

DEPARTMENT OF HEALTH AND HUMAN SERVICES

ADVISORY COMMITTEE BLOOD SAFETY AND AVAILABILITY

Twenty-Sixth Meeting

VOLUME I

Monday, May 16, 2005

9:00 a.m.

Bethesda North Marriott Hotel and Conference Center
5701 Marinelli Road
North Bethesda, Maryland 20852

P A R T I C I P A N T S

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Arthur W. Bracey, M.D.
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Susan D. Roseff, M.D.
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Mark W. Skinner, Jr.
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Wing Yen Wong, M.D.

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Matthew G. Kuehnert, M.D., Centers for Disease
Control and Prevention
Jay S. Epstein, M.D., Food and Drug Administration
CDR Michael Libby, Department of Defense
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P R O C E E D I N G S

Call to Order and Conflict of Interest

DR. HOLMBERG: I would like to call the 26th meeting of the Advisory Committee for Blood Safety and Availability to order, and we will start the meeting by having roll call. If I can just sort of jump ahead of the schedule a little bit just to mention that, as I do read off the roll call, we have two additional new members. The third member was not able to join us today. We have with us Dr. Art Bracey and Dr. Bracey is from St. Luke's Episcopal Hospital in Houston Texas. Art, would you like to say a few words?

DR. BRACEY: Well, just that I have been following the important business of this committee for some years and I am very pleased to be a member, and I hope to contribute.

DR. HOLMBERG: Thank you so much. The second new member and, by the way, they have both been sworn in already this morning; the ethical training will come later and every year we have one session of ethical training--our second new

committee member is Susan Roseff. Susan, would you like to introduce yourself and where you are from?

DR. ROSEFF: Good morning. I am from the Virginia Commonwealth University School of Medicine, Department of Pathology, formerly the Medical College of Virginia, MCV--that is how most people know us. I too am very excited to be here and am happy to have the opportunity to serve on the committee.

DR. HOLMBERG: Our chair has a picture of the swearing in if anybody would like copies of that. By the way, I do have a copy of my new grandbaby--

[Laughter]

--two weeks old yesterday and, as you can tell, this is my first so I am extremely proud.

If we can just go down through the list as far as committee members, Judy Angelbeck?

DR. ANGELBECK: Here.

DR. HOLMBERG: Celso Bianco?

DR. BIANCO: Here.

DR. HOLMBERG: Arthur Bracey?

DR. BRACEY: Here.

DR. HOLMBERG: Paul Haas?

DR. HAAS: Here.

DR. HOLMBERG: Andrew Heaton?

DR. HEATON: Here.

DR. HOLMBERG: Jean Linden?

DR. LINDEN: Here.

DR. HOLMBERG: Karen Shoos Lipton?

DR. LIPTON: Here.

DR. HOLMBERG: Pearl Toy is also a new member, however, she was not able to join us for this meeting. Gargi Pahuja?

DR. PAHUJA: Here.

DR. HOLMBERG: Susan Roseff?

DR. ROSEFF: Here

DR. HOLMBERG: Gerry Sandler?

DR. SANDLER: Here.

DR. HOLMBERG: Merlyn Sayers?

DR. SAYERS: Here.

DR. HOLMBERG: Mark Skinner?

DR. SKINNER: Here.

DR. HOLMBERG: On your list you have Marc

Thomas listed. Marc was also an appointed member to the committee. Unfortunately, he passed away about two weeks ago. He was associated with the Sickle Cell Association of Austin, Texas, and we regret his passing and send our sympathy to his wife and family. John Walsh?

MR. WALSH: Here.

DR. HOLMBERG: Wing Yet Wong?

DR. WONG: Here.

DR. HOLMBERG: Mat Kuehnert?

DR. KUEHNERT: Here.

DR. HOLMBERG: Jay Esptein?

DR. EPSTEIN: Here.

DR. HOLMBERG: Harvey Klein is not with us today. He will be with us tomorrow. CDR Mike Libby?

CDR LIBBY: Here.

