this. This really can begin and it needs to begin.

(Slide.)

DR. KUEHNERT: In developing a model for biovigilance, the group thought that what was needed was central reporting, biologic product adverse events, errors and outcomes, again, emphasizing outcomes. But again, what is the incentive to ensure compliance? It really comes down to who is going to use this system and why are they going to use this system. We need to think about accreditation, reimbursement and simplification. It needs to be very, very simple for the end users so that they know exactly what to do. Tell them what to do. They do

it and you tell them what to do again when they forget. It's as simple as possible. Perhaps there needs to be some things as far as performance parameters, but there needs to be some sort of a plan on how to ensure compliance.

(Slide.)

DR. KUEHNERT: Again, thinking about this comprehensively about tracking, which for blood, organ and tissues is at different levels of sophistication I think. And thinking about it, from the source to the end user would be the best approach to prevent errors and improve quality assurance.

(Slide.)

DR. KUEHNERT: A wide spectrum of partners, I think, are essential in this effort from government, industry, trade organizations and patients also. Patients should be educated that they have a responsibility also to be able to effect events and bring it to the attention of their healthcare provider. They should be included in the system in a number of different ways -- accrediting, healthcare, clinical organizations, IT companies,

media and the general public. All these are really essential.

(Slide.)

DR. KUEHNERT: That's the end of the summary of the discussion from last time. I wanted to just illustrate a little bit about these concepts. One is with donors. We are moving back to the concept of donor surveillance. This is one piece of biovigilance. West Nile is one example of something where this could be applied. This is the CDC website for viremic blood donors and reported cases, reported viremic blood donors in the United States. You can see a map, basically, counting the number in each state. These are reported through a chain from blood backs to health departments and from the health departments to the CDC. There's a pretty significant time lag between the time that the donor test positive to the time we actually get these data.

(Slide.)

DR. KUEHNERT: The new AABB West Nile virus biovigilance network is an important step forward. It's data that's a little bit closer to the

source and therefore has a little bit of different perspective. And you can see here this map of the United States and Canada. As I said, this will be explained tomorrow, but I just wanted to use it for an illustration. There are some real important aspects of this I'd like to point out. One is how you display the data is important in understanding the meaning of the data. These include confirmed positives and also some pending data. It's a little bit more dynamic. Also these are numerator data, so when you don't have a denominator it becomes a little bit harder to look at magnitude. So you see a hot spot here in southwestern Idaho and in California, the upper Midwest and South.

(Slide.)

DR. KUEHNERT: If you compare this to, for instance, race this is from the CDC website of human neuroinvasive disease incidents in the United States, which takes into account the human population. You see that the hot spots are in Idaho and the upper Midwest, a little bit less in the South, although there's a point here in Mississippi, a little more of

a clarifying picture of what's going on. So I think it's very important to look at all these data in concert. I really do think that there is some promise of having the donor, the viremic donor data be useful for public health because there have been times when these donor data have preceded human activity that has been reported clinically. But it's just a matter of figuring out how to display and how to coordinate with other sources of data. I think it's a very good example of biovigilance in action.

(Slide.)

DR. KUEHNERT: I wanted to just mention organ and tissue safety briefly. There's over 25,000 organ transplants annually. But there's 100,000 patients on the transplant list. There is a real inequity between the availability of the organs and what actually get transplanted. Transplanted transmitted infections are rare, but they do occur. And when they do, they're often fatal -- a very high proportion are fatal. This is a partial list of some of the ones you can see certain acceleration and at least recognition of these events starting with HIV

in the 1980s, hep C at the turn of the century, then rapidly accelerating with Chagas Disease in 2001. There was another case this year actually West Nile virus; in 2002, 2005 lymphocytic choriomeningitis; in 2003, 2005 and rabies in 2004. These were all events that resulted in significant illness and death in organ transplant recipients.

(Slide.)

DR. KUEHNERT: For allografts, tissue allografts the picture is a little bit different, but similar issues. Over a million tissue allografts are implanted annually, probably almost two million now. This is just an exploding industry. There's an incredible amount of work being done to expand the number of the tissues that are being transplanted resulting in life-enhancing and life-saving events. Some but not all tissues can be sterilized. This is really important for people to know, particularly clinicians that are not always aware that when you have these tissues come in nice packaging, nice plastic packaging it looks sterile so sometimes the assumption is that these tissues are sterile, but

they are not in many cases. There have been multiple investigations of tissue transmitted infection involving a wide spectrum, including bacteria, fungi and viruses.

(Slide.)

DR. KUEHNERT: Organ and tissue recovery is a complex process. It's a little bit different from blood, maybe closer to plasma because you have one donor and so many recipients even up to over a hundred recipients from one donor. So the donor is screened and tested according to regulations hopefully and then there are a number of products procured, including organs, eyes and skin, which are classified as tissues, but have some unique aspects and then the other tissues, which include a wide array that I mentioned earlier.

So there's a number of links in the chain concerning organ and tissue recovery and distribution and implantation that really involves a lot of coordination and also creates a lot of complexity. When you have realization of an infected donor trying to trace forward and trace back to all these

recipients. And then, for instance, if there is an infected recipient conversely tracing it back.

(Slide.)

DR. KUEHNERT: Last year, CDC and FDA and HRSA put on a workshop to look at organ and tissue safety. This is really a unique event. It isn't something that had specifically been done before.

There isn't an organ and -- and tissue safety availability committee. There is one for organ transplantation ability but really there had been no focus on organ and tissue safety per se, and communication between these two communities. Not surprisingly, looking at the priorities, one of the conclusions was that we needed a better communication within and between the organ and tissue communities who interact but don't have any formal system to communicate.

Also when I mentioned tracking as a real objective, what is needed is a unique donor identification linking organs and tissues, because that does not exist right now, and clear mechanisms for adverse event reporting by health care facilities, stronger information dissemination to a broad array of clinicians, health professionals and patients and notification algorithms for trace-back and trace-forward tracking. These are the things that overlap the themes of biovigilance, themes that we need to take up in looking at a comprehensive approach.

(Slide.)

Looking at the critical points in the pathways that I mentioned, you see the themes and where they can be applied: communication of donor information, systems tracing and notification, hospital tracking -- which is a real challenge. Remember, the regulations don't go into the hospitals. It's really important to look at recipient adverse recognition.

(Slide.)

Subsequent to the workshop, there's a cooperative agreement that was put out by CDC for a network to detect and prevent emerging infectious diseases, focusing on improved communication, improved identification and tracking of tissues, improved diagnostics through pathologic and microbiologic capability on donor specimen samples and development of recommendations to improve organ and tissue safety.

(Slide.)

What resulted was a cooperative agreement that was awarded to the United Network for Organ

Sharing or UNOS, which had not done any work on tissues, so they couldn't do it alone and so they propose a collaborative effort between CDC, HRSA, FDA, UNOS, the Association of Organ Procurement Organizations, the American Association of Tissue Banks and the Eye Bank Association. So it's really a collaborative and comprehensive effort to really coordinate detection of transmission of disease through transplantation. And this was named to Transplantation Transmission Sentinel Network, or TTSN.

(Slide.)

At TTSN they've started work now -- I use this to really illustrate how you can really take a piece, a doable chunk of biovigilance. And what they've started to work on is tracking tissues.

What this is here is hard to see in this diagram, but it's a donor ID generator. And how do you start? Being able to have a unique ID assigned to tissues. And so what you have at the end here, it says TTSN donor ID is archived into donor records as a unique health care system identifier. And again,

this goes back to the secretary's principles and goals for integration of the health care systems, so the idea is to have this number that then is put into a database and that database then allow you to track all the way from the donor to the recipient. That's an important thing. That's a thing that is done in blood.

I think, as a matter of course what needs to be then built onto that is a database that then is used to track denominators so you know exactly what tissues are being used and use characteristics and also adverse event reports.

Once you have a comprehensive national system, it's much easier then to overlay the other objectives onto it. So in that way maybe building from the ground up is an advantage, I don't know. We'll see.

(Slide.)

Finally, I just wanted to focus or bring into the focus other issues and products. We need to just keep in mind that even in the large universe of biologic products, we need to synergize with drug

surveillance and vaccine surveillance. One example is in drug surveillance the federal collaboration between CDC, FDA and the CPSC in the national electronic injury surveillance system and cooperative efforts. It's an active surveillance of adverse drug events. Maybe we don't need so much to combine efforts as much as learn best practices from them.

(Slide.)

In learning the steps that need to be done from the time the patient realizes that there's an adverse event that they need to seek clinical care for to the way the clinician charts it, the way it's coded and the way it gets reviewed and analyzed and the way the findings are disseminated. We may be able to get some ideas on how to do this for biologic products.

(Slide.)

In summary, for biovigilance, the discussion group from last meeting took home the following: that it's important to consider three main components, donor surveillance, recipient surveillance with an outcome focus and the ID

monitoring, that there needs to be incorporated error detection in the way of product quality assurance and, in that framework, there also needs to be in the framework monitoring of availability and use and there needs to be comprehensive tracking and adverse event and error reporting source to recipient. Finally it's important and critical, essential, that -- collaborative partner involvement and education is essential and take best practices from all systems.

(Slide.)

My own suggestions, particularly I'll put the disclaimer here, but now is the time to do this. There's a lot of confluence of events right now where I think surveillance at the CDC is increasingly important and outcomes are seen as increasingly important. These are evident in the strategic plan or should be evident in the strategic plan and we should consider aligning with the secretary's principles. And I would call this maybe moving fragmentation to integration, just looking at some of the secretary's themes on the health information technology standards and safety boards for monitoring

and response. We can see where there would be some definite overlap where we could include ourselves in this framework. And finally, public and private sectors need to be in partnership for this to work, in my opinion.

(Slide.)

This is just the working group recommendations in more complete form, and perhaps we can come back to this when we discuss recommendations from the committee.

DR. BRACEY: Thank you, Dr. Kuehnert.

I'll open up the floor for questions and comments. Dr. Sayers?

DR. SAYERS: Thanks. We've had some preliminary discussions about what a local biovigilance program would look like in north central Texas. A couple of points have emerged in the discussions with hospitals, particularly as far as biovigilance relates to recipients: availability, usage, errors, inventory management. Ideally, that would be coordinated out of the hospital blood bank.

I think particularly the larger hospitals

agree that for this to be done well ideally it should be the responsibility of a single individual at that blood bank. Hospital blood banks are under such intense scrutiny from a budgetary point of view that it's very unlikely that they be able to devote a salary to somebody who's exclusive responsibility is going to be carrying out this biovigilance task. So there are monetary concerns here.

The other concern has to do with this: it's undeniable that there is significant competition between hospitals. Any voluntary reporting system which reveals that one hospital might be prone to more errors or near misses than another is going to lose the hospital's enthusiasm for a voluntary reporting system that reveals that that hospital is less safe than other hospitals. That hospital's enthusiasm is going to be tainted at best.

DR. KUEHNERT: Could I maybe start and see what other comments people on the committee have?

I think there is an answer. I don't think we have the answer. But if you look at the history of infection control, you can see how some of these

problems were addressed and solved. I am not old enough to know intimately the complete evolution of how this happened, but it's amazing to me that in the early 1970s this was -- all these problems were brought up for infection control and somehow now we have infection control practitioners in almost every hospital. And the administration of each hospital is convinced that if you don't have an infection control program, you have increase in adverse events.

I think we need to look at how that happened. The Joint Commission may have some insight into this and we have a speaker tomorrow, Teresa Horan, who is involved with the infection surveillance system that is put together for infection control in the Seventies and is now the national healthcare safety coordinator. And I think that is a great model to look at some of these issues.

The second part of Dr. Sayers' comment was about benchmarking and about hospitals being reticent to sharing data. This is a big issue right now in healthcare. Now they're talking about national

reporting. So all these issues are being looked at now. It is do-able but, and there's a big caveat here. It has to be done very carefully. Everyone has to be punctual. There are confidentiality issues. There's no reason for us to re-invent the wheel. I think all these issues have already been looked at. I think the solutions may be a little different, but I think we need to look at what's been done in infection control. I think there's going to be a lot of solutions there.

DR. BRACEY: I would certainly agree in terms of the point of trying to position us in a way that those who ultimately would pay for these activities would see a gain rather than negative reporting. I think as you mentioned the model from what happened with infections and the development of infection control offices offers a great deal that we should study and learn. We do have representatives from JCAHO who will be talking to us later today.

Dr. Sherman?

DR. SHERMAN: The Joint Committee has been aware for a long time that the data it has about

adverse events is fragmentary and quantitative information on transfusion-related death, for a long time we pushed for getting systems of non-governmental quality organizations being able to get legally confidential material reported such that the organization would have assistance in drilling down, if you will, to the causes of events.

But more importantly, or as importantly in what you're talking about, identity stripped data be out there for two reasons: one, that other organizations see where the pitfalls were, and additionally there will now be more benchmarks out there as far as what people should be able to hold themselves against.

DR. BRACEY: Additional questions for Dr. Kuehnert? Dr. Katz.

DR. KATZ: As somebody who's worn both hats, hospital infection control and transfusion medicine, the big revolution of course was the SAIN study which put some numbers on it. When you look at the results of the study, it showed us adverse events occurring orders of magnitude more frequently than

what we see in transfusion medicine. That's really the issue, a surveillance and control model for infection control is a valid model to deal with this. But in a certain sense, hospital infections are low-hanging fruit so they got picked. Where we are in transfusion medicine, I'm very hopeful at least at this point is not that prevalent.

So my blood center is saying well every hospital isn't going to hire this person. We'll hire this person. So we hire the transfusion safety officer and find that in our system there were some 30 hospitals -- the response of the hospitals is that it's nice that you're creating employment, but to the degree that we have to feed this person the information, collate this and package it confidentially, it ain't high enough on our priority list.

So I think Merlin made the point, it's a matter of resources and the problem is big enough but I --

DR. KUEHNERT: It's just a short comment. I agree. It depends which events you define as

significant as far as how frequent the events are. There, I think, you have to look at what the impact is. The beauty of the SAIN study was that it actually quantitated going from adverse events and what impact those had on how many resources it would take to actually prevent those infections. Perhaps the same thing needs to be done here, look at adverse events in transfusion, which ones are significant in terms of morbidity and also cost and compare that against if you had a safety officer, how many more could you report and how many more could you prevent. Do the math. It's not really that easy, but it's a start.

DR. BRACEY: Dr. Ramsey, did you have a comment or question?

DR. RAMSEY: Just to add to Dr. Sayers' concern, I guess it would be -- we're edging around this issue and maybe it's not worth it for us to get into this point. But just to mention in passing, the real implications of this type of program, the potential barrier, another source of concern for healthcare.

DR. BRACEY: To keep people on track, we'd better continue. We will then move on to our next speaker. The next speaker will speak on the biovigilance as a quality system. This is Mary Malarkey. Mary Malarkey is director of the office of compliance and biologics quality at the CBER. The talk will be on characteristics -- biovigilance as a quality system.

MS. MALARKEY: Good afternoon.

(Slide.)

MS. MALARKEY: Just to put where I fit into perspective here, in the Food and Drug Administration I'm the director of the office of compliance which, by its name, suggests that we are the office that works with all the product offices within the center for biologics: the office of blood, the office of vaccines and the office of cells, tissue and gene therapy.

We are the ones that unfortunately have to sometimes take enforcement actions against the industry. For us, quality systems are an extremely important part of the process. About four years ago,

the agency initiated the 21st century CGMP initiative for pharmaceutical products, a risk-based and science-based approach.

One of the big ticket items we looked at were both the internal quality systems at FDA and the quality systems that are out on the street today. This is an area we think improvement was needed and that we have put out some guidance on.

(Slide.)

MS. MALARKEY: From the industry perspective, this is not just the FDA-regulated industry, but we've looked at the aerospace industry and the conductor industry.

I think it's very clear, where the quality is all about. Time is money; failure is about money; investing in quallity, really is about success, getting more products on the market that are safe and effective.

(Slide.)

MS. MALARKEY: Our own regulatory perspective on quality systems, is that a quality system addresses the public and private sectors' mutual goals of providing high-quality drug products to patients and prescribers.

A well-built, quality system should prevent -- adn that is the big word here, "prevent" -- prvent or reduce the number of recalls, returned or salvaged products, and defective products from entering the marketplace.

This has to do, of course, with patient

outcomes and the idea of preventing quality issues up front. So, we don't have to worry so much in terms of surviellance, although, clearly, surveillance is absolutely necessary.

(Slide.)

MS. MALARKEY: I think it's fair to say that the ultimate goal is consistent between FDA and the regulated industry. It's a good place to start.

(Slide.)

MS. MALARKEY: For your information, if you are interested, we did issue a draft guidance under the inititiave in September of 2004, that talks about quality systems approaches to pharmaceutical current manufacturing practice regulations.

This is really a high-level document, and it speaks to what are the most robust quality systems all about, and the importance of sucy systems.

I'll be perfectly honest with you: Our regulations aren't as explicit. They are much broader and provide flexibility for manufactures to put into place, their quality control or quality assurance functions.

But this is really more of a conceptual, the way we would like to see industry going.

(Slide.)

MS. MALARKEY: Basic quality system principles -- again, prevention, preventing quality defects before they occur. This what this all about, detecting prodcut quality defects before distribution, and also detecting trends, if you will, reallly looking at relevant data, and I'll speak to that in a moment.

Here is where I do want to inject an issue. Manufacturers need reportrs of adverse events and reactions. They need to hear from the medical community. That's how they know what's going on out there, too, and that's how they can adjust their manufacturing process or what they're doing, to ensure that they're building more quality in.

I don't want to lose that link; that is very important for them to receive the information, and, actually, that's what they're required to report to us at teh FDA, correct manufacturing systems to prevent recurrrence, and also to prevent occurrence,

if trends are indentified, adn to take appropriate action, if defective products are distributed.

Those are really the points of a robust quality system, and, I think, most importantly, we're talknig about being proactive, rather than reactive. Often, we are reactive. Industry is, and we can be, as well.

I think we'd all like to see ourselves in a more proactive stance, preventing problems.

(Slide.)

MS. MALARKEY: In terms of prevention, this is really an agglomeration. We have a number of regulations that govern our products.

Sometimes there's a combination of regulations that govern our products, but these are kind of an initial list. Certainly robust donor screening and testing, is a huge preventive measure.

Process control: The validation of the manufacturing process, the systems that are used in the facility, the assays or tests that are run on a product before the proceesing is final; qualification of equipment, to ensure consistency of manufacturing,

and design controls, where you design quality into the product in the early stages.

Personnel is probably one of the biggeset areas that we have problems in, quite honestly. Human error: While we are seeing more and more automated systems, certainly personnnel are an integral part of any manufacturing process.

The fact that they are adequately trained and educated, is essential, but I think the second point, the fact that they're engaged and empowered, is something we have found in successful organizations in our industry.

By that, I mean, rather than just being taught what to do and where to do it and how to do it, they're being taught why they're doing it, and really understand what they're doing, and there is mangement empowering them to bring things to management's attention that go wrong.

Procedures should be, of course, established and followed; recordkeeping practices should be in place, that is, accurate records, and then management is always key. Management really

drives the culture of the operation.

So, the fact that they are actively concerned about providing needed resources to ensure compliance, this could be apllied anywhere. It's not just FDA-regulated product; it could apply to any industry or any operation.

(Slide.)

MS. MALARKEY: Dection -- here is where the adverse event reports and the deviation reports come into play. Certainly, some things, incoming materials, testing and sampling, whatever you accept for whatever use, is okay; in-procss controls of the manufacturing process, is another detection mechanism; where appropriate, monitoring of environmental conditions.

While it may not be an issue in the blood industry, certainly when you're talking about vaccines, it certainly is. It will depend, again, on the product.

Regular review and trending of all relevant data to detect negative trends, that's really the big issue here. That is why manufacturers

do need these reports.

Then, performance of audits: It's always a good idea to audit yourself, but also performing external audits of suppliers, for exmaple, all of these things are good detection mechanisms that should be deployed in the industry.

(Slide.)

MS. MALARKEY: We're talking about relevant data, and there's a lot of it out there. There's deviations, failures, and nonconformances that happen during production and can be investigated during production, as well as those reported after distribution.

Then there's in-process and final product data; of course, environmental data; product complaints; adverse event reports; reportable deviations; product recalls; the audit and inspection findings, that is, FDA and inspectional findings from other regulatory authoriteis; and, finally, personnel proficiency testing results.

All of these things are relevant data that we want to be reviewing on a regular basis, and

adjusting accordingly.

(Slide.)

MS. MALARKEY: Finally, correction: Of course, investigating deviations prior to distribution, ideally, of the product; investigating all product complaints, including review of manufacturing records; investigating all fatalities, obviuosly, and unexpected adverse events.

In the drug world, there are, of course, labeled adverse events; site reactions, injection site reactions. That's not uncommon, but it's certainly one that one periodically needs to look at, all those reports of adverse events, and put them together.

Implementing corrective actions, as appropriate, to prevent recurrence, and, in the case of an identified trend, to prevent occurrence of a problem, and, finally, assessing the effectiveness of teh corrective action.

(Slide.)

MS. MALARKEY: In terms of reporting to FDA, which is the biovigilance part of this,

manufacturers are required to report deviations in manufacture and unexpected or unforeseen events that are discovered after the product is distributed.

Obviously, our preference is that this doesn't happen, and, if it does happen, we can expect a throuogh investigation as to why it happened, that is, including how it was missed and how it was missed with this information onhand.

Sometimes these may result in a recall. A small percentage of them do.

(Slide.)

MS. MALARKEY: There is also, of course, reporting blood recipient or donor fatalities that is required under our regulations. For many of our products, there's adverse event or reaction, medical device reporting, as required by our regulations for certain types of these events, as well as periodic reporting of all adverse events; reporting deviations and unexpected or unforeseen events, and then notifying us if there is prodcut recall.

(Slide.)

MS. MALARKEY: There are a couple of other

things, just to mention, that are in place to try to prevent medication errors that are in our control at FDA. That is the labeling.

We certainaly review labeling for many of our products, and we require -- or the regulations require that we provide the information to the end user the manufacturer provides the directions to the end user and the circular of information is usually a term of art.

We have the recent addition of the bar code label requirements to the regulations, that should apply to the biological drug products, as well.

(Slide.)

MS. MALARKEY: Other activities we do -- and this is exclusive to the biological world -- we look at proprietary names, that is, the tradenames or trademarks that one has on the product. Here, we're trying to prevent potential mixups. If the name is very similar to other products that are on the market, and has the same dosage and may be used in the same clinical setting, for example, it varies.

When we identify these, we work with the industry to try to suggest other ways of dealing with this, because tradenames and trademarks are patented. The industry is very interested in identifying the product.

(Slide.)

MS. MALARKEY: Just a final thought: Henry Ford had a thought about a company he founded way back --

(Laughter.)

MS. MALARKEY: And quality does really mean doing it right when no one is looking. That's what we ought to be looking for.

DR. BRACEY: Thank you. Questionsn for Ms. Marlarkey from the Committee?

(No response.)

DR. BRACEY: Thank you. In the interest of time, we'll go ahead with one more presentation this morning, and then we'll break for lunch. I know we're all probably famished, but Dr. Sherman is an internist and clinical pathologist and Professor Emeritus from Northwestern Medical College in

Chicago, and a very active AABB past President. He's also on the Council of American Patahologists.

He's currently an assessor with the Joint Commission for Accreditation of Healthcare Organizartions. Dr. Sherman?

(Slide.)

DR. SHERMAN: Thank you. I was not orginally scheduled to do this presentation. As indicated, although retired, I intermittantly work for the Joint Commission.

I should say, as far as a disclaimer, although I still have some activities at Northwestern, I'm on the Board of the Chicago Consortium for Transplantation Ethics. What I'm having to say today, doesn't bear their impramatur.

What the Joint Commission wanted me to -- and they asked me last week to sit in for Marvin Peck -- was to, one, cover some aspects of what the Joint Commission's role is, vis a vis accreditation, since it may not be familiar to some of the people on the Committee; then focus and continue the relationship to blood and tissue, and also organ transplantation,

to a degree.

I'll try to go quickly through some of this background.

(Slide.)

DR. SHERMAN: This was started in the early 20th Century, when the American College of Surgeons, to improve quality in hospitals in the mid-20th Century, assumed a board and structure similar to the ACS, the American College of Physicians, the American Medical Association, the American Dental Association, and the AHA.

It also has an affiliated educational arm.

(Slide.)

DR. SHERMAN: In the '50s, it began more extensive accreditation of hospitals for a fee, and was known as JCAH. Subsequently, it has added other healthcare areas.

About 17,000 healthcare organizations are now accredited, and the name has been changed to recognize this.

(Slide.)

DR. SHERMAN: Some of the other

categories, which don't involved blood, tissued, or organs, except in critical-access hospitals, are listed here.

(Slide.)

DR. SHERMAN: For what this group is interested in, there are 4,700 hospitals and 3,300 laboratories that are accredited, and, for both of these groups, deemed status agreements yield either Medicare or CLIA approval, respectively.

(Slide.)

DR. SHERMAN: When the organization is joint-mission accredited, the accreditation system involves onsite review, either every three years, for hospitals, et cetera, or two, for labs, and the teams, depending on the organization, will have docts, RNs, MTs, administrators, et cetera.

The survey is designed to be both accreditation and, hopefully, an edcuational process, and those of you involved with other kinds of accreditation systems, are aware that sometimes education may get second shrift.

There's a published group of standards

similar to FDA, et cetera, and with other systems, the deficiencies are divided and are measured with required changes and supplementals, a computer-based scoring system, and a post-survey accreditation with correction of major deficiencies, is a private, interactive dialogue between the institution and hte Joint Commission, which has abandoned a numeric scoring system.

(Slide.)

DR. SHERMAN: There are ongoing newsletters, et cetera, standard intepretations. There's now intra-cycle reviews, additionally.

There are onsite reviews for cause, for what I call serious mal-events. This would include transfusion deaths, transfusion-related testing errors, transplant mishaps, et cetera.

These occur in Joint Commission-accredited hospitals, regardless of whether or not the lab happens to be Joint Commission-accredited. If it's another agency group that's accredited to the laboratory, this is generally done in conjuction to the other organizations, such as, for example, the

CAP.

Just as a personal comment here, on having been involved in some of these and also meeting with the newspapers, et certera, one of the things that stands out, are issues relating to communication, rather than technical errors or the like. I'll come back to this partiuclar point.

(Slide.)

DR. SHERMAN: In general, Joint Commission institutions don't collect blood. For those that do, there are applicable standards.

From a volume standpoint, the chief Joint Commission focus is on the laboratory and transfusioin processes. Because the Joint Commission's purview is the entire institution, it can and does look at entire systems and departments, including the medical staff involvement in blood utilization.

This latter, again, for a personal comment, I think this is a difficult area on accreditation. From the standpoint of having good benchmarks out there on blood utilization, when you

say to a hospital transfusion committee, you are not reading benchmarks that are widely available, that are published by various professional associations, such as the ACS, et cetera. If they are available, the benchmarks are available, it's then possible to focus then on the medical staff.

Blood utilization is one of those areas where there isn't sufficient information, from my standpoint.

The Joint Commission's standards for institutions doing tissue transplantation, is this year developing requirements for those doing organ transplants.

A comment about tissue transplantation: On adverse events, I think there were several different things that are problems in data gathering. One is that the great majority of adverse events in tissue transplants, occur post-discharge from the hospital.

Secondly, the definition of what is an adverse event, is variable. I think that if you look at the package inserts for bone grafts and the like

for different suppliers to hospitals, htey differ greatly in what they're describing as an adverse event, if they describe them in detail at all.

Lastly, from a reporting standpoint, in general, what's required, based on the package insert, is to report it to the supplier, rather than developing anything going through alternative products.

(Slide.)

DR. SHERMAN: I'm not going to go into some broader things that relate to biovigilance, just to say that as related to blood, the Joint Commission has broad requirements about hazard vulnerabilities, in a prospective way; participation in drills; looking at blood refrigerators on emergency generators; gnerators on a high floor, if you live in Houston or New Orleans, et cetera.

I direct you to Dr. Price, who has experience in this regard, and also the requirement of reporting biological agents to state and federal agencies, et cetera. Again, that would apply across the board.

(Slide.)

DR. SHERMAN: On some of the Joint Commission's quality foci, they're broader, compared with those readily avaialble external benchmarks such as how long until specific intervention, from when the patient gets to the ER; the percentage of patients having a heart attack; the percent of patients having cultures before antibiotics; institutions that have individualized events, which could include tranfusion medicine, so this rarely occurs.

(Slide.)

DR. SHERMAN: Sentinel events were mentioned by another speaker. These are institution-associated deaths or permanent injury. From the start, they have included transfusion fatalities, and they are reported to the Joint Commission and analyzed for systemic flaws.

In addition to their being reported to the Joint Commission, they are picked up, if you will, from newspaper reports and other kinds of things, maybe to the kind of onsite reviews that I mentioned

a few minutes ago.

The instiutions are required to have root-cause policies, and to do analysis of sentinel and related events. Periodically, based on sentinent events and other kinds of reporting, there are periodic newsletters to institutiosn about particularly dangerous areas and suggestions for change.

There was one of these related to transfusion deaths, several years ago, and, also for years, blood transfusion ahs been explicitly listed as a required area for quality monitoring by hospitals and their staffs.

These are regularly looked at, as well as observation of actual transfusions during the course of hospital and lab surveys.

I mentioned already, the problem with data on blood utilization.

(Slide.)

There's an annual conference on quality in patient safety. The commission recently started an international center on patient safety and has a journal in this regard. The last few years, they have developed national patient safety goals.

(Slide.)

What these are are accredited organizations are required to implement certain policies or goals designed to improve patient safety. New goals are laid down every year and the old ones are retained as such or incorporated into standards.

(Slide.)

Some that are particularly germane to blood -- there's a requirement of two identifiers not including a room number or the OR number on a patient before blood administration, blood sampling, medication, et cetera. A standardization of communications when there is a change in caregivers, whether shift to shift, unit to unit or on the road to recovery, et cetera, verbal order and result readback measuring critical result reporting

including intra- and extra-laboratory aspects such as timeliness and completeness and up to notification of primary licensed caregiver.

Laboratories get a good handle in this regard. Most laboratory IS is information and once samples hit the lab and -- when the primary caregiver has not got the information, that's often difficult to track. I think this is one of the more difficult things people are having trouble with these days and hopefully will be improved. However, the standard requires not only that you do it, but that you improve. There are some hospitals where blood orders are critical items and it's a way of looking at this issue and how consistently they perform.

(Slide.)

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And I think the FDA, which has been doing unannounced for decades I guess, would probably agree that unannounced surveys or inspections or the like certainly has a way of keeping people on their toes, if you will.

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Additionally, the survey method of following an individual patient through their hospital stay, the so called tracer, places more emphasis on the systems of communications and additionally on line staff interviews. I'll come back on an aspect of line staff at the very end. There are now mid-cycle accreditation reviews wherein

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they did indeed do it.

My point is that even electronic information systems can be subverted and it's the task of institutional validation to be sure they cannot be subverted. I'm emphasizing that, one, because of this example. Two, I've seen IS systems in hospitals where this was a possibility based on the way the systems were designed and also from conversations I've had with software consultants as far as the way HIS systems are actually implemented.

Thank you.

DR. BRACEY: Thank you, Dr. Sherman. One of my observations working in a hospital environment is that, a, the nursing arm of the hospital is a very strong arm these days and, b --

DR. SHERMAN: On steroids.

DR. BRACEY: -- and b, that they aren't as focused intently on JCAHO initiatives. I guess what I'm trying to get around to is something that Dr. Katz mentioned, the magnitude to us -- transfusion errors are of great magnitude. They're very important.

Would you think that among many things that JCAHO sees now that it would view transfusion problems, errors, et cetera, as a problem warranting something along the lines of PE management of patients, falls, things of that nature? Do your initiatives that you put out to the hospitals follow point to point?

DR. SHERMAN: One of the issues or problems the Joint Commission has, and I think it's reflected in the standards, is certain systems or organizational structures can't fit all different sized hospitals and hospitals of varying kinds of complexity of focus. However, what I've seen increasingly is that hospitals take certain areas and combine them -- in other words, infection control is really part of a quality assurance structure and starts to move things like transfusion and those kinds of issues into that area as well. I think there's a lot to be said for that sort of approach, whatever size institution there is.

DR. BRACEY: Thank you.

Dr. Ramsey?

DR. RAMSEY: Does the Joint Commission have information on the trends or problems that have emphasized their assessments? In other words, for example, is there information available on whether the rate of problems goes down?

DR. SHERMAN: I couldn't catch the last part of what you said.

DR. RAMSEY: For example, on patient safety goals, if you take a patient safety goal, is there information on whether there's a trend for improvement of that citation for example in subsequent inspections across the country?

DR. SHERMAN: Yes, actually they publish annually in what I call perspectives. They look at the compliance rate for the safety goals and it's broken out by whether it's long-term care in a hospital laboratory, et cetera. That data is out there. And again, in general, it's been improving. It's not -- well, one would like to say it's 100 percent safe for things like two patient identifiers and like that.

I might add, a moderate amount of the data

the Joint Commission has on two patient identifiers is not just what institution the internal audits are, but just watching what people do when they're going into a patient room, which is part of the issue, the follow-up issue with the patient.

DR. BRACEY: Dr. Kuehnert?

DR. KUEHNERT: I had a comment and a question. The comment is I appreciate your observation about tissues, that there's no standard adverse event definition. I just wanted to point out that the American association of tissue banks at their annual meeting next month in San Diego is going to try to come up with adverse events definitions.

For those that are tissue banks, that will be helpful when they try and standardize that. For those that aren't members, of course, that won't help things. We'll have to think of some more creative solutions for that.

My question was just about the Joint Commission process. Let's use tissue as an example. I wondered, the standards are often somewhat vague about exactly how to do things. Like it'll say you

need to do this, you need to do A, B and C, but it won't tell you you need to do it this way. I understand that's because there's multiple possible solutions to how to do things. But how do you handle when you do an inspection and the hospital seems to have no concept on how to do something, do you suggest to them what the possible solutions are? Particularly I'm talking about when you put in a new standard, how do you guide hospitals to figure out a solution?