DR. HOLMBERG: And I think that that is everyone.

Just a little bit about housekeeping, we do have a Federal Register Notice out--

MR. WALSH: Excuse me, Mr. Chairman, we

worked so hard to get somebody from CMS here and Jim Bowman is here.

DR. HOLMBERG: Oh, I am sorry. Jim, you should have waved your hand. Jim Bowman, from CMS, is also here. Jim, you were not on my list here and we will have to make that correction. We all cannot live without CMS! Thank you for bringing that to my attention.

We also have a Federal Register Notice out that came out at the beginning of May. That Federal Register Notice is open until the end of May. we are looking for new members and, as many of you are aware, your term of office will be expiring at the end of September. We do have a meeting in September and we will be looking at new committee members to fill your positions. One of the things, as we noticed with the renewal of this new charter and also with the appointment of new committee members, the time sometimes gets extended and so one of the options that we do have within the charter is that the charter does specify that if new committee members have not been appointed,

the old committee members can be asked to come back and serve additional terms or additional time on the committee. So, we have that option if we do not get all the paperwork through on the new committee members.

The minutes for last meeting have not been cleared through the Department. The Department is still reviewing those and they will be posted as soon as possible. I will turn the committee meeting over to our chairman, Dr. Mark Brecher.

DR. BRECHER: Thank you, Jerry--or should I say grandpa? By the way, I am also present.

[Laughter]

DR. HOLMBERG: I assumed that.

Chairman's Comments

DR. BRECHER: We had hoped to have a response from the Secretary and the Assistant Secretary to the recommendations we made at our last meeting but, again, due to the changeover in the power at the top that has not come to fruition by this meeting. Nevertheless, I just wanted to quickly review the three recommendations that were

made at the last meeting because they really serve as jumping off points for much of what we are going to be talking about in this meeting.

So, in brief, there were three recommendations made at the last meeting. The first one had to do with the bacterial blood safety initiative, and the committee recommended that the HHS Secretary request the cooperation of appropriate agencies with blood organizations and transfusion facilities to establish an ongoing program to, one, monitor residual bacterial contamination risks and generate the summary reports; two, provide resources for surveillance of transfusion-associated sepsis; and, three, make such additional recommendations as may be needed to maintain recipient safety.

The second recommendation dealt with reimbursement of plasma-derived products and their recombinant analogs. The committee recommended that the Secretary take steps to augment reimbursement of plasma-derived products and recombinant analogs. The committee endorsed the

following principles to get at such efforts: One, plasma-derived products and their recombinant analogs should be reimbursed at rates consistent with the true cost, including cost of distribution and administration; two, reimbursement should be sufficient to ensure an adequate supply of these therapies; three, individual products within product classes should be recognized as therapeutically unique; equivalent reimbursement should be provided in different care settings and the life-long cost of treatment to the individual patient should be addressed in any pricing structure, including extraordinary impact of co-payments.

The third recommendation had to do with support of policy of the financial burden for patients with bleeding disorders. This one had sort of "whereas's" and I am just going to cut to the bottom line. The advisory committee on both safety and availability urges the Secretary of HHS to support any proposed policy and/or legislation to address the extraordinary financial burden for

these patients. We are awaiting HHS response but, as you are going to see, this meeting addresses many of the same issues.

I would also like to welcome the new members. I am just going to remind everybody that we will stay on time and if we get ahead of schedule, so much the better. So, I would just like to move into our first area of discussion which is intravenous immune globulins. Our first speaker is Dr. Dorothy Scott. Dr. Scott is the Branch Chief for the Laboratory of Plasma Derivatives in the Office of Blood Research and Review. Her group is responsible for regulation of 40 immune globulin products and she is involved in issues of immune globulin supply, post-marketing adverse events and safety of plasma products with respect to CJD and variant CJD.