DR. SHERMAN: One, on a new standard in general, there is an attempt to, through the account representative at the Joint Commission for hospitals, to take the fresh queries on possibilities. Secondly, onsite, again when there's a problem -- and as you said, the hospital may not have a clue. Whoever is doing the survey will try to give them possibilities.

For example, in the tissue arena, the easy comparison is with the kind of two way traceability that one has in the blood arena -- in other words, that you can track from a patient with the right

adverse event to the supplier and, conversely, the supplier says XYZ lot or the unit number, you can track to the patient. That kind of information, whether you do it in a paper log or whether you do it in software, it depends on how you want to do it. But you want to be able to insist that you do it.

There are varieties of other kinds of suggestions. There's a nurse surveyor I know, who views herself as a bumble bee.

She carries pollen from place to place, and drops ideas. Whether they take or not, is up to the institution, but, ultimately, the institution has to show in its followup, that it, a) has made corrections, and, has made corrections that are rationale.

DR. KUEHNERT: Just as a followup, the pollen that's disseminated, is there any way -- that seems to be sort of a personal communication. Is that posted anywhere, some of these solutions?

DR. SHERMAN: Some of them are posted in what are called FAQs on the Joint Commission website. There are also newsletters and individual programs, accreditation categories, and, in addition, as I said, for specifics, going through their representative at the Joint Commission, they raise questions that can be dealt with, if they are having trouble, particularly meeting something that's a new standard, a new requirement.

DR. BRACEY: Dr. Epstein?

DR. EPSTEIN: Thank you, Larry. It was a very illuminating presentation. Hearing your presentation and the antecedent presentations from Mary Malarkey, I'm struck by the fact that there is a lot of similarity, in that FDA is focused on quality systems for products, and you seem to be focused on quality systems for practices.

That kind of raises a question, ultimately, for the Committee, about how much integration is needed and is desirable in what would appear, just at a superficial level, to be parallel systems in independent domains, which are really sharing common principles.

The principles seem to be very highly applied in what the JCAHO does. That's the remark.

My question to you, is about your comment about the fact that JCAHO works towards systems of confidential reporting of malevents to nongovernmental quality organizations.

Do you include an audit from JCAHO under that rubric? Secondly, what is your general comment

on why it's important that such nongovernmental reporting should be done? After all, governments are highly capable of confidentiality.

They are very well positioned to integrate large amounts of data. They operate -- if you have a conflict of interest, a public health interest, where does that particular sentiment come from?

What do you think are the pros and cons of government involvement in malevent reporting? I ask that question, principally because it's one of the chief questions at the end for this Committee, about the federal role in all of this.

DR. SHERMAN: Frankly, I am not sure. My impression -- and I'm saying it's an impression -- on initial discussions a number of years ago when I was at Northwestern, when I was the General Counsel at the Joint Commission, is that this was thought to be the most practical way.

And I don't know whether the Board or the Joint Commission felt this, but let me just make -- I mean, let me just stress one other thing.

What I'm talking about in common issue

reporting, what I'm talking about, is obviously not that a bad event should be thought of as being protected from the public, if you will, or from any liability complaint; the issue is primarily related to the analyses and elucidation of what seems to be the cause.

But I would ask Hal and the General Counsel's Office, to get in touch with the Committee specifically on this aspect. I would not want to state the Joint Commission's opinion.

DR. BRACEY: Thank you. Ms. Lipton?

MS. LIPTON: Just having sat on a committee where we were looking at these issues -- and there was a significant JCAHO representation -- I think the concern in a lot of the organizations, is why should it be nongovernmental? It's really the advent of a legal aspect to a lot of this information. That was really the driving force.

I think that's been one of the problems in collecting data, and any communication system has the same problem. I think now that the legislation, if we take the organization legislation, it will offer

some legal protection to nongovernmental organizations, although I'd have to ask my colleague, does that apply to nongovernmental ESOs?

She's not sure, either, but, in any event --

MS. WEIGMAN: I think so, and then they share the information.

MS. LIPTON: Thank you. The problem is the that the situation, historically, has been that the information really can't be protected. I mean, you can protect it from the employer, but you really can't protect it from the legal.

I don't know whether that's true anymore.

The second issue that I heard, that resonated with a lot of the professional organizations, was the issue of not giving something to the enforcement agency, that there was great concern that people, if they thought there was going to be any kind of punitive aspect attached to this, would not be as forthcoming.

DR. SHERMAN: There's also been an issue in this regard, that's been more complicated, vis a

vis public hospitals, wherein they have an additional potential access to freedom of information, and they're being concerned with reporting that may be a loop coming back, one way or another.

DR. BRACEY: One thing that comes to mind, is one of the Secretary's strategic points, which is to eliminate unnecessary liability issues. It's not stated exactly that way, but, clearly, this is something we need to think through, because having the aggregated data, is really the goal, and we have sort of data that's existing in two pots.

How do you handle that at FDA?

DR. KUEHNERT: Theresa is here, and maybe will be able to explain this a little better. All I can say is, there's an exemption for FOIA under the surveillance. That exists.

Maybe she could briefly describe how -- well, just basically, could that be then applied to an individual and system.

MS. HORAN: Teresa Horan from CDC, from the National Monitoring Safety Network. What Matt is talking about, is that system and the three systems

integrated into it.

That's called an assurance of confidentiality under the Public Health Service law, and what it allows us to do, is to keep the institution information confidential, as well as the patient information confidential, so there's no disincentive for the institution in reporting their data to CDC, because CDC has not regulatory authority and is not subject -- when we have received a Freedom of Information Act request for information, we can deny those.

MS. LIPTON: I don't think the issue that has been the prime stumbling block, is FOIA; the issue has been the legal system. I don't think that has been developed.

MS. HORAN: As far as I've been told by our General Counsel, they are not available for subpoena under this protection.

DR. BRACEY: With that, we're close to the lunch hour. Unless there's a burning comment or question, we'll continue in one hour's time. That would be about 2:00.

(Whereupon, at 1:00 p.m., the meeting was recessed for luncheon, to be reconvened this same day at 2:00 p.m.)

AFTERNOON SESSION

(2:05 p.m.)

DR. HOLMBERG: May I please have the Committee members come to the table?

DR. BRACEY: Good afternoon. In the interest of time, I'd like to go ahead and start the afternoon session, even though we went into the afternoon in the first session.

The first speaker for this afternoon, is Robert Pinner. He will speak to us on characteristics of surveillance.

Dr. Pinner is the Acting Director of the Coordinating Center for Infectious Diseases at the CDC. Dr. Pinner, thanks for coming.

DR. PINNER: Thank you, and good afternoon.

(Slide.)

DR. PINNER: When Jerry Holmberg and Matt Kuehnert asked me to talk in general about public health surveillance to this Advisory Group, I collected some information from Matt and others, and quickly figured out that lots and lots of good

thinking and accomplishment has gone into issues around what you're calling biovigilance now, and is called surveillance and other things.

(Slide.)

DR. PINNER: Not only that, many of you are the authors of the documents that we're going to look at. It became clear to me that it would be daunting and presumptuous to try to assimilate this information, then use it to critique or recommend specifically about biovigilance in blood safety.

But when I did think that I spotted some general themes that come up in your discussions, and have already come up this morning, I'll draw from examples that I know about, hoping they'll provide some useful perspectives to you in your deliberations.

(Slide.)

DR. PINNER: Here are some of the general themes that I picked up on: One, the general issue of authorities, incentives; the specter of punishment, and what making it reportable, so-called, either does or doesn't accomplish.

Sometimes it's useful, but, all by itself, it doesn't mean that you get the information that you're after. I've been very interested to hear and think about the relationship between quality assurance on production and distribution processes, on the one hand, and surveillance for health events, on the other.

It's been useful for me to think of them as related, but not the same thing. Obviously, informatics in using evolving standards and technology, is critically important, but also provides the risk of being lured into the technology and sort of getting stuck in garbage-in/garbage-out scenarios, so that's a theme here.

Then, lastly, there is the issue of framing the questions, deciding what it is you want to count and why, and then think about how to approach it.

The conversation on influenza preparedness was interesting this morning. For folks who are uncomfortable putting up a slide that preparedness equals waste, it's certainly something to think of, I

suppose, returns on investment for different levels of preparedness.

The way that plays out in surveillance, is deciding what events do you want to count? Everything? Severe? Mild and severe? What's the range of things that we need to count?

What's the detail, the level of detail, about each case? There's a cost to additional detail, and how will you use it? What are the tradeoffs of that additional information, and also the general framework, how active a surveillance do we need to enter into?

Will passive surveillance approaches get you the answer that you need, and how will you know if they do or not?

Let me draw on a few examples, then, to look at this:

(Slide.)

DR. PINNER: A couple of basic level-settings, no surprise here in the definitions. Public health surveillance is an ongoing, systematic collection that uses feedback.

(Slide.)

DR. PINNER: There are several different purposes and not one size fits all. Therefore, detecting or responding to outbreaks, or following the burden of disease and trends, and, particularly for evaluating interventions --

(Slide.)

DR. PINNER: Lots of sources, as well -- providers, laboratories, vital statistics and the like; the promise of new information systems, is the key to making information more powerful, but also the concept of ranking the different sources of information.

(Slide.)

DR. PINNER: Back to some first principles, this is the Preamble to the Constitution. In the middle is, "promoting the general welfare," and so that establishes, I guess, the federal interest in public health.

(Slide.)

DR. PINNER: In the Bill of Rights, the power is not delegated or reserved to the states,

respectively, or to the people.

These two features of the Constitution in public health surveillance, play out in substantial local- and state-level authorities and responsibilities for public health surveillance, in a general way, and, in particular.

(Slide.)

DR. PINNER: Here's a couple of examples from notifiable diseases surveillance in the United States, that show different aspects of case definitions and how you count what you count.

(Slide.)

DR. PINNER: This first one is in 1993. The surveillance case definition for AIDS changed. Obviously, nothing different occurred in the natural history of the disease, and unless you were paying attention to what was going on, it may have looked like a big jump in incidence, but, of course, it jumped from the change in definition.

(Slide.)

DR. PINNER: Here's an example of the surveillance of viral hepatitis. The example here,

of course, is how evolving technologies, in this case, lab tests, changed how you perceive what's going on with the syndrome or entity, and how you characterize it, from a single line for viral hepatitis, although it was pretty strongly suspected that there was more than one kind, even in the '50s.

But then tests in the mid- and late '60s, showed the distinction between A, B, and C, subsequently. This kind of thing also happened at the same time with surveillance for jaundice.

There was a curve for virus-specific surveillance.

(Slide.)

DR. PINNER: This is an example or reportable diseases for poliomyelitis in the United States, from 1950 to the end of the century. The case definition of polio, per se, is acute flaccid paralysis.

The point I wanted to make here, is that when there's a lot of polio in the 1950s and thereabouts, the case definition that uses the syndrome of acute flaccid paralysis, has a very high

predictive value, positive, in fact, for a case of polio.

As the incidence of polio declined, the predictive value of that case definition goes down further and further. Then at very low levels, it became important to get viral confirmation to establish whether, in fact, a case of paralysis wasn't really a case of polio.

Then, near zero levels, it becomes important, not only to get viral confirmation, but to learn whether this is viral type or vaccine transmitted disease.

(Slide.)

DR. PINNER: Here are a couple of examples from a collaborative effort that CDC and 11 state health departments and their collaborators are involved with, the emerging infections programs.

(Slide.)

DR. PINNER: The collaborators are local health departments and academic institutions, and, in many of the states, the infection control professionals in those states. Active survey

elements were applied, applied research and some highlighting of prevention.

(Slide.)

DR. PINNER: ABCs refers to the term, active bacterial core. This was a method for surveillance to be placed for invasive pneumococcal disease.

There is case ascertainment, strep pneumonia values in normal sterile blood or spinal fluid, and case report information and the isolate itself.

(Slide.)

DR. PINNER: This is an example of how powerful this kind of integration and surveillance can be, albeit, expense and labor-intensive.

(Slide.)

There's an annual conference on quality in patient safety. The commission recently started an international center on patient safety and has a journal in this regard.

The last few years, they have developed national patient safety goals.

(Slide.)

What these are are accredited organizations are required to implement certain policies or goals designed to improve patient safety. New goals are laid down every year and the old ones are retained as such or incorporated into standards.

(Slide.)

Some that are particularly germane to blood, there's a requirement of two identifiers, not including room number or the OR number on a patient before blood administration, blood sampling, medication, et cetera. A standardization of communications, when there is a change in caregivers, whether shift to shift, unit to unit or on the road to recovery, et cetera, verbal order and result

readback measuring critical result reporting including intra- and extra-laboratory aspects, such as timeliness and completeness and up to notification of primary licensed caregiver.

Laboratories get a good handle in this regard. Most laboratory IS is information. Once samples hit the lab, and when the primary caregiver has not got the information, that's often difficult to track. I think this is one of the more difficult things people are having trouble with these days and hopefully will be improved. However, the standard requires not only that you do it, but that you improve. There are some hospitals where blood orders are critical items and it's a way of looking at this issue and how consistently they perform.

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blood bank. It would print the labels at the bedside, then you'd be able to indicate in the computer, this little handheld, that the samples had been drawn. And this was done with a light pen that was attached to the handheld.

We thought this was a great device, we wanted to adopt it for blood administration itself at Children's Hospital. However, about a month later somebody who was on the team and went down there and was hospitalized and was just out of the hospital and discovered that the nurse assistants who were drawing blood did the phlebotomies on the floor and weren't using the light pen.

They had discovered a way to get around the process entirely and to do all the stuff with the handheld on multiple patients at the nursing stations. So if they had to draw four patients, they could label from the computer, the handheld, all four sets of twos at one time in advance and didn't have to even look at the wristband when they went into the patient's room. If you're thoughtful, you may be able to figure out how they were able to do it, but

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Thank you.

DR. BRACEY: Thank you Dr. Sherman.

One of my observations in a hospital environment is that, a, the nursing arm of the hospital is a very strong arm these days, and, b --

DR. SHERMAN: On steroids.

DR. BRACEY: And b, that they aren't as focused intently on JCAHO initiatives.

I guess what I'm trying to get around to is something that Dr. Katz mentioned. The magnitude to us -- transfusion errors are of great magnitude. They're very important.

Would you think that among many things that JCAHO sees now that it would view transfusion problems, errors, et cetera, as a problem warranting something along the lines of PE management of patients, falls, things of that nature? Do the initiatives that you put out to the hospitals follow point to point?

DR. SHERMAN: One of the issues or problems the joint commission has, and I think it's reflected in the standards, is certain systems or organizational structures can't fit all different sized hospitals and hospitals of varying kinds of complexity, of focus.

However, what I've seen increasingly is that hospitals take certain areas and combine them. In other words, infection control is really part of a quality assurance structure and starts to move things like transfusion and those kinds of issues into that area as well. I think there's a lot to be said for that sort of approach, whatever size institution there is.

DR. BRACEY: Thank you.

Dr. Ramsey?

DR. RAMSEY: Does the joint commission have information on the trends or problems that have emphasized their assessments? In other words, for example, is there information available on whether the rate of problems goes down?

DR. SHERMAN: I couldn't catch the last part of what you said.

DR. RAMSEY: For example, on patient safety goals, if you take a patient safety goal, is there information on whether there's a trend for improvement of that citation, for example, in subsequent inspections across the country?

DR. SHERMAN: Yes, actually they publish annually in what I call perspectives. They look at the compliance rate for the safety goals and it's broken out by whether it's long-term care in a hospital laboratory, et cetera. That data is out there -- and again in general it's been improving. It's not -- well, one would like to say it's 100 percent safe for things like two patient identifiers and like that.

And I might add a moderate amount of the data the joint commission has on two patient identifiers is not just what institution the internal audits are but just watching what people do when they're going to a patient room, which is part of the follow-up issue with the patient.

DR. BRACEY: Dr. Kuehnert?

DR. KUEHNERT: I had a comment and a question. The comment is I appreciate your observation about tissues, that there's no standard adverse event definition. I just wanted to point out that the American Association of Tissue Banks at their annual meeting next month in San Diego is going to try to come up with adverse events definitions. For those that are tissue banks, that will be helpful when they try and standardize that. For those that aren't members, of course, that won't help things. We'll have to think of some more creative solutions for that.

My question was just about the joint commission process. Let's use tissue as an example. I wondered, the standards are often somewhat vague

about exactly how to do things -- like it'll say you need to do this, you need to do A, B and C, but it won't tell you you need to do it this way. I understand that's because there's multiple possible solutions to how to do things, but how do you handle when you do an inspection and the hospital seems to have no concept on how to do something, do you suggest to them what the possible solutions are? Particularly I'm talking about when you put in a new standard, how do you guide hospitals to figure out a solution?

DR. SHERMAN: One, on a new standard in general, there is at attempt to, through the account representative at the joint commission for hospitals to take fresh queries on possibilities.

Secondly, on site, again when there's a problem -- and as you said, the hospital may not have a clue. Whoever is doing the survey will try to give them possibilities. For example, in the tissue arena, the easy comparison is with the kind of two-way traceability that one has in the blood arena. In other words, that you can track from a patient with

the right adverse event to the supplier, and conversely the supplier says XYZ lot or the unit number you can track to the patient. That kind of information, whether you do it in a paper log or whether you do it in software. It depends on how you want to do it. But you want to be able to insist that you do it.

(Slide.)

This example of public health surveillance is public health surveillance and the use of standard laboratory protocols connected to EPI information and molecular -- it's called Pulsenet.

(Slide.)

It's the national network of CDC and partners, which does two things: One, it involves standardized laboratory protocols for subtyping a set of organs. Then it uses strong information technology to share information and compare laboratories.

(Slide.)

They're trying with this to identify clusters to implicate causes of outbreaks.

(Slide.)

This is a little bit about the distribution of the labs that signed on to the common protocols and are part of the information system.

(Slide.)

Quickly, two quick examples of how this kind of information is used. This is a cluster of E. coli 157H7 that came out in North Carolina a couple of years ago.

(Slide.)

In the Pulsenet bank you can see in the outline those common patterns associated with that cluster. So this is a case report with molecular subtyping and a standard way to get a handle on what's going on without risk.

(Slide.)

In this other example, this is listeriosis, which is interesting because of -- well, for several reasons. One is it's because it's rare and because of food distribution patterns. Here's an example of Pulsenet.

(Slide.)

Taking a look at human islets and comparing them to the suspected sandwich, which had a totally different pattern, so it wasn't the guilty party. But this kind of technique has proven useful in a number of publications.

(Slide.)

So public health surveillance of the future and also lots of laboratory methods and molecular and epidemiologic methods, as well as reportable cases.

(Slide.)

Lots of attention has been given in the past few years since 9/11, since the anthrax events just after that, thinking about how to establish or set up surveillance to detect outbreaks. Here are a few general considerations.

(Slide.)

Obvious but pretty important, this is the idea of the last few years. Lots of the surveillance that we have historically done has been at the point of diagnosis at the site. The idea is that if you could do surveillance say at the time of syndrome

onset or even earlier, at the time of exposure to organisms say after -- that you could have more time and be more effective in your response.

The problem, of course, is that it's very hard. The further to the left you move in this time arrow, the less specific your signals are likely to be. So it's very hard to figure out how to optimize the promise of surveillance to detect things earlier with the practical challenges that that poses.

(Slide.)

One of which is this sort of obvious phenomenon, which is that if you think of trying to set a threshold for declaring an event an outbreak or what have you, if you set your threshold too low or follow the squiggly lines, you'll be treated in the way of a response with whatever expense that occurs for just perturbations in the baseline and of wasting resources that way. And getting into the boy who cried wolf syndrome. On the other hand, if you make it so specific and so high, we'd be responding after it was about to go away anyway.

(Slide.)

This last sort of statistics 101 reminder, thinking about surveillance for detecting outbreaks to try to figure out what you can count on even where you have a specificity on the order of whatever 99.99 percent of a positive event, you know. If the incidence is whatever, one per 100,000, that's 10 percent likely to be indicating a real event. So these kinds of trade-offs you keep thinking about between detecting outbreaks or carriers or whatever, these are the practical considerations lots of folks are wrestling with as we try to implement these systems.

(Slide.)

Near the end now, a reminder that for all of the promise of information technology, the examples of detecting outbreaks over the last forever are really filled with examples of skilled and attentive people who found a virus, pulmonary syndrome, anthrax or West Nile, it's obvious that infection control professionals are applying sort of skill-retentive people to the kinds of issues that you are wrestling with.

(Slide.)

Back to the general considerations, it's been useful for me to think of process improvements and health outcome surveillance -- it's organized in your agenda. And to try to think of public health surveillance as the kind of thing that informs decisions about quality improvements for production and distribution, which has an error rate consideration and regulatory considerations in that realm, which is less of a focus per se than public health surveys.

The last two points are to understand, adapt, and take advantage of evolving standards in information technology and to be clear about understanding and framing the questions. Knowing what needs to be counted and why and then go about designing the system.

These last two are obvious, but in practice they play against one another sometimes. There's no issues between those two, in the vision, but there may be in deciding what you need to do today, a need to counter or maybe transfusion-related

bacteremias, you may need to set up a system for that per se.

On the other hand over time as information systems get more competent to link information about bacteremias and transfusions, there may be more of an issue of bacteremia surveillance with information about transfusions or other causes. So I think even though using the technology and being clear about the questions are not contradictory. They make for some difficult decisions.

Thank you.

DR. BRACEY: Thank you, Dr. Pinner.

Questions or comments from the committee?

(No response.)

DR. BRACEY: It's clearly an area we need to gain some more expertise in. Hopefully, we can solve the problems to try to make this somewhat easy.

DR. PINNER: Please let me know when you have that need.

(Laughter.)

DR. BRACEY: Thank you.

Our next speaker will continue on the

theme of hemovigilance. This is the Canadian hemovigilance experience. This is going to be presented by Nancy McCombie from the Public Health Agency of Canada. She's a senior program consultant of the transfusion injury section of the blood safety surveillance and health care professions division of the Public Health Agency of Canada.

MS. MC COMBIE: Thank you.

(Slide.)

Mr. Chairman, members of the committee and participants, I'd like to thank you all very much for inviting us to speak on behalf of the Public Health Agency of Canada and to present our Canadian hemovigilance system at this important forum. We appreciate the opportunity to share our experiences and let you know how we came about this system.

(Slide.)

We are from the blood safety surveillance and healthcare acquired infections division in the Public Health Agency.

(Slide.)

Public Health Agency is a new agency in

the last two years. They have a mission to promote and protect the health of Canadians through leadership, partnership, innovation and action in public health. And of course the vision is health Canadians in communities in a healthier world.

In order for you to understand where we are situated in the public health agency, we have a chief public health officer who reports to a minister of health. The public health agency was actually -- was divided off from Health Canada in 2004. It's part of the public service, but we do report to the chief public health officer. Our center is the center for infectious disease prevention and control.

Underneath of that center is blood safety surveillance and healthcare acquired infections. Underneath broad safety surveillance is transfusion transmitted injuries section, which is the section that has developed the surveillance system which I'm going to talk about today.

(Slide.)

Also, in order for you to understand how this came about, we need to know how our government works. We have the federal government.

(Slide.)

Then in the federal government we have the regulatory arm, which is Health Canada, and the surveillance arm, which is the public health. Then

we have the provincial territorial governments, and within these provincial territorial governments, in almost ever province and territory there is a blood office. That's where the data comes from for our surveillance system.

The federal government has Health Canada, which oversees the manufacture of blood and plasma derivitives. By law, blood and plasma manufacturers must report deaths within 24 hours and serious adverse events within 15 days. So they perform surveillance on the product. They're interested in product safety. The surveillance effort as to transfusions are carried out by the public health agency. We focus more on recipient safety and recipient health.

The blood coordinating officers are in the provicial territorial government because the provinces from the hospitals will also fund the blood manufactures. In order for us to get information from the hospital, we need to go through the provincial territorial government and the blood office.

(Slide.)

In Canada, as I'm sure you're all aware, we only have two blood manufacturers, which makes it quite a bit easier for us than it is for you. We have Canadian Blood services who collect about 850,000 units a year, about 77.8 percent of the units, and HemaQuebec, who collects 22.2 percent of the units.

So it's a little over a million units in a year, which is quite a bit more than in the U.S.

(Slide.)

MS. McCOMBIE: In the transfusion-transmitted injury section, we have three surveillance systems we're working on: The transfusion-transmitted injury system, what we call TTISS, the transfusion error surveillance system, that we call TESS, and our cell tissue, organ, and assisted reproduction surveillance system. I'm not going to discuss that very much today, because it's in its infancy.

The goal is to capture data on moderate and severe adverse events. We do not collect primary adverse events.

This includes the risk of transmission of infectious diseases due to transfusion of blood, blood components, or blood products, which are plasma derivatives and transplantation of cells, tissues, organs, and assisted reproduction.

We also capture data on serious errors, near misses of blood, blood component transfusion.

Then we perform data analysis to determine the risk of blood transfusion.

Of course, this data is also used to monitor the trends and the recommended improvements to practice.

(Slide.)

MS. McCOMBIE: How did this all come about?

(Slide.)

MS. McCOMBIE: Everything in Canada revolves around Kraver. After the Kraver Commission, one of the recommendations in the final report, was to have a surveillance system, a national surveillance system, so there was a working group set up called the Surveillance and Epidemiology of Transfusion Working Group.

They provided a report and recommended the initiation of the Division of Blood Safety Surveillance and Healthcare-Acquired Infections.

In March of 1999, the Federal Authorities requested the ten provinces and three territories to submit proposals for funding each part of this

surveillance system.

(Slide.)

MS. McCOMBIE: From November 1999 to March 2002, we had four provinces who participated in the pilot of the TTISS project. Their mandate was to develop and implement transfusion adverse event reporting in Canada.

Those were the only four provinces, actually, that came forward with a proposal to fund it.

From April 2002 to the present, we've been able to implement the system nationally. Starting in 2004, we had four provinces, again, participating in the pilot for the Transfusion Errors Surveillance System.

We're still in the pilot stage for that project, and we'll be receiving our first data from that group this September. In 2005, there was a submission approved by our Treasury Board, to develop surveillance systems for cells, tissues, and organs.

As you can imagine, we are just in the very beginning stages of that system.

(Slide.)

MS. McCOMBIE: Now, I'm going to talk about the TTISS system and what the materials are that we have. We started with four provinces -- British Columbia, Quebec, Nova Scotia, and PEI, so we had two large provinces and two small ones.

We also had a Health Canada regulator and a the blood manufacturers in the working group. This working group is actually the group that did most of the planning and decided on the definition.

We had a great deal of help from the Quebec system, because they had started a couple of years ahead of us. So, they had actually to agree on certain definitions, and we were able to tap into what they had accomplished.

(Slide.)

MS. McCOMBIE: At the end of the pilot, we had a standardized reporting form, standardized definitions. We have a users manual; we have an agreement on what data elements are exported to the Public Health Agency, which is non-nominal and aggregated.

There is no provincial data reported on the national level, because there are so many small provinces, it could be determined that they may be identified, people may be identified as to who the adverse event was for.

We also have an agreement on the conditions of reporting of national data. When we put out our national report, we have strict guidelines as to what we can report, how we report it, who reviews it.

The TTISS system is used for reporting for Health Canada regulatory. They receive the same forms, and also for the CBS and Hema-Quebec, and these were developed by the Public Health Agency of Canada.

We had an agreement to use the same form for everybody who needs to report.

(Slide.)

MS. McCOMBIE: This shows you a copy of what the form looks like, and one of the screening shots from the database.

(Slide.)

MS. McCOMBIE: The database is developed, maintained, and provided free of charge to the provinces by the Public Health Agency. It started as an MS Access database, but we're moving toward a web-based one with our next version.

We have approval from all provinces to move in that direction. The Provincial Blood Coordinating Offices actually export the data, encrypted, non-nominal data, to the Public Health Agency, quarterly.

The patient privacy issues are dealt with at the provincial level. PHAC does not receive any nominal data. We only get the IDs, and we know what province it came from.

If we need to go back, if we need to go back for additional information, we go by the case number, and we do that at the Public Health Agency level.

The only information we have on the patient, is the month and year of birth.

(Slide.)

MS. McCOMBIE: This just shows you how the

data is used. The hospital, of course, is the first contact.

There is a link between the hospital and the blood suppliers. We also have a link with public health within each province, because of the reportable diseases and the community clinicians within that province.

So the hospital actually reports their data to the Provincial Territorial Blood Offices, and also Public Health. They, in turn, send the selected data elements that we have negotiated, to the Public Health Agency.

As you can see, the blood supplier here, is required to report to the Health Canada regulatory branch, and there is communication between these two groups, the Public Health Agency and Health Canada, and also with the Public Health Agency and the blood supplier.

So, at the hospital level, it's the recognition of the adverse event, collection of the information, and reporting to the province.

Most hospitals in Quebec have transfusion

safety officers, but it varies across the country with disposition. Some provinces have instituted transfusion safety officers; others do not have that position.

At the provincial/territorial level, they're responsible for data validation, completeness, and accuracy, and to do their own analysis at the provincial level. They have the capability to make their own reports, then, of course, it's their responsibility to report to the Public Health Agency, where further validation is done for completeness, and we do reports and feedback to stakeholders.

(Slide.)

MS. McCOMBIE: As of March 31st, 2006, the only province that is not participating at this time, is Alberta, but we expect that they'll be signing their agreement within the next two weeks, so we have nine provinces and two territories participating.

Actually, Nunavut is not participating, but they have such a low level of transfusions, that we're not really concerned about that. In provinces

where there's a small portion of sites that are participating, the sites are usually the largest ones, and represent a high percentage of transfusion activity in these provinces and territories, so we have approximately 70 to 80 percent of blood components transfused in Canada, captured by sites participating in the TTISS.

(Slide.)

MS. McCOMBIE: Of course, we always have working groups to help with these projects. We had a National TTISS Working Group, which comprises all provinces and territories, who are in the project -- the blood manufacturers, CBS, and Hema-Quebec, and the Health Canada Regulatory Branches.

This group will identify issues related to the national surveillance program, to determine the risk of transmission of infections, and they recommend future directions for quality, efficacy, and effectiveness of the TTISS as a national surveillance program.

They hold these meetings three to four times a year. Each province presents their own

recent data, and we discuss unusual cases.

This group deals with all the logistical issues related to this system -- reporting, documents -- meeting the needs of the hospitals, and recommended changes.

(Slide.)

MS. McCOMBIE: And we have a yearly data quality meeting, to which we invite the actual people from the hospitals who are inputting the data, so that we have a representative from every province there, as well as the blood manufacturers and regulatory branches.

At this meeting, we discuss the quality of the data, why some other cases might be excluded, and why they're included. Does it adhere to the definition?

We ask them for comments on changes to the form and the definitions in the manual. It is really to improve the quality of the data.

This probably is one of the most important meetings. It's very productive, and it's very appreciated by the participants, who are the actual

users of the system, and it provides networking opportunities and gives them a feeling of participation and process.

We produced two program reports: One for 2001 and 2002, and one for 2002 to 2003. The data for the 2004 is being validated at this time.

It will contain reconciled data from the Health Canada regulators and the blood manufacturers, so it will be a comprehensive report for all adverse events reported in Canada.

(Slide.)

MS. McCOMBIE: In order for this system to work, the Public Health Agency has certain responsibilities and the provinces have certain ones. Public Health's responsibilities are to provide the funding to the provinces and territories.

We provide communication to the provinces and territories. We organize and we fund the working groups.

We prepare the data agreements, do the national data validation, also fund the data quality meetings. We provide the database, and we

communicate with our expert groups, and we produce annual reports.

(Slide.)

MS. McCOMBIE: So, the provincial and territorial responsibilities are that they must send a proposal in, in order to get the money from the contribution agreement, their deliverables, invoices, cashflow forecasts, and reports for them to put in.

(Slide.)

MS. McCOMBIE: They have a member on the working group, they attend the data quality meetings, they have to agree on the data agreements. They communicate with the hospitals, they are responsible for the training of the transfusion safety officers in the hospital.

They input the data to the database, do validation and analysis, and they export it to the Public Health Agency. They also provide feedback for publication, to their P/T, provincial/territorial stakeholders.

(Slide.)

MS. McCOMBIE: I'm just going to show you

a few slides of the data that we receive. This comes from the 2002/2003 report.

It just shows you that the largest efforts that are reported to us, major allergic and anaphylactic, are 36.6 percent; major allergic/anaphylactic is actually the largest effort that has been reported to us for all blood components.

Transfusion-related lung injury was at 13.1; circulatory overload at 12.7. At the time of this publication, only severe cases were reported, but in our next report, all cases of circulatory overload will be reported to the Public Health Agency.

Acute hemolytic reaction is at 11.6; bacterial contamination is 10; ABO incompatibility is at 5.2 percent. We feel that's under-reported, because, at the time, we only received reports on those that caused an adverse event.

In the next report, we are receiving all reports of the product, if it was transfused, regardless if a reaction occurred or not. Then all

of these cases are further broken down to relationships, transfusion, definite/probable/plausible, and severity; life-threatening, long-term quality of life, et cetera.

(Slide.)

MS. McCOMBIE: Bacterial contamination is still a major problem in transfusion. We've seen the number of cases decrease by 40 percent from 2002 to 2003 and we think we'll probably going to have that decrease again in the next report. We feel this is due to the implementation of a diversion pouch on all blood bags in Canada and bacterial testing of platets. This slide just shows the organisms identified in the blood product culture there than 23 out 27 cases that were definitely or possibly related to transfusion and that is with positive blood culture. Two of these cases resulted in deaths. One of those deaths was related to the transfusion. The other was probably related.

(Slide.)

MS. McCOMBIE: The rates of adverse transfusion events by 100,000 units of blood components transfused not issued for 2002/2003. The rates do not differ significantly except for the bacterial contamination, which we talked about previously.