Review of Workshop on Intravenous Immune Globulins
in the 21st Century: Progress and Challenges in the
Efficacy, Safety and Paths to Licensure

DR. SCOTT: Thank you. It is a great pleasure to be here, and good morning. I am just

going to report a brief summary of the IGIV workshop. I can't really do it justice. We had 18 speakers and about 150 people attended. It was a very compressed day. From the feedback we got the most common criticism was that we should have had it for two days. I guess that is not so bad.

This workshop was co-sponsored by FDA and the Immune Deficiency Foundation, which is a non-profit organization involved in safety and efficacy of products and the health of people with primary immune deficiency. Recognizing the need for this workshop, Dr. Beato's [?] office funded the travel for speakers through its advisory committee's office, for which we are very grateful.

The planning group included Immune Deficiency Foundation, FDA, PPTA, CMS and this office. We have posted the transcripts and we hope to post most of the talks in the next couple of weeks. That is the web site for the transcripts.

the goals of the workshop were to discuss current issues in efficacy and safety of immune globulins; and to examine and analyze the results

of FDA's 1999 paradigm for IGIV licensure. Also, for the first time presented considerations for licensure of subcutaneous immune globulin, which is being studied for use in primary immune deficient people in similar fashion in which IGIV is used but may have some special advantages for some patients. We also wished to generate outcomes that will enhance the future safety and efficacy of our products.

There are a lot of unresolved issues in efficacy so I am going to go through efficacy, safety and then the other issues that we addressed. I am going to have to miss a few things simply because of time.

The unresolved issues in efficacy--there are actually quite a number in spite of the fact that we have many products licensed for treatment of primary immune deficient people. Nevertheless, the best dosing for infection prevention has not been defined on an individual basis, that is, the frequency and amount of IGIV you might need for a particular patient,

Even the monitoring is controversial. What are the best markers for efficacy? What dose goals should you have for your patient, the IGIV

peak? The trough? The area under the curve?

In addition, clinical outcome measures are also controversial. That is, which are the most relevant parameters out in the field? Remember, immune globulin intravenous studies really involve around 40-60 patients and don't necessarily reflect the great spectrum of patients that are out there.

The infection frequency obviously is important and that is an endpoint of the pivotal trials but these are certain serious infections. There are also many other minor infections and other more rare infections that wouldn't fall into these categories that people out there get.

Pulmonary function is believed to be a long-term measure of outcomes because, of course, people with primary immune deficiency get a lot of pulmonary infections which lead to end-organ damage. Of course, this can't be measured in one-year clinical trials very easily, and frequency

of antibiotic use.

Related to this was a talk given by Dr. Stiehm about surrogate markers for IGIV efficacy, and these would be for use in trials for licensure. In other words, can we shorten the time of the clinical trial? Could you use fewer patients if you had some other surrogate marker for efficacy? In particular, the surrogate markers that he spoke of were specific antibody levels in serum of people treated with IGIV, and how do those correlate with lack of infection.

He proposed a number of surrogate markers and these will continue to be discussed but, certainly, trough IgG levels which are used by many people out in the clinics; antibody titers to important pathogens; pulmonary function tests; and acute phase reactants.

Some other unresolved issues in IGIV that were discussed are infections in patients that are already receiving IGIV, and the understanding of the natural history of people with primary immune deficiency treated with IGIV isn't complete,

especially regarding chronic infections and end-organ damage. End-organ damage probably increases the infection rate in IGIV-treated patients and the question is how can their treatment be improved, and what can you do about people who already have fixed end-organ damage?

There are cases of people with chronic infections with mycoplasma and echovirus and it has been very difficult for them to resolve these. One of the things that came out of the meeting was the question whether IGIV's can be selected for high titers against pathogens for certain patients, or can they be combined with monoclonal antibodies as therapeutics?

Dr. Buckley talked about the need for early diagnosis of these diseases in order to prevent end-organ damage. I am just going to go through a couple of her slides. She mentioned that population surveys suggest that primary immune deficiency affects about 50,000 people in the U.S., which is certainly on a par or greater than the number of people with cystic fibrosis, Huntington's

disease or phenylketonuria and these are all screened for at birth. But, of course, the true incidence is not known because there isn't population screening and some of these people aren't diagnosed until adulthood, and some die as infants after they receive live vaccines.