(Slide.)

MS. McCOMBIE: This diagnosis of adverse events related to plasma derivatives, again, the major allergic is the top reported followed by aseptic meningitis and hypotensive reactions and these three diagnoses represent 70 percent of the ATEs.

(Slide.)

MS. McCOMBIE: This comes to the fatal event definitely, probably or possibly related to transfusion. We had 11 fatalities related. Ten were related to blood components. One was related to plasma derivatives and recombinate products. Two deaths were definitely associated with transfusion, but this is a small number of deaths respect to more than three million units of blood components issued in Canada in that time.

(Slide.)

MS. McCOMBIE: This just shows the incident of death associated with blood components. The incident was highest from bacterial contamination followed by TRAILI and post-transfusion purpura. If

we consider only the fatalities definitely related to transfusion, the overall incidence was 1 in 483,000.

(Slide.)

MS. McCOMBIE: This slide just shows you the number of reports that we received in the last three years in 2002, 2003 and 2004. The numbers, of course, are going up because we have more sites reporting and probably there is more awareness to adverse events in the hospitals due to increased training.

(Slide.)

MS. McCOMBIE: In summary, the TTISS is an evolving surveillance system. As more provinces and territories come on board we will have more data in the future, but it will take some years to estimate the trends and the incidence of adverse transfusion events in Canada. TTISS is not an alert system at this point because we receive the data six months after the event, possibly when its a web-based system we'll be able to have more of an alert. It is not a substitute for reporting to the blood manufacturers and to the Health Canada Regulatory for action to be

taken on products and we are actively involved in the international standardization of definitions. We belong to the ISBT Hemovigilance Committee and also to the European Hemovigilance Network. As you can see, there are always changes. Things are always being updated, so it's an evolving system and it's moving all the time.

So now I'm going to switch gears for a few seconds and talk about our transfusion error surveillance system.

(Slide.)

MS. McCOMBIE: Four provinces -- British Columbia, Ontario, Nova Scotia and Quebec -- it's voluntary, non-punitive. I must say TTISS is also voluntary. We receive non-nominal data, which is exported to the public health agency. The same sort of process takes place from the hospital to the province and the public health agency. The public health agency only received high-level errors. We don't receive the lower level ones. It's a web-based technology. The exports are quarterly, the same as TTISS and we have agreements in place to what data we

receive. Since we started putting data into a database, we have about 3500 cases as of December 2005 on all levels of severity.

This system is going to be more of a sentinel surveillance system to use for hospitals for benchmarking. We realize we can't have a system in every hospital in Canada. We divided the sites by number of red cells transfused within a province. They could have three or four sites and they transfused at one place 10,000 red cells, they're at a certain level, between 2 and 10,000 red cells at another level and less than 2000 red cells another level.

As a public health agency, we do not know the names of the hospitals that are participating in the program. We only know the province. This system was inspired by the Merge system of Dr. Kaplan who's sitting in the audience, and Jenny Callan involved with the Merge system and she played a large role in the development of the Canadian system.

(Slide.)

MS. McCOMBIE: And of course, we have a

working group of which Jenny Callan is the chair and there are there to help develop and implement a transfusion surveillance system.

(Slide.)

MS. McCOMBIE: We have another working party. This is a group of experts.

(Slide.)

MS. McCOMBIE: This is actually our expert sort of advisory group who are selected for their individual and medical and scientific expertise in the fields of public health, infectious disease, epidemiology, transfusion medicine, cells, tissues and organs. Then of course, we have our regulatory people there and the blood manufacturers. This group reviews and evaluates the data based on epidemiological data they develop research questions and hypotheses for further investigation. They identify signals or unusual events that should be investigated further. They've already recommended the changes for the definition to the consensus conference held in Canada held by CBS and Hema-Quebec. They've asked them to develop standardized

guidelines for the investigation of bacterial contamination cases and we have a small group working on that.

Also, they've been a great support of the reconciliation of data from all stakeholders, including the regulatory group and the blood manufacturers. This group oversees all the surveillance systems in the TTISS section.

(Slide.)

MS. McCOMBIE: The partners and collaborators are the hospital and the blood bank transfusion physicians, all the provinces and territories, the regulators and the blood manufacturers. I think we've proven to ourselves that we're all able to work together and collaborate and have a truly national adverse event reporting system in Canada to help identify optimal transfusion practices and provide safe products to patients. It's actual a Kiever recommendation fulfilled. Thank you.

DR. BRACEY: Thank you very much.

MS. McCOMBIE: This is just the website if

people want access to the annual report, the form or the manual. We're in the process of updating the manual and they will be put onto the website as soon as they are implemented.

DR. BRACEY: Thanks very much. That was quite informative material.

In the interest of time, I'll limit it to maybe two questions so we can get through the rest of the presentations.

Dr. Epstein?

DR. EPSTEIN: You mentioned there's concurrent reporting to the regulator as well as to the product manufacturer. Is this burdensome to the regulator? They're essentially getting aggregated information from some entity and then direct information from other entities. You mentioned this reconciliation. For example, event reports.

MS. McCOMBIE: Actually, we sit down in a room with all of our information and try to identify each key individually. There are not that many cases actually. If we reconcile the data with the blood manufacturers, that is a bigger job. But that

actually -- if we do that, then we have the data. From the biologic side, it's a marketed health product from the blood derivatives where we sit down and go through each case. Then we also go through each case with CBS and Hema-Quebec goes through their cases with the vigilance group so that biologic group feel that their data is covered in that way because they only receive data from the manufacturer.

DR. BRACEY: Additional questions? Mr. Matyas?

MR. MATYAS: I don't know if you have an answer for this, but do you know how much Canada is expending yearly for the TESS and TTISS programs?

MS. McCOMBIE: I don't know how much Canada is, but I can tell you that several governments are only spending about $3 million, $3 million at the federal level. We don't know how much the provinces are spending, but it comes under their blood offices. The blood office also has the mandate of utilization and other things. So it's just part of what that office does.

DR. BRACEY: Thank you. We'll move on to

the next presentation by Dr. Jeanne Linden. Dr. Linden is a board certified pathologist and transfusion medical specialist. She was the director on resources for the New York State Department of Health. I'm she's familiar to many of you. Thank you.

DR. LINDEN: Thank you very much. It's good to be back here again. I'm going to be speaking about actually two different things in terms of surveillance. One is the event reporting related specifically to transfusion and also about the hospital-acquired infections.

By way of background, which you may not be familiar with us. We transfuse about 900,000 units of red cells per year. We have about 240 transfusion facilities or hospitals and little over a hundred that are limited transfusion services.

(Slide.)

DR. LINDEN: The event reporting system was established in 1989. We've been doing it for a little over 15 years. It is a mandatory system which, of course, requires compliance, however, the

surveyors do look at whether there have been any events and whether they've been reported or not. This is separate from the hospital patient occurrence, a separate effort. Tissues and transfusions do not go through the hospital system. This covers transfusion, also transfusions associated with infectious diseases, which we look at in collaboration with the disease reporting system and also tissue transplantation events and also so near misses. Whether or not it was transfused, it does solicit information on underlying contributory factors, root causes and corrective actions done by the facility and we do assist them with those efforts, and do give some feedback, specific feedback to the facilities, a general advisory alert on occasion. Although its a mandatory system, it's not used for enforcement purposes at all unless they don't report. We think that's an important feature.

(Slide.)

DR. LINDEN: I want to just very briefly show a few of the things. I also mentioned the advantages of our particular setting is that we also

record activity data, so we have to nominate our information available about transfusion and transplantation. It's going on -- I think New York is unique in that we have licensed tissue transplant facilities and have data available on those -- the individual piece of data, the parts of components, the blood groups and the types of personnel and some of the attributes. These numbers are a few years old.

(Slide.)

DR. LINDEN: My general impression is that some of the categories remain a little better. I think the efforts are pretty good. We have found about 1 in 40,000 ABO incompatible transfusion, about 40 percent of patients having a symptomatic reaction to those and overall this number is pretty consistent with other numbers for the systems in the UK and France. Just to put it in perspective, there are the infectious disease risk.

(Slide.)

DR. LINDEN: This I only show to point out this is my team's No. 1 area of vulnerability in the

entire system at the time of the blood administered to the patient.

(Slide.)

DR. LINDEN: Over half of them have outside blood banks. Just a little over a third have compounded error.

(Slide.)

DR. LINDEN: When one looks at the nature of the error, the No. 1 error by far is identification as identified. In my opinion, as you can see, the identification process is not the stage where the nurses feel comfortable. They check the paperwork, but they don't identify the patient against the unit as a part of the process because of identification and so forth. We are looking at structuring that process.

(Slide.)

DR. LINDEN: Some of the specific things we have found there are issues about being able to pre-print labels. It's a big group to choose from. They routinely look alike, sound alike. They have similar names. It happens all the time, and

secondary identifiers that continue to be problems.

(Slide.)

DR. LINDEN: Communication continues to be a big problem, hand-off problems, signing off to the next group. A big concern with everybody thinking the other person is doing something and not really having clear designation of who has done what and making the same person responsible for certain things. Lack of delay is also an issue we're looking at because right now Elkins and York are about to administer blood, complete absence of SOPs isn't so much absent as in the past, but it continues to be a big problem.

(Slide.)

DR. LINDEN: This is one of my examples of a predisposing underlying contributory factor. This nurse is left-handed but the workspace she has to work in allows only for right-hand writing where she has to work, so that she has to cross her hands in order to do her job. She should clearly not be doing it that way.

(Slide.)

DR. LINDEN: This Sue Bodner's artichoke approach, looking at different contributory factors in many different systems -- personnel issues, environmental -- I think we show that there are good things within the organization. There may be environment issues in terms of noise, lighting and those sorts of things. How is the task necessary to be performed? These are something that should be captured in any sort of surveillance system.

(Slide.)

DR. LINDEN: Safe transfusion is an entire process and having a safe product to the blood bank or the blood center and then having the blood bank having a compatibility issue is just pieces of things. The big issue is really that our getting it sent to the right patient, particularly when there is storage. Our refrigerators continue to be, in my opinion, a major, major problem historically. We've really been focused a lot in infectious disease testing and donor screening. They have been major, major areas of resources to date. We've done pretty well with that, but there are still major areas of

vulnerability, as I mentioned, to getting the proper unit to the proper patient.

(Slide.)

DR. LINDEN: These are some data that we compiled from the UK series on transfusions. Excellent reports that really show that the incorrect component being transfused is an important event being reported to them. We have found very different from ours, but the rate is approximately the same. The transfusion transmitted infections are really a pretty small part of what they see.

(Slide.)

DR. LINDEN: Just to put it in perspective, this is old -- just again to prove the viruses are under pretty good control, but bacterial contamination are the things that are most frequent.

(Slide.)

DR. LINDEN: I'd like to switch gears a little bit now. Jerry asked me to talk a little bit about what we found in terms of hospital-acquired infections surveillance. We had legislation passed last year regarding addressing hospital-acquired

infections. It provided for fully confidential reporting. The transfusion reporting I've just been reporting is also protected by law as confidential. It's my understanding that you can get a court order and they're releasable. I don't recall that ever having happened. I know that we don't get, in most cases, patient identification. In the case of the hospital-acquired infections law it is so broad that specifically court orders and subpoenas also we would not be able to obtain this information.

It also specifically requires reporting of the results and making them available publicly on our website the first year in the pilot project specific information. It was because consumer advocates who are major players saw that this law passed. Fortunately, there are actually appropriations to fund this effort for both department staff as well as additional resources to allow the funding of pilot projects to look at some specific issues at some facilities.

(Slide.)

DR. LINDEN: The goals in implementing the

law are two -- develop and implement a meaningful reporting system with the ultimate goal of preventing hospital-acquired infections or reducing them. The system is intended to evaluate interventions, what the risk factors are and what risk adjustment strategies could be implemented.

(Slide.)

DR. LINDEN: The group working on this, which is not my group, by the way, I've learned a lot about it recently, looked at existing systems and they looked at certain things they call "administrative data." These are things like discharge data, billing data -- those sorts of things that have been sent to the health department for quite a while and we eventually found that these are not useful, which has been my experience as well. It turns out people really do have the infection or they had acquired the infection in hospitals or in a surgical procedure, but they didn't really have the surgical procedure. So unfortunately, using that type of system would not be productive.

Expert advisors got together and they felt

that having standard case definitions would be really important and standard methods and protocols in the facilities, and that 70 percent of surgery, in New York at least, is done on an outpatient basis. How are we going to capture those because of the fact that many of those infections might occur after discharge from the hospital.

(Slide.)

DR. LINDEN: So looking at the differences, we finally decide to use CDC's National Healthcare Safety Network. The reason it was selected is because it does have these standardized case definitions and methods, and also would allow for benchmarking which is very important for facilities to prepare themselves against regional and national types of data.

(Slide.)

DR. LINDEN: Some of the benefits specifically in addition to comparing themselves to other facilities is the incentive to standardize and also utilize the health provider network, introducing web-based systems to support many other functions and

in fact, there is going to be efficient reporting starting next year. It's pretty easy to use and the information exchange is quite good.

(Slide.)

DR. LINDEN: The expert panel, we looked at which agencies it specifically focused on and the legislation specifically talked about infections and that's not very broad. It's not intended to capture anything but transfusions and these items were selected for a variety of reasons. They're common problems easy to identify and so forth. So Central-line-associated sepas is one of them and surgical site infections, to prior ones. CABG and colon surgery were selected because we've had existing intensive effort in cardiac surgery monitoring in New York that we wanted to be combined with these.

The status of the effort is that training is actively going on and will be going on this fall. Accordingly, in January of 2007, it begins for one year. Statistical advised that selecting a certain number of procedures, 150, would be sufficient for each facility for each of these types of procedures.

For small facilities or medium-sized, it might be all of their procedures. But in some very large facilities, they might report for only a few months and not each report on an ongoing basis. As I mentioned earlier, they have called for some reporting results in aggregate in the first year and after that facility-specific in some regard, but that is to be determined.

(Slide.)

DR. LINDEN: In conclusion, my recommendation, and this is Jeanne Linden speaking from experience.

(Slide.)

DR. LINDEN: When considering looking at a system, you want thoroughly sufficient detail and meaningful information. You need to consider the entire system and all the players, major ones of whom are the nursing staff as has been mentioned. They are not always particularly amenable to influence from people like lowly pathologists and transfusion medicine people. That could be a challenge. In fact, we're working very closely with the Education

Department for Nursing, especially on some of the nursing issues in New York. Individual hospitals, if one is going to have a truly thorough system, then the nurses -- there are a variety of different players in the system and they will need to be included. And again, that's a challenge for us.

Events that occur shortly after, during a transfusion are a lot easier to capture than events that may happen later. Transfusion issues only become identified much later, for example, and they may require a different approach. If one wants to improve and prevent, one needs to look at the root causes and the underlying factors. We have found that some of the participants may need a lot of assistance or prompting in terms of getting the information, doing a thorough investigation. But some of the facilities, in that regard, they need to given a lot of help. And in fact, some that are suppose to have internal existing systems may not always have motivation or corrective action to really address the problem.

Those are issues to consider. It would

really be nice to use it to assess -- the existing data sets are unlikely to be helpful, the data to be used.

(Slide.)

DR. LINDEN: It's desirable to have standardized definitions, uniformed reporting. It should be easy to report and get the information in the format that's sufficient information that it facility analysis and ultimately the idea is to be able to develop interventions for risk reduction strategies to kind of decrease whatever kind of incidents one is looking at and interventions need some sort of impact that's measurable.

(Slide.)

DR. LINDEN: If you want the facilities to really comply and participate in the program, they need to buy into the fact that it's valuable. It should be easy for them to use, not consume a lot of resources; particularly, personnel resources. It should not be punitive, used for educational purposes only to help people learn from the system so the facilities can benchmark themselves and others,

perhaps.

It should not be releasable other than in aggregate form, summarized findings and even individual case examples. On occasion, I do use as a learning tool but nothing beyond that. Unfortunately, resources are going to be an issue. It therefore maybe necessary to look at how one can get at expenses.

(Slide.)

DR. LINDEN: There may be new issues we need to learn about, new pathogens or perhaps look at our most frequent problems and reduce those and be protecting the largest number of patients with the effort. Also, if we get problems that are amenable to intervention, then you might be able to do something about them. If you're simply studying something you can't really do anything anyway, it could be, perhaps, a bit of an academic exercise.

(Slide.)

DR. LINDEN: Focusing on some of the smaller issues that maybe problematic, but don't introduce major risks information about donors is

available later in some of these systems. You can help pick and choose from particular types of things that ought to be studied.

As I say, these last comments are just my personal views based on my experience looking at some of these things. I think that's it. Thank you.

DR. BRACEY: Thank you, Dr. Linden.

Questions from the Committee? Dr. Sandler?

DR. SANDLER: Dr. Linden, I have two questions. The first question is I noticed we were getting off the track on the statistic slide. I think it was 1 in 14,000 of the transfusions reported to you had an error. My question is were those actual mistransfusions or were they near misses?

DR. LINDEN: You're not the first person to ask me that question. That number is units that were erroneously transfused to the wrong patient, either the wrong blood issued by the blood bank or whatever. The patient didn't get the blood he or she should have for red cells only. The only caveat is that because of the preponderance of the ABO

incompatible amongst transfusions there tends to be under reporting of the fortuitously compatible erroneous transfusions that weren't detected or reported or whatever. So we did make a slight adjustment for that in the estimated figure.

DR. SANDLER: In the small print down at the bottom, it said "2000," which meant the data was six years old or more. There have been a lot of transfusions in New York State since then.

Do you have a sense that that number is persistent? Is there an inertia in it, or have you really great progress because of your bringing this to the attention of the blood suppliers of the state?

DR. LINDEN: That is something I hope to be able to study definitively in the near future. My impression grossly that the blood bank and transfusion services are doing a better job. Outside of the blood banks on the floor, we continue to see a lot of the same old thing.

Overall, I'd say the number of reports that we're getting is fairly similar to what it's been in the past. However, we're getting more trivial or minor types of issues. I think the major ones may be less frequent.

CHAIRMAN BRACEY: In looking at or hearing one of your comments regarding the culture, if you will, of the institutions, it seems there was a

problem in terms or difficulty in terms of generating the culture of safety within the environment.

I guess the question is among the recommendations, and I think one of the things that I thought resonated terribly clearly is to make sure that you have the clinicians involved, and you don't just have the laboratory involved.

DR. LINDEN: Along that line, I would also say that a lot of what we have seen is very similar to the mitigation errors as well. Because of the involvement of the nursing staff as well, involving us in the overall efforts to define issues, makes sense.

DR. EPSTEIN: Thank you very much. It's a very illuminating presentation. Your state has been very proactive in this effort. My question is this. I've been struck by presentations in the past, that the first thing that happened was that you do a lot of laudable things that many people would say would be ideal.

The data elements of the standard definition, investigation of root causes, etcetera.

Has your state ever considered utilizing that format for a reporting system and have the participating hospitals used those?

DR. LINDEN: Yes, we did consider it and yes. Some facilities do use it, but not very many. But I may not necessarily be aware of them all.

I think our system incorporates certain aspects and features of that system. We did not feel it was suitable for our use in a large part of internal types of efforts.

It is extremely difficult to learn and resource by yourself. At the time, it wasn't something we felt could impose on our facilities. It was fairly simple and easy for them to use, to encourage compliance, in whatever format they wanted to use.

We asked them for more information. We do that routinely, but certainly we definitely support and endorse pulling pieces of that together.

Just to follow up Dr. Sandler just on one more thing, as a specific example, not large statistically, you're probably aware that I reported

a series of five fatal cases of air embolism associated with blood recovery that occurred in the 1990's.

We did a series of several advisories to hospitals about preventing those types of events. In the last ten years, we haven't had any recurrences. I can't prove it was because of our advisories, but it certainly could have been the reason.

CHAIRMAN BRACEY: Good report. In the interest of time, we'll move on. Our next speaker is Dr. Ruth Solomon. She will speak on the FDA's tissue safety. Dr. Solomon has been with the FDA since 1993. She's a federal officer in the Office of Blood Research.

We are certainly thankful for her coming and talking to us on this topic.

(Slide.)

DR. SOLOMON: Good afternoon. If you have read the next few sentences, I'm not actually in the Office of Blood Research. I'm in the new office of Cell Tissue and Gene Therapies. I'm going to talk today about the tissue safety team as an example of a

coordinated effort to deal with adverse reactions related to tissue transplantation.

(Slide.)

DR. SOLOMON: The objectives of my talk are to tell you about why TST was formed, some background on tissue regulation, the composition of the team, what procedures we follow, what was accomplished so far and what we hope to accomplish in the future.

(Slide.)

DR. SOLOMON: The Tissue Safety Team is only about two years old. It was set up to provide a coordinated approach to the receipt, routing, investigation, evaluation, documentation and trending of reported adverse reactions involving human cells, tissues and cellular and tissue-based products, which we abbreviate "HCTP" across five offices and the Center for Biologics, and also beyond the Center.

We wanted to communicate with one voice within the Center and beyond. We also want to give guidance to industry on how and when to report adverse reactions, and provide outreach and education

to industry, health care professionals and to the public about tissue donation and transplantation.

(Slide.)

DR. SOLOMON: First, some definitions. An HCTP is an article containing or consisting of human cells or tissues that is intended for implantation, transplantation, infusion or transfer into a human recipient.

Examples would be bone, tendon, cornea, skin, human heart valve, human dura matter, vascular grafts and most recently we've started to regulate hematapoletic (ph) stem cells and reproductive cells and tissues, and also cell therapies such as islet cells.

The way HCTPs are regulated at the agencies is they can be regulated as what we call tissues, 361 tissues, or as biological products -- blood is a biological product -- or as medical devices.

If they are regulated as tissues because they meet certain criteria, which I'm not going to go over, there is no pre-market review. So the tissues

are on the market, and we have rules designed to prevent introduction, transmission or spread of communicable disease, and the compliance review is determined by detection.

Obviously, biological product and medical devices require pre-market review and approval, to ensure they are safe and effective. I'd also like to mention that in regulating tissues, we are restricted to communicable disease transmission.

So any of the regulations that we promulgate have to be related to communicable disease transmission, and that's because the legal authority for regulating tissues comes from Section 361 of the Public Health Service Act, which promulgates rules to prevent the transmission of communicable disease.

Biologic products are related not only under Section 361, but 351. So they require licensure. Then we do have the definition of adverse reaction. The definition is a noxious and unintended response to an HCTP for which there is a reasonable possibility that the HCTP caused the response.

We also have a definition of what we call

an HCTP deviation, which we used to call error or accidents. I'm not going to give you that definition now. But again, it is limited to prevention of -- we have to tie it to that, in order to even record a deviation.

(Slide.)

DR. SOLOMON: We have been regulating tissue since 1993, but that regulation was restricted to donor eligibility requirements. More recently, we've put out three rules, first proposed and then final. They all became effective May 25th, 2005.

So there are rules and registration and listing under HCTP, rules on donor eligibility similar to blood donor screening and donor testing, and also current good tissue practice rules, which are similar to current GMPs, except more limited as to infectious disease type things.

So in the good tissue practice rule, there is a requirement to report adverse reactions for tissues. You must investigate any adverse reaction involving a communicable disease related to an HCTP that you made available for distribution.

You must report to FDA within 15 days an adverse reaction, again involving a communicable disease if it is fatal, life-threatening, results in permanent impairment or damage, or necessitates medical or surgical intervention.

On these reports, we use a Medwatch system, which is an FDA-wide reporting system. Again, there's a form for mandatory reporting by the tissue bank, and a similar form for voluntary reporting by patients and health care professionals.

(Slide.)

DR. SOLOMON: So this Tissue Safety Team is comprised of representatives from five offices within the Center for Biologics. Actually, the Office of Biostatistics and Epidemiology, my Office of Cell Tissue and Gene Therapies.

Then there's the Office of Communication, Training and Manufacturer's Assistance, the Office of Compliance, and our Center Director. There are points of contact within each office.

Also, the team we say consists of outsiders. As I mentioned, some HCTPs are regulated

as medical devices. Then we have the Office of Regulatory Affairs and the Office of Criminal Investigations, and if necessary, we involve other federal agencies such as CDC, HRSA and CMS.

(Slide.)

DR. SOLOMON: We do have an SOPP, standard operating procedures and policies, which describe the responsibilities and procedures for the TST and each office. This team deals with reports received from various sources. Most of them are Medwatch reports that come to the Office of Biologics, Biostatistics and Epidemiology.

But we can receive reports directly from hospitals, physicians or recipients. Those usually come in through our Office of Communications. We can receive reports directly from tissue banks or from other agencies.

One of the most important things we realized was you have to have proper routing of these Medwatch reports. Many of them that should have come to our Center were going to other centers. I will tell you later how I managed to correct that.

Once they come to the correct center, they're entered into a database and forwarded to the Office of Biostatistics and Epidemiology, where they're entered into a smaller database.

Then an e-mail alert is sent to the points of contact, who have access to this database. The initial information we receive, the question we ask is, is the adverse event related to communicable disease? If the answer is yes, then we'll follow up.

As I said, legally we don't have the authority to go after adverse events that are not related to communicable disease.

(Slide.)

DR. SOLOMON: So what happens is, for instance, if the Medwatch report is not complete, or it doesn't have all the information we'd like, the Office of Biostatistics contacts whoever, the hospital or the reporter.

They have a standard set of questions. They ask for a description of the event and what is the physician or health care worker's impression. Was it due to the tissue or due to some other cause?

Then our Office of Compliance contacts the tissue bank. Sometimes they know about the adverse event because the hospital reported that to then. Other times, they don't.

We ask them a standard set of questions. Then if they have done an investigation, we have to review the things they've looked into, such as donor records, processing records, the pre- and post-processing culture results and also complaints from other consignees who received tissues from the same donor.

Sometimes it's necessary to involve the field investigators, to do a for-cause inspection to get additional information. The next step is to discuss and evaluate the information that we have. Senior management is notified at any point along this time line, and also CDC and other agencies can be brought in.

(Slide.)

DR. SOLOMON: Then there may be further action that's required, such as notifying the hospital that received tissue from the same donor.

The tissue bank may voluntarily recall the tissue.

If they don't do that, we can order them to recall tissue and to destroy them, and we can even issue an order for them to cease manufacturing.

Then the Center sometimes put out public health notifications or press releases. There's a decision amongst the team to close a case if no further action is indicated. So the last slide --

(Slide.)

DR. SOLOMON: We are trying to classify the adverse reactions as possibly, probably or definitely related to the tissue. But we just started trying to do that if we're involving industry first. They have draft definitions of these different classifications, and also outside people if they have classifications.

(Slide.)

DR. SOLOMON: They really communicate with each other. The TST points of contact meet every two weeks. The whole team meets monthly. Then we provide an update to the Center Director and senior management quarterly.

(Slide.)

DR. SOLOMON: Just to give you an idea of the adverse action reports we have received, this is a nine-month period from November 2005 to July 2006. There were a total of 152 reports. The majority were tissue-related. But there were about 30 percent that were cell-related.

Amongst the tissues, as you would expect, the percentage is parallel the distribution of the different tissues. Bone was the most frequent type. Ocular, skin, soft tissue and cardiac.

We also tracked -- it was about equal distribution whether the report came from the tissue banks themselves or from the patients or health care workers, and then you can see. There were some non-infectious adverse reactions, simply because people didn't realize the distinction. We need to do more education.

So approximately 80 percent were infection-related, and 20 percent were not infection.

(Slide.)

DR. SOLOMON: Our accomplishments so far

have been to improve the reading of Medwatch reports.

For instance, the contractor that initially received these reports at the two centers, we provided them with a list of what we consider HCTPs, and basically all HCTP reports should come to us.

We also have access to the CDRH database. We can do that to see if accidentally some reports went to the Center for Devices. As I mentioned, we set up a standard operating procedure. There have been revisions to the Medwatch form, to make it more user friendly.

In the past, there were sections to complete if you were a device or a drug. So the tissue people didn't really know where to enter their information. Now, instead of "drug" it says "product."

So we've made guides to inform them that that's a section they should fill out. As I said, there is now guidance for completing the Medwatch form.

We've improved the database, so that when

we get additional information and it's entered into the database, and all the points of contact and all of the offices have access to the database, and can read the additional information.

We've also improved our training and communication with field investigators.

(Slide.)

DR. SOLOMON: We still have a ways to go, as I mentioned. We want to try to classify the Medwatch reports. We want to more definitively determine when to follow up and when not to. When we think we've got all the information, we possibly can.

So we would close the case and we want to trend these reports. But since it's only been in existence for about two years, that hasn't started yet. Also, we want to do more outreach to consumers and health care providers. This is a passive surveillance system.

But it would be nice if there were active surveillance work on tissue reactions. Some projects are underway. For instance, there's an active surveillance system called Medsun operated by the

Center for Devices and tissue work sort of tagged onto that. So that now Medsun also operates in surveillance of tissue-related adverse events.

Also, as you heard, the CDC has the NHSN. It's an in-hospital infection surveillance system. So we have a tissue module under development.

Lastly, as was mentioned by many speakers, we want to stimulate reporting, make it easy. Right now, you can obtain the Medwatch report on-line, and for the monitoring reports, you can fill them out and submit them electronically.

We don't have that capability yet for the mandatory reports. But we're hoping to, and eventually everything will be electronic, which is easier to fill out and submit.

(Slide.)

DR. SOLOMON: These are some helpful websites. The first one is a wealth of information. There are links to just about everything, rules and guidance on tissues, consignment programs.

Any recent events that happened with tissues would be posted on this website. In case

you're interested in the SOPP, there's a website for that.

Then the general Medwatch website is the third one, and gives you information on how to obtain the form, how to fill it out, etcetera. Then for HCTP deviation reporting, we also have a separate website.

We do those deviation reports for general biologic deviation reporting mechanisms, although we keep track of the tissue deviations separately.

(Slide.)

DR. SOLOMON: Here's some additional ways to reach me if you have additional questions. Thank you.

CHAIRMAN BRACEY: Thank you, Dr. Solomon. Questions from the Committee?

(No response.)

CHAIRMAN BRACEY: What I was thinking is if there are no questions, we could take a ten minute break. Then reconvene to finish out the meeting with the last three presenters. Any questions? Yes. One from the audience.

MR. WISE: Just a real brief comment. Dr. Solomon's Tissue Safety Team has been so effective that the Center Director, Dr. Goodman, has gotten a working group to develop a Blood Safety Team, which is just getting started. Similar coordination among multiple offices.

CHAIRMAN BRACEY: Thank you.

DR. THOMAS: I would like to make a comment. I'm really glad to hear the comment about a Blood Safety Team, the kind of model that's going on. I think that's very necessary. Thank you.

CHAIRMAN BRACEY: We're off the record.

(Recess.)

DR. HOLMBERG: Will the Committee please come back to the table?

(Pause.)

CHAIRMAN BRACEY: We want to try to wrap this up. What we've decided to do in the interest of time, so that we have ample time for discussion, is to have two public commenters today that we had scheduled.

Then we're going to move the ARC, the AEC

and the AABB presentation to tomorrow morning. So we will have ample time to discuss what we've heard today in committee.

With that, I'd like to invite Paul Brayshaw of the Hemophilia Federation of America to the floor. Paul? Is Paul in the room?

(No response.)

CHAIRMAN BRACEY: If not, is Dave Cavanaugh here?

(No response.)

CHAIRMAN BRACEY: They stepped out for a moment? Okay.

(Pause.)

CHAIRMAN BRACEY: Let's do this. Let's go ahead and start the committee discussion. We can have the public comments at the end of the discussion. We've heard a lot today. We've heard some recurring themes. Oh, okay. Mr. Cavanaugh, are you ready to make your statement?

MR. CAVANAUGH: I am. Cory would be here to present himself, but he's ill. Mr. Chairman, members of the Committee, as always, the Committee

appreciates the opportunity to address the Advisory Committee.

The Board members have the concept of COTS. As you know, COTS is instrumental in the creation of this important committee from every meeting since the beginning.

We come before you today to discuss our serious concern and our frustration over the critical issues and continued absence of deliberations of the Committee.

This discussion of biovigilance has created a vacuum. We are assured that this discussion cannot be effectively undertaken without a clear understanding of the real-time conditions that exist within the many components of our nation's blood system.

A significant budget constraints, a serious lack of coordination in the blood system, and an unwillingness to confront serious issues leads us to conclude that both the Committee and the DHHS have lost their collective memory of the crisis that went into the IOM study, and the empaneling of the ACTSA.

Historically, government has a very short memory and a limited attention span. We do not share the government's short attention span. The needs have not been met. Nearly 8,000 persons with hemophilia have perished as a result of this.

Beginning with the investigation of what went wrong, COTS committed to assuring that that does not occur again. We have at the present time, along with members of DHHS and FDA and other government agencies, made some important gains in safety and care.

Certainly, we have increased safety for hemophilia and other bleeding disorders. However, there are serious issues where this is minimal or non-existent.

The members of the COTS board of directors are representing a declining number of long-term survivors, as well as parents, who are pained by the loss of one or more children.

We remain absolutely committed to honoring our surviving loved ones and to make the necessary changes. While HIV devastates persons with

hemophilia, affecting over 90 percent of those with severe hemophilia, it is the result but not the whole story.

The story is four decades of hepatitis contamination of the American blood supply, and the inaction, unwillingness and indifference of the government and all segments of the blood industry to address this perpetual nightmare.

In 1976, HCV became a leading killer of persons with hemophilia. It's the leading cause of death in our community. HCV held that distinction for just seven years, as by 1983 it was clear that HIV-AIDS replaced HCV as the leading killer of persons with hemophilia.

Twenty-three years later, liver failure associated with HCV is again asserting itself as a leading cause of death from hemophilia. We could certainly have prevented the majority of the HIV infections that overwhelm us today.

Let me restate this simple fact. Aggressive action by the government could have prevented the deaths of 8,000 of our loved ones. Yet

we stand before you today again to highlight the ongoing deaths in the hemophilia community and in our nation.