She pointed out, in terms of cost, that most people are not diagnosed until later and that there is a great burden to society certainly and, most important, to the patients of having this disease not being diagnosed, with repeated, frequent infections. Most patients have been hospitalized before diagnosis and the hospitalization costs, obviously, are greater than the cost of actually preventing their disease.

She proposed screening at birth and at a later time point for primary immune deficiency diseases, that is hypogammaglobulinemia IgA levels, and if these are low then measure IgG. For SCID, the absolute lymphocyte count as a screen and, if that is low, then assess the absolute T cell count. So, a lot of these kids, as I mentioned, die early

because their disease isn't recognized when they get an infection.

Also in the efficacy category are the potential threats for people with primary immune deficiencies, and the question of how well IGIV can prevent these possible infections and some of them are emerging, such as West Nile virus and also, as I think people here know, we had a campaign to have a mass--not mass, I am sorry--a primary responder smallpox vaccination. We expected that half a million civilians would be vaccinated against smallpox. In fact, far fewer people were vaccinated but, as a result, the people with primary immune deficiency were quite worried that they contract vaccinia and have severe infections from the virus, not necessarily because they got the vaccine but because they are exposed to people with active infection from the vaccine.

The other place to look for possible problems in people who are treated who have primary immune deficiency is the changing epidemiology of infections in this country. For example, for

varicella or chicken pox we now have a vaccination but how well those antibodies are represented in immune globulins in people vaccinated versus natural infection is really not known, but it may be that vaccinating titers are lower or weigh in earlier or have antibodies of somewhat low affinity over time. So, this is one worry. Also, measles titers appear to be going down in immune globulins. Again, people are vaccinated; they are not getting natural infections and it is believed that that has something to do with the decrease in titers over time.

How can we actually check for these things? Well, we proposed an IGIV repository really for research purposes so that we can monitor trends of those antibody levels in the products to these particular pathogens, but there may be others of interest and we would like to assess the emergence in our products also for potential protection against new pathogens, for example West Nile virus.

I am not going to go through this because

it is pretty long but we did propose this repository, and this would receive yearly deposits on a voluntary basis from the industry producers of immune globulins and they would be used really for research, certainly not for the purpose of comparing products per se. But there are a lot of details to be worked out, and one of the things that we are planning to do is to form an internal working group to generate a draft proposal for consideration internally and then, of course, externally.

The other outcome of this session was formation of a working group. We actually have volunteers to address these three issues, the association of dose and trough levels with clinical outcomes over long periods of time; the optimization of treatment in people with end-organ disease who aren't necessarily often studied in clinical trials; and validation of surrogate markers of efficacy. Some of these are pretty tall orders but we feel that we should get started and find out whether it is feasible to learn more about

these diseases and their treatment.

The next set of issues were safety issues, and you are going to be touching on a lot of these today. As I mentioned, IGIV clinical trials, by necessity, are fairly small trials of selected patients and the products are generally not compared to each other, unless a manufacturer switched from one process to another so that is within the same manufacturer.

Clinicians who presented at this meeting and who spoke in discussion feel that adverse event labeling is difficult to compare among products, and they suggested that more standardized ascertainment of adverse events over clinical trials would be useful. A part of the reason that we see this disconnect in the labeling is because we have licensed these products over a very long period of time and how the studies were done and how the labeling was done has necessarily evolved.

We are also all very interested in post-marketing adverse event rates in the population in the field, and these are really not

known. We have spontaneous adverse event reporting. I should also point out that IGIV trials are unlikely to detect rare adverse events.

We had some presentations about models of surveillance for adverse events, including several that you will hear today I think, probably somewhat modified since the last meeting. But we felt it was important to present these models so that we could start to figure out how we can do things better and do we need to do things better for the people who receive IGIV. First Bob Wise, who will be here this afternoon, spoke about the FDA surveillance methodology. Mike Soucie, who also will be here, talked about their active surveillance system and Octapharma spoke about an industry model of post-marketing surveillance.