The number of Americans with hemophilia and HCV is at six million. The United States remains the only large western democracy that does not address the problem of blood-borne HCV, and this has been so since the 1970's and 1980's.

From our perspective, the government and the blood industry are reluctant to act, are hoping that the HCV cases will pass, and hope that liability and accountability questions will never be addressed.

Where is the look-back in the Code of Federal Regulations? Since 1991, COT has been demanding that the government address the HCV epidemic. Thirteen years have passed. Neither of these demands have been met.

The contamination of the American blood supply has not even been seriously considered. We also are troubled by a discussion of biovigilance, when it lacks a look at the context in which this is given.

The nation's blood system continues to be a source of great concern. Fourteen years later, the American Red Cross appears unable to extricate itself from a consent decree imposed by the federal courts regarding ongoing, consistent violations of policies and procedures.

We continue to see serious geographic differences in the quality of heart operations, and an apparent inability to address these difficulties. HHS suffers from a serious lack of vision and leadership to cope with threats looming on the horizon.

Good surveillance is the first tier in any response to known and unknown threats to the safety of our blood supply. We continue to see FDA as the so-called "old man." Years of funding constraints, a lack of serious focus by those in power and a lack of creative and aggressive leadership in health care has left that standard unchanged.

This, combined with a serious lack of funding, has left us vulnerable and we believe unprepared for the challenges ahead. For example,

mad cow has not been mentioned today. COTS continues to be committed to working with the FDA, CDC, DHHS in the quest for a safe, available blood supply.

However, it cannot focus on these issues, which we believe are not being addressed. We must have strong biovigilance. However, the vigilance is unrealistic if the discussion is not rooted in the reality of material conditions. Thank you for your attention.

CHAIRMAN BRACEY: Thank you. The next comment is from Paul Brayshaw from the Hemophilia Federation of America. Mr. Brayshaw.

MR. BRAYSHAW: Thank you, members of the Advisory Committee on Blood Availability. I'm Paul Brayshaw, the voluntary co-chair of the Hemophilia Federation of America, for their Advocacy Committee.

I thank you for this opportunity to provide comments on behalf of the HFA regarding hepatitis C. As a consumer of blood products, I'm here to remind you all today why your duties are so important for me and other individuals in my situation.

The Hemophilia Federation of America is a national non-profit organization that assist and advocates for the blood clotting disorders community, and seeks to remove all barriers to both the choice of treatment and quality of life for individuals who are affected by blood clotting disorders.

Based on this Committee's efforts, the FDA has recalled potential adverse incidents, and is more diligent in the inspection and enforcement of good manufacturing practices at blood collection and manufacturing facilities and blood screening.

Activation of the Louisville methods have been refined. The consumers and the medical public has benefitted. There have been no reports of Hep-C transmissions that have been treated with these new processes.

This is all very encouraging. But I want to ensure that it remains an improvement of biovigilance.

As you know, nearly four million or up to six million are undercounted for, according to COTS statistics. But there are people in the United

States with Hepatitis B. Ten percent are through blood transfusions.

Overall, there are 6,200 people with bleeding disorders infected by Hepatitis B, representing 44 percent of people with hemophilia and five percent of persons with other disorders. The rate is especially high among people 21 and over.

My comments today are in regard to the current treatments available for Hepatitis B. The current FDA fastest-track program does not allow for the study of Hepatitis B drugs by themselves. FDA does not allow only heart-only study arms.

However, for all tested individuals, Hep-C heart trials must also include standard combination therapies. The problem is it doesn't help people who really need it the most.

The therapy is contraindicated for a large number of people affected by Hepatitis C, who are in serious shape with end stage liver disease. While we don't know if Hep-C hard drugs will work on them, we do know that these people are in dreadful shape.

There is no drug therapy for them, and

they're not likely to get liver transplants or survive for long, even if they do get one. People in the bleeding disorders community with end stage liver disease have little hope with experimental therapy.

It is unacceptable that these people cannot be given any promising experimental therapies. I challenge this community to pursue efforts that will encourage true fast tracking for heart type drugs for Hepatitis C.

By this, I mean we should have demand testing. Heart drugs by themselves, without combination with the normal standard combination of retroviral and interferon therapy, are ineffective. Of these drugs, there's one in the Phase I trial that tries to reduce Hepatitis C in the blood level by four orders of magnitude.

The bleeding disorder community requires new treatment for individuals affected by Hep-C. This includes improved blood product safety, and a diagnosis of Hepatitis C for liver biopsy, as well as access to Hepatitis C clinical trials and increased federal funding for Hepatitis C disease research.

Thank you for your time.

CHAIRMAN BRACEY: Thank you. Comments from the Committee?

(No response.)

CHAIRMAN BRACEY: Thank you. Now, we'd like to open up the general discussion. We've heard a great deal, some in great detail about the various systems. What I thought we would do is open up the discussion.

We do have the framework of questions that were previously submitted. Perhaps we could start discussion under the broad topic of the definition of biovigilance. With that, I would ask how the Committee feels about the broader diagnosis of bio versus hemovigilance. What should be considered? Dr. Angelbeck?

DR. ANGELBECK: I was on the working group that worked on it, and the idea there was to come out with a comprehensive program that included not only transfusion blood, but plasma derivatives; also tissues, organs, etcetera.

Having said that as a definition of

biovigilance versus hemovigilance, I was very impressed with the presentation that Nancy McCombie did from Canada. This is an enormous task.

You have to do it in chunks that are doable. You have portions, perhaps, of surveillance, sentinel activity going on now, that can begin to form a platform for how you do that.

I think it's extremely complex within this country to do this. So when you look at biovigilance, while that can be a goal and I think that's part of the finding, you may have to start with a smaller, more focused effort, for example, in adverse event-associated transfusions, with the ultimate goal that you have.

CHAIRMAN BRACEY: Ms. Lipton?

MS. LIPTON: I would agree with that. I don't think we can design this here. I think what we should be sort of focusing on with the so-called architecture is what we were trying to put it in?

I think we should talk about putting tissues and everything in it. I agree. But what we're really talking about is setting up the scope.

We would really have to start project by project.

There are a lot of pieces that are out there. I think what everyone sees as lacking is the integration of all these pieces. I also note that the Canadians, by my quick math, the federal government talks about there are three million, and they're talking about 14 million.

I think we're going to have to think creatively about maybe doing -- we talked about this -- a combination of systems. I would encourage us to start small, if we can think broadly about what we want to see entirely in the future.

But it will have to be building block by building block. I don't see how we can possibly do this any other way.

CHAIRMAN BRACEY: One of the things I think you're talking about is right on. We will not create a system. The form is really what we need to think about. A major consideration is, is it necessary?

At least from my vantage point it is, because the system as it exists now is fragmented.

There's no comprehensive nature to the system. We are one of the few industrialized Western nations that really doesn't have such a system.

So I think yes, it's necessary. Then the other element is the role of government. You know, there are health care systems where there is centralized governmental health care. That's not the case in the States.

I think the concept of partnership is key here in terms of government serving as a partner, private enterprise, non-profit hospitals, etcetera. I think clearly I believe we need to have this endeavor.

So one of the critical issues is what is the role of government in the process.

MS. LIPTON: I didn't know we were talking about that particular issue, but I do agree with you. One of the things that we get concerned about, I think there may be a role for government.

I am concerned about the issue of funding for this type of thing. As I sit here today, we're talking about a project that's going to easily take

two years to get our arms around, and there's going to be a change in administration.

I just think we want to create something that has both the private sector and the government pushing on one side. Even cutting it short on the other side, so that we're both pushing that issue of partnership. Everybody has to have some skin in the game.

DR. BRACEY: Dr. Sandler.

DR. SANDLER: Again, it's the physicians at the hospitals who paid for HIV testing and a variety of safety initiatives before the government picked up the tab for its own patients. The ones that belonged to HCFA and CMS, I would like to answer the question by saying the role of the government is to pay.

(Laughter.)

DR. SANDLER: I think that's very, very clear. The United States has the responsibility to the people in Medicare and other aspects of this. It's very clear nothing's going to happen unless the government pays for its own patients.

DR. BRACEY: Dr. Ramsey?

DR. RAMSEY: I'd like to offer a comment about one thing. It's to establish what the goals for looking out for such a large enterprise should be. The goals might include new regulations. It might include contributing to improved standard practices. It might include epidemiologic intervention in specific problems that arise. It

might include establishing risk assessments for patients and healthcare providers. There are probably a lot of goals.

I think it should be very clear at the outside of the large enterprise what these goals should be, what everyone stands for. Everybody would love to see all these kinds of data for the country at large, but what do we do with that data, you know, in terms of improving the entire picture? I guess maybe it's obvious. I just wanted to throw that into the mix.

DR. BRACEY: One of the areas that I see serving as a goal is to establish meaningful data points so you'll be able to assess different interventions. For example, we had some data that was presented in terms of some systems are able to look at the impact of eliminating, say, female plasma. They can go back and assess and see what the impact is.

One of the things that we're lacking is an ability to assess interventions. So a goal would be to at least have some system whereby if you implement

that intervention it is considered as providing more safe product, if you can actually manage it.

Dr. Angelbeck.

DR. ANGELBECK: This ties in with the comments of Dr. Ramsey and Dr. Sandler. I think I completely agree. I think the role of the government is to pay.

Having said that and listening to Dr. Ramsey talk about goals, I guess the question is what is the incentive for the government to pay and to feel accountable to pay for this. You know, coming from the commercial side of the world, there's something that I call in advertising and marketing personal but true. That is, if you put out a website and put out an ad or something like that, there's a first moment of truth, that's what gets you to buy the magazine, buy the car, go further and learn more about whatever it is.

I don't know what that first moment of truth is. Is it an important enough issue that it has an outcome that the government's sufficiently interested in to fund it? Without that funding, it's

hard to imagine how it will come together.

DR. BRACEY: Mr. Walsh?

MR. WALSH: This may be a naive observation, but I would hope the primary goal is safety. Consumers of health care in America expect nothing less. I know that's understood by everybody on the committee. That whole focus, in my opinion, a major focus, that should be enough for the government given what we've been through in the past it ought to be. Not just the devastation in the hemophilia community but in other communities. The IOM report. I just hope that safety is the primary goal and that's already established and that's reason enough.

DR. BRACEY: Dr. Holmberg.

DR. HOLMBERG: I can't resist the opportunity to say something, especially after Cory's words there that Dave Cavanaugh read. You can tell Cory, David, he hit me with his words.

I think one of the things that struck out to me when I heard both from the Canadians and also from the Committee of Ten Thousand was their motivation was the key to the report. I think my

moment of truth is the safety.

I hear what the Committee of Ten Thousand is saying. Let's not forget the past. And I don't think we want to see ourselves go back to what happened with HIV. And still hepatitis C is an issue. We need to make sure they get back on the radar screen.

DR. BRACEY: Dr. Sandler?

DR. SANDLER: I'd like to make quite a distinction between where we were with hepatitis C and HIV and other things and where we are today. My definition of higher vigilance to me is the early alert for infectious diseases and biological aspects of blood safety. It includes tissue and organs as well.

Let me put -- and that's one of my major interests, hospital error, off to the side for a moment in order to focus on the fact that we are not at ground zero. The Center for Disease Control is doing a fantastic job of picking up early phases and disseminating them between the gumshoe work that they do, picking things up and promulgating them and

disseminating them, morbidity and mortality reports.

I know that the choriomeningitis virus has potentially spread. We're not at ground zero. There's a lot of information.

So we do have, I think, good people doing very good work, disseminating it very well. And I think you can build on that as part one of where we are and then part two, the grandiose thing that will never get done, but we can write up more papers than we've done for the last 30 meetings.

DR. BRACEY: Other comments?

Ms. Thomas, as the public member, what would your thoughts on biovigilance be?

MS. THOMAS: Actually I have several thoughts. Hearing our different speakers earlier, each one making a different speech, I would like to see them all come together for the betterment of consumers.

One area in particular, when they were speaking of donations and how they were disseminated, I think it was Dr. Linden, I really agree 100 percent when she talked about how they're at one end when the

blood actually gets to the core on another. I've been on that side a dozen times and I've seen real negligence. I am definitely in favor of biovigilance. I would like for us to always keep the consumer in the forefront. That again goes back to the safety concern. That's pretty much my thoughts.

DR. BRACEY: One of the big questions that's been revolving around resources, how is this going to be funded? There has been a lot of discussion in terms of well, this is what the government should pay for because it should make a commitment to safety. But, on the other hands, I heard arguments about well, this should be incorporated within the fees for providing the service. So perhaps again could we hear some more on that? Is it the overriding position of the committee that this really is something that needs to be funded by government or would this be something that would be considered worthy of having it grafted into whatever the fees provision is. Dr. Duffell.

DR. DUFFELL: We had talked a little bit

about how this could be covered through reimbursement. But I think in addition to the safety issue which is really important, there can be a payback from this. If we gather more knowledge and information on the actual use of these blood products and the side effects that occur, hopefully we can take that knowledge and turn it into preventive action. So the payback would be longer term to the government or to however it's funded. That knowledge that we'll gain through this information may lead to lower use, better use of blood products. But like I said, the knowledge on the safety and side effects may be preventive medicine. I think we are focusing very heavily on the upfront costs and not thinking about the back end.

DR. BRACEY: Thank you.

In terms of the issue of impact, we talked about integration of the various parts of the system within the U.S. Is this something that, for example, in Canada, it appears that they are well moving towards sort of an international integration. What is the committee's feeling about if we design the

system where it should be vis-a-vis systems that are already in existence?

Dr. Duffell?

DR. DUFFELL: I think the Canada system looks pretty impressive to me. I very much appreciated that presentation. I think it's a starting point for us to consider for sure. But I think the closest thing right now is our MedWatch form that we already have. If you really want to start, consider that as kind of a precedent. I would start with MedWatch. That'd be used to meet some of our information needs on an immediate basis. And building something that might be a little bit more complex like they have in Canada.

DR. BRACEY: Dr. Holmberg?

DR. HOLMBERG: I hear what you're saying. But one of the things that I heard was that there's a need not to just collect data, but there's a need for analysis. What concerns me, I think that MedWatch may be one element of what we're looking for. But I'm concerned that that's the regulatory element. We can glean a lot of information from that MedWatch,

but I think there's other things that are happening that may not be picked up on MedWatch.

I would like to ask you to do this. I think it would be very beneficial to me to explore the possibility that Dr. Ramsey had mentioned about what are the goals. Maybe if we could spend some time this afternoon to really look at the goals of what we're trying to do, that might be very beneficial to really focus us.

DR. BRACEY: Dr. Sandler.

DR. SANDLER: I'd like to speak favorably about MedWatch and how it brought in something. The details may not be correct on this, but my recollection is as follows. A blood product by the name is Winrow has been out there in what I would call post-market surveillance. It was observed to cause hemoglobinuria. A lady by the name of Van Gaynes collected these reports, put out one report, kept her eye on it, put out another report.

Those of us who are familiar with the product are very much aware of a subject that wasn't in the radar screen. It's not an error. It's acute

hemoglobinuria mediated probably intravascularly. So it's kind of a broad mechanism out there. But whatever it is, whether it's infectious, who would have thought that hemoglobinuria would have caught your eye on safety. But it picked it up in the government system that's in place, put out two reports in the Journal of Blood, everyone is familiar with the drug now. There's an adverse warning on the package insert. We do have something out there that we can build upon without building some whole new system. We might be able to put some of the elements that are already out there to work for us.

DR. BRACEY: Dr. Duffell.

DR. DUFFELL: I don't know if Ruth back there from FDA can comment on this. If I recall, Jay Epstein told me at the last meeting that the only thing that the hospitals were required to report on blood use right now is deaths. So there's a whole scope of things. Is that correct, Ruth? She's shaking her head yes.

Looking at that format that exists already, if we were to apply it to biologics or

pharmaceuticals, there's a whole host of information out there that could be reported in a form like that that presently is not. Because the only rule is reporting deaths. We're only getting the most severe reporting information.

But to Jerry's point, I do think we ought to take a look at what other goals that we're trying to accomplish and whether or not that particular formula will meet those goals.

DR. BRACEY: Dr. Kuehnert.

DR. KUEHNERT: I think, first of all, I'm very happy to see this discussion have some legs. We've discussed this now at several consecutive meetings. It's probably been discussed more in the last year than it was in the last 10 years before that as far as the idea of surveillance for adverse events.

But I guess I'm struck by, now that we're sort of turning the rocks over and we're seeing how fractured things truly are, there are many, many different methodologies. Given the blood products, there's at least three different surveillance methods

involving the regulatory agency, you've got organs, tissues, and I guess I'm trying to look at a broader perspective on what is the process for integration. Because there are many efforts that I see being involved with these different aspects and I don't see a lot of communication between the efforts except maybe on the common thread actually in a lot of them. But that's not very reassuring. I think we need more than that.

DR. BRACEY: Would one of the potential goals of the system be to design a system that integrates all aspects of transfusion safety? I mean it's sort of an overdone turf, but without segmenting or separating it into the various elements.