There are a lot of advantages to enhanced surveillance. Certainly, it might be more likely that we would detect unusual or severe adverse events early. One might characterize the adverse event profile and associated underlying factors. We would certainly have more complete data than we

sometimes get from spontaneous reporting, and it might be easier to identify long latency events.

But as we found out at the workshop, there are a great number of hurdles to this. When you see what Mike Soucie and what CDC have done, you will find out how much infrastructure and funding is really required, and it is difficult to apply any of this without funding and a great deal of intellectual effort on the part of a lot of people.

But some possible improvements for people who receive IGIV and the surveillance of those people were proposed. One would be a patient and Immune Deficiency Foundation-generated adverse event reporting system. This would still probably be spontaneous for the most part but there may be some intermediate that could be designed; enhanced industry post-marketing surveillance and surveillance in select institutions with PID expertise which would be getting, in a sense, closer to the CDC model.

We also had some case studies and adverse events. I am going to skip these. These are in

your handout. They were excellent. These were the outcomes of the safety session. FDA and IDF will discuss the feasibility of patient registries for the purpose of more active patient-driven surveillance. We also would like to know whether funding can be obtained to enable active surveillance at select institutions because there are some institutions which take care of a moderate number of these patients. And, we also question whether active surveillance can be combined with monitoring of long-term clinical outcomes, as discussed in the efficacy workshop.

This is the session on IGIV licensure. I just want to mention that from 1996 to 2002 no new IGIVs were licensed. But in 1999 FDA proposed a paradigm for licensure that was more streamlined and we had announced that publicly, and since that time, and I think certainly also as a result of the IGIV shortage, we have been able to license four new IGIV products. The most recent was just last month.

Finally, we talked about the paradigm for

licensure of subcutaneous immune globulin. For people who are interested, I would refer you to Paul Aebersold's talk, which is in the transcript and we will be posting his slides. We presented the current thinking about how to design a study for IG licensure and, as I mentioned before, I think this is the first time that we had presented anything like this in public. I will be glad to discuss it more if people are interested.

We also had a session on Critical Path topics and identification of projects in the field of immune deficiency and intravenous immune globulins that might be useful.

We finally had a topic that was not on the agenda but that is of particular importance to this committee as well as to us, and this is IGIV availability. Marcia Boyle, the chairman and CEO of IDF, stood up and noted that there has been limited availability of IGIV for primary immune deficient patients. There was a fair amount of discussion near the end of this session, and we had already heard some rumors of this; we were very

interested and, to make a long story short and to compress a lot of work in a few sentences, Dr. Holmberg and others, as well as us, had discussions that began on April 29 and some of that will be culminating in this committee today. The topic of availability of IGIV is quite complex, as I think you will find out. But we were very glad that there was at least an opportunity to get started on this important issue.

So, thank you for your attention and I will take any questions. Dr. Bracey?

DR. BRACEY: Well, with blood transfusions it is very easy to follow the tracks from donor to recipient. One would assume that in the hospitals the lots are traced but that is an assumption. What do you know about the ability to link a given lot to a given recipient in a hospital setting?

DR. SCOTT: Well, I had the good fortune or misfortune to look at a lot of the adverse event reporting, and it is the case that often enough you don't receive the lot number. Typically, the manufacturers do go back and try to make a phone

call to obtain that lot number. It is very hard for me to tell if that is because the lot number was never recorded or because it wasn't sent in with the report. I can't give you the exact statistics on that but Bob Wise will be here this afternoon and he may know more.

One of our goals is actually to go through the most recent year of adverse event reports and look for the proportion of missing information in order to get a better handle on how to improve it. But I looked at four years, from '98 to 2002 and if I had to guess I would say we are missing about 20 percent of the lot numbers. I can't remember whether they were inpatients or outpatients.

DR. BRACEY: I guess what I was thinking is that perhaps one could consider a standard that the pharmacist could then use because there are systems for tracking that are available; it is just a matter of making it a standard.

DR. SCOTT: That is right, it is standard on our adverse event report forms but a lot of things don't always get filled in there. I think

also that because a great number of patients, at least previously, received these as outpatients or even at home you are adding a layer of possibility for losing these numbers.

DR. BRECHER: Anyone else? John?

MR. WALSH: Nice presentation. Were there any discussions regarding the education on what an adverse event is for individuals on plasma derivatives, and how to report obviously? Were there any discussions about how that would be translated and disseminated amongst the patient populations?

DR. SCOTT: There was a recent discussion of what actually gets reported because we do know that there are people out there, for example, who have very severe headaches, to the point where they miss a day or two at work, and we won't see those reports. They are accustomed to it; they don't like it; but they continue to receive it and it is very unlikely that we would receive those reports. I would say we don't get that many reports compared to what we have heard is out there from the Immune

Deficiency Foundation. Many are already in the package insert and it is more common to get a report of an adverse event that is in the package insert, but much more extreme or serious--aseptic meningitis still might be reported, or something that is really unexpected, or the question of whether an infectious disease was transmitted. I would say those are the main categories and not even the very intolerable, more day-to-day adverse events.

DR. BRECHER: Mat?

DR. KUEHNERT: Just one question about the repository, that is a proposed repository and where would that be based, and are there resources for that currently identified?

DR. SCOTT: The resources have not been identified. It was my naive concept that we could do this ourselves. We have a couple of people who do lot release samples, for example, in a controlled setting but it still takes time, energy, personnel, and a mechanism up front for deciding to whom these get released and how. We actually did

compose such a bank in about 2000 ourselves and we use it for research. We also send it out to others but always coded. So, yes, we would like some resources of course, if that was your question. The other idea was to have another facility maintain such a bank.

DR. BRECHER: Last question, Gerry?

DR. SANDLER: From a clinical point of view, there is a dichotomy between increasing the safety of blood products by selecting those who have had limited exposure to infectious diseases and, on the other side, trying to maintain a pool of antibodies in an environment where polio is decreasing, hepatitis is decreasing, etc., etc. Was any data presented that showed the impact of improving dose selectivity for blood products, the impact of that on the quantity and the potency of antibodies that we are looking for in IGIV products?

DR. SCOTT: Nothing has been done in a formal fashion in that respect. But what we have noticed just in our own studies, with unvalidated

assays, is that sometimes recovered plasma products have higher titers to certain things than source plasma products. They are all very high, let me make that point. None of them are so low that you would predict people would be at risk for infection. I think that may be because the recovered plasma donors in general epidemiologically are a different subset of people. They tend to be older and they may be more likely to be exposed to natural infection. With the vaccinated people growing up who are receiving a larger number of vaccines--H. flu, varicella and so forth--it may be that we will see titers rising in that population. We don't know what is going to happen as these people become donors.

DR. BRECHER: Thank you, Dr. Scott. We will move on to our second speaker, Patrick Schmidt. Patrick Schmidt is president and CEO of FFF Enterprises. FFF is the nation's largest distributor of IGIV.

Update on IGIV Supply and Reimbursement
FFF Enterprises

MR. SCHMIDT: Good morning, ladies and gentlemen of BSAC. My name is Patrick M. Schmidt and I am president and CEO of FFF Enterprises, the

largest distributor of immune globulin.

I would like to thank Dr. Holmberg, and our newest grandfather, for inviting me to visit here with you here today. I plan on sharing factual data with you that I trust you will find credible, helpful and enlightening. I believe that is why I was invited to appear before you this morning.

For the past 17 years FFF has earned a reputation for supply integrity. Our reputation has been painstakingly earned in a variety of supply situations. As an example, in the past five challenging years FFF has grown to become the leading distributor of flu vaccine in the United States. Our innovative delivery model for flu vaccine was learned from our experience in blood products distribution. This year we will distribute in excess of eight million grams of IVIG and nearly four million equivalent units of human

serum albumin. In this position we have a unique