DR. KUEHNERT: I think you're not going to have a comprehensive, uniform system before you have a fractured system that you're trying to integrate the pieces. So I think it is going to take time, you almost need like a vision statement about where you want to go a thousand miles from here within the short term. We're going to take the first step and just -- the first step is trying to know what's out

there and trying to get all those things together.

I was also really impressed by the Canadian system. Not only did they have the data quality meetings, they had a theater review meeting -- I think what's missing here is a forum to discuss all these issues across biologic products. When I mentioned the workshop we had last year, that was the first of its kind. That's amazing.

But it's just the nature of things that people are focused on their own product and it takes the federal government or some other entity to say well, you know, there's value to communicating with each other and sharing ideas, that's sort of what we need across all these activities.

DR. BRACEY: That's interesting. I remember the meeting and some of the materials related to biovigilance. Many of the systems where this evolved over the years and changes in essence start with a party of those with common interests in a working group to get this together to hammer out a product. It takes years. I think that we won't have a final product today, but maybe that will be a goal

to establish such an entity.

Dr. Angelbeck.

DR. ANGELBECK: I agree with that. I was also very impressed with the Canadian system, the amount of different points in their system of integration. The idea of the working group, the representation on the working group, the data quality review, et cetera.

So if you pick a point somewhere in advance -- and you have to do that ultimately -- and you have existing fragments and pieces right now. We've discussed CDC, what MedWatch does, et cetera. It would be possible for the government HHS, this committee, to sponsor bringing together this group and setting up or establishing a schedule for integration through building and design of working groups, annual meetings to begin to assemble that information. Perhaps that's more achievable than a platform for doing this.

DR. BRACEY: One of the things that's a problem in terms of -- there is a beginning effort that we will hear about tomorrow from AABB. In

essence, it speaks to what you've addressed and that's this forming a working group. So again the concept, and I guess the issue would be is it imperative where that working group exists or just simply that there is a working group.

DR. ANGELBECK: You know, that's where you work on communication and engaging people. And I don't think personally, I don't care where it is, but if you engage people in it and they all have a role and an opportunity to participate, you go from there.

DR. BRACEY: Dr. Duffell.

DR. DUFFELL: I personally think HHS is the place for it because of its oversight of Medicare and Medicaid, as well as FDA, as well as the organizations within FDA that regulate blood. It's really sitting right on top of all these things. It should act as the sponsor for something like this.

PRESIDING JUDGE: Dr. Ramsey.

DR. RAMSEY: I know most people are aware of this. There are any number of other countries that have various types of vigilance programs in Europe and Asia. Perhaps more information about that

can be presented. From that standpoint, those are all countries with different types of healthcare systems in the U.S., for example, in funding, so they have a little different setting. But certainly there is a lot of information available.

As an aside, the current issue on Loc Sanga, there are a number of presentation abstracts in that journal that belong to individuals and countries around the world. Including this kind of information or their tracking improvements in safety that have resulted from various interventions, it's very encouraging to see.

Also another aside. I don't see it on the agenda -- perhaps we'll get to it tomorrow, but there is reporting adverse events to the FDA is intimately connected to the issue of vigilance. I was just commenting -- there was a comment earlier about how the tallies -- I was reminding people about the proposed rule for reporting adverse events.

DR. EPSTEIN: There's been a lot of industry objection focusing mainly on the threshold for reporting and the argument that it would cause a

great deal of reporting beyond that which would be warranted. The agency is commenting on that.

DR. BRACEY: Ms. Lipton.

MS. LIPTON: One thing I was going to say, AABB has done a lot. They're trying to be involved in this to bring people together, trying to take a look at this. I think that our effort has really also focused on getting people in the hospital to do that. We cannot build a system without understanding the implementation. Jay's point -- to go back to Jay's point, I think the issue is mandatory reporting, if hospitals will accept. We don't have the resources. We must think very carefully about who in a hospital is actually going to sit down and capture this information and transmit it reliably.

There's a lot of work that's been done around this. We had to sit back, look at the system that exists and this needs to be a pretty broad participatory group. That's what we're trying to do. I do think that HHS has a duty on this, but I think also the private sector of the hospitals that are out there doing the work need to sit at this table from

the get-go. It cannot be superimposed from the top and this is our idea. We can do whatever we want to. When it hits the ground it is not going to work unless we design something that is easy for hospitals to do and we're not going to get that kind of information.

DR. EPSTEIN: First of all, I agree with that without buying the systems don't work and it's been looked at in previous meetings. Systems of mandatory reporting, ultimately somebody has to do something to ensure cooperation. I was struck by the fact that the JCAHO system involves reporting the very things we're talking about, so the question is how good is the reporting of transfusion-related events.

DR. SHERMAN: The difficulty, as I alluded to the desire and the information to have a protected form of reporting, the numbers that I've seen from JCAHO and triage reports from the FDA on transfusion-related fatalities, JCAHO captures a minority of them.

I personally think it relates to the confidentiality, the mandatory aspect, as part of FDA reporting, and, conversely, the fact of the fears that what gets reported to the Joint Commission, could be viewed as subpoena-able in some fashion or another, which would then depend upon the state and a variety of other things.

I think, of the material that does come into the Joint Commission, it is looked at, particularly as to how the institution evaluates the problem as far as the institution's capability, both for that problem and subsequent problems.

You won't mind if I also add one thing for your consideration, if you will. You talked a lot about getting information in and integrating it.

I would hope that part of this perspective

-- again, you also consider how you're going to get the information out, as far as the conclusions that some hypothetical group derives, otherwise, it's going to be preaching to the choir.

DR. BRACEY: Right. I think that's an important element. That was included in Dr. Kunin's remarks.

We really need to have a way to make sure this information becomes useful and that it goes in the right direction.

DR. SHERMAN: I think that this is where government plays a role. Not every organization is the Joint Commission, et cetera, et cetera.

Government plays a role in the dissemination.

DR. BRACEY: Dr. Epstein?

DR. EPSTEIN: I think we've heard a couple of times today, that the core issue is funding. You have to fund people to get the data.

But you can't accept that it's going to happen on its own, and there has to also be a consensus; there has to be some concept of a value-

added for anybody who -- short of a government-funded program, but, you know, if the industry is going to self-fund a reporting mechanism, the industry has to have a really good reason to want to do it, and that economic case has to be made.

We really have to think about two alternatives: One is that we come up with an effort that self-funds a comprehensive reporting system, or we have to figure out whether sentinel reporting on a smaller scale has targeted funding from a designated source, is an adequate alternative.

And I'm not sure that I see any other option. We've heard repeatedly that this doesn't work, unless you have a responsible individual onsite.

If you really want comprehensive data, that's what it takes.

DR. BRACEY: Dr. Duffell?

DR. DUFFELL: Jay just used the word, "sentinel." I was using the word, I think in that study. You could also address some of the cost issues.

Again, you can update and speak to some of the points that I addressed earlier from the standpoint of safety in transfusion medicine, as well as utilization of blood products.

A titled study might provide the momentum that you need to go on to a larger scale.

DR. BRACEY: Dr. Ramsey?

DR. RAMSEY: Most quality improvement activities, often save money for somebody. For example, reducing infections, improves the healthcare system for all.

So, any one of the secondary goals permits me to save money, or at least be able to show that this effort is worthwhile for the system, whether it's manufacturing, whether it's hospitals, whether it's patients, the payors.

DR. BRACEY: You know, it seems as though the low-hanging fruit or part of the low-hanging fruit, would be the adverse reactions that we know of, the more difficult is sort of parsing out benefits to be derived, that we don't clearly understand as to savings.

Again, I go back to -- and we'll hear more about this tomorrow -- that if one has truly a comprehensive system that goes beyond simply looking at the number of reported adverse events, that use of some education, can actually improve the efficiency of blood utilization. So I think we have the element related to utilization and education, and that's an important piece to consider. That could make for a lot of realization of savings.

Other comments from the Committee?

(No response.)

DR. BRACEY: We will be hearing more tomorrow, and, again, I think one of the things we really want to leave with tomorrow, is this notion of, again, where would this best fit in the healthcare system in the U.S.? Not simply to take the model of Canada, the model of France or other nations, but I would like to be able to walk away, knowing that I think we all are in agreement that this is a good thing to have.

I think we're evolving towards being a working group. We do not have a final product, but I

think what we're unclear on, is the role of government.

Or maybe I'm not clear on that. Dr. Sandler?

DR. SANDLER: Mr. Chairman, maybe it's because I missed the last meeting, but I'm not clear on this particular distinction. The subject we are on, is something, in my mind, intervention of infectious disease, and with 40,000 people getting tested for infectious disease every day, a whole bunch of people going back to the hospital, sick, after they got a blood transfusion, and learn that they've got an infectious disease?

We seem to be putting very much of it automatically under that umbrella of blood-safety-related efforts. I'm not clear, in my mind, that errors are biovigilance.

Could you tell me what this Committee has defined as biovigilance?

DR. BRACEY: Again, biovigilance, as I view biovigilance, is broader than simply dealing with infectious issues related to blood transfusions.

Again, looking at the international, the shock and the serious hazards of transfusion, incorporating biological adverse events, but not necessarily infectious adverse events --

Ms. Lipton?

MS. LIPTON: I was going to say that I was par of the working group that worked on this, and I think they did a nice job. They said it was broader than just infectious disease; it really is blood transfusion safety.

Adverse reactions that are related to what's going on, if that's the most serious risk of transfusion, that's what you focus on, not just the product. You think that this must become part of the process from day to day.

DR. BRACEY: Dr. Duffell?

DR. DUFFELL: I thought Matthew's presentation was a good summary of the things that we've learned. That's why utilization comes up as well.

I think that if we go back there, to that summary, at least, I think we can come to terms with

it.

DR. KUEHNERT: I heard some deafening silences in the last couple of minutes, and I think it's due to the overwhelming task here. There's so much to consider in terms of the spectrum of products and in terms of the spectrum of what we're looking at, that it would be helpful, maybe, for the Chair and the ExecSec to maybe help the Committee, either now or tomorrow morning, with what the Committee should focus on in terms of scope.

There are a lot of questions here, and we're being asked to answer in detail, every single aspect of what a biovigilance effort should look like.

I guess I'm struggling with what we are being asked to specifically address in terms of trying to set a path as far as process and how detailed is that path going to be?

DR. BRACEY: I think we'll need some time to discuss this, but, again, what I see is that we need information in terms of what is the scope? How broad should this activity be? And we'll address

that.

I'm not necessarily looking for a process that would lead us to the final product, but, in essence, a concept of how we would form, I think, really, the working group. What is the structure we will put together, that will take us toward where we want to go?

What are the elements that are important? Who needs to be at the table, as we discussed?

You know, where -- here's the umbrella. Is the umbrella totally under the government? Is the umbrella a partnership umbrella of private sector and government?

Those are things, I think -- that's a concept that I'd like to be able to walk away with. A question -- and this may be premature -- but where is the funding, obviously? This is going to be resource-intensive, and what would be the best way to go about trying to get this funding?

DR. KUEHNERT: That's very helpful, for me, at least. This whole funding thing is just so difficult, because sometimes, you can sort of take

the sure thing and start very conservatively, and just take baby steps over a long, long period of time.

On the other hand, you also have to be ready, in case lightening strikes, to take advantage of an opportunity. That's where I think there's an advantage to having a wide spectrum, as far as the vision is concerned.

I think a lot of the issues concerning tissue right now, create a potential for the other products, so that one product may drive the others, as far as opportunity to create an infrastructure.

DR. BRACEY: Can I get Dr. Holmberg's perspective, because he has had preliminary discussions with the Secretary on this.

DR. HOLMBERG: I put down three elements here of what I think would be very beneficial. That is: The vision, the goal, and the process.

I'm looking at the goal, and I've heard some recurring themes -- the integration, as I like to call it, avoiding reporting fatigue -- so I think those are some of the goals.

I sort of have to apologize to you, because I think that if we would have listened to the presentation from Dr. Whitaker this afternoon, I think it would have probably been clearer as far as what preliminary activity has already take place as far as some of the goals for vigilance.

Now, of course, in the initial discussions that have taken place at AABB, it has been primarily focused at hemovigilance, versus biovigilance, because of the various attitudes.

Like Judy has already mentioned. it's too big to get your arms around, and we really need to take discrete steps or chunks. So I think that if you'll think about this tonight, about the vision, the goal, and the process and how do you get there from here, I think that we've heard good information today, especially from the Canadians, and then also Dr. Sherman.

I think we learned a lot also from the JCAHO on what they can bring to the table, too, in terms of what is being collected out there. I guess that's where I would like to maintain the focus.

DR. BRACEY: Ms. Lipton?

MS. LIPTON: I would like to make a comment about the process. Healthcare, in large part in this country, is not delivered by the Federal Government. I see the government as having an associative role, a leadership role, a role in creating incentives that are needed, but it really does have to be something that, again, is built with great participation by the officials who are delivering healthcare.

That's why I keep going back. I guess I don't really agree, Jerry, that we can just turn around and say everyone's got to pay for this. We have to be creative and figure out how we're going to do this, because, frankly, on the government's agenda, this may not come out very high.

But I think it should be a very high priority for this meeting, to figure out how to do it, and it may not be one of these systems with all the denominator data. I think we have to get a process that lets us get together all the elements that give us the greatest insight into what's causing

the greatest harm or the greatest benefit to the patients.

DR. BRACEY: Dr. Angelbeck?

DR. ANGELBECK: Karen is engaged in some of this process already, and what I've heard to date -- a couple of things occur to me, and I'm going to sort of think out loud here.

Tell me if this makes sense: Certainly, the idea that you have to do a pilot project to initiate some of the activities at a scale you can work with.

The second thing was, I'm impressed with your comments over and over and Dr. Sherman's comments, that it's the hospital that we have to get engaged in the process of the vigilance effort.

So there has to be some grass roots pilot project, if you will, to engage hospitals in the importance of this role to educate, literally, the market advantage of this to the hospital. If you can achieve that in a pilot program, perhaps you have a model for expanding. Does that make sense?

MS. LIPTON: Yes. I'm sorry that Dr.

Whitaker didn't speak, but these are some comments that have come out, and I think that's exactly right; we have to talk about pilots, scalability, and we have figure out where the cost line is. Does it work for an infection control officer in a hospital, to take on this responsibility?

He's continuing with the challenge to use resources and the systems that exist. It's not going to be by designing a huge system and rolling it out; it's going to be by figuring out how we can make it work.

DR. BRACEY: Dr. Epstein?

DR. EPSTEIN: I think Matt Kuehnert stated a very important point this morning, which is that many of these issues are the same as were faced with hospital infection control in roughly the 1970s. I think it would be helpful for us to understand that history. How was it that hospital epidemiology became an accepted norm, funded within the hospital?

And yet where we do actually have national acquisition and nobody's worried about lawsuits, you have a model here that could actually work.

It seems to have many of the same parameters that you're looking for from data from the hospital, and I just think we should draw on that experience. I don't know, Matt, if you're in a position to talk about any of the administrative details further, but, if not, I think it's something that we might report back to the Committee.

DR. KUEHNERT: I think Teresa is a much better historian than I am. Do we have some time now, or do we want to do it tomorrow?

DR. BRACEY: I think we're at a point where there are some important presentations to be heard tomorrow, including Teresa's presentation. Why don't we break?

I'd like -- Dr. Holmberg, would you begin the charge that you have for people to think of tonight, in terms of what we would like?

DR. HOLMBERG: Just to reiterate very quickly, the three elements: The vision, the goal, the process. Some of the goals that have already been identified, are: Safety, integration of systems, and avoiding reporting fatigue.

I would throw in a fifth one there, involvement of the hospitals.

DR. BRACEY: Mr. Walsh?

MR. WALSH: I'm assuming we're finished with this discussion or almost ready to adjourn? I just have a brief comment.

As a different perspective for the consumer, I think it's always good for us to challenge ourselves on a consistent basis, to reinforce our process as we move forward and do our jobs on the Committee. It's good to refine our goals; it's certainly good to reaffirm our responsibilities on a firm basis.

My dad always said, never forget where you came from. I've sat on this Committee since its inception, and I have to say that the deliberations we've had on the ACB look-back, the CDC, the West Nile virus, all the errors of omissions issues, have been a phenomenal exercise in transparency that was mandated for the Committee, and openness.

We've had open meetings. We've had valuable comments at every session. I think the

leadership of the Committee has always been open to input from the outside, bringing in experts, if necessary, and I'd like to thank you from our consumer community who have sat on the Committee, for the dedication and commitment of everybody that's served on the Committee, including this new round of Committee members and the expertise they've brought to the table, with all the challenges related --

We all have conflicts. I have a conflict. I take a plasma derivative, but I think this is remarkable leadership, both at the Executive Secretary level and at the Chair level. I'd like to thank everybody here.

I think the biovigilance program and the exercise of strategic thinking that we went through at the last meeting, demonstrates that the Committee can stand fast with our initial charter. So I'd like to thank the Committee.

DR. BRACEY: Thank you. We'll adjourn and reconvene tomorrow at 9:00.

(Whereupon, at 5:30 p.m., the meeting was recessed, to be reconvened on Thursday, August 31,

2006, at 9:00 a.m.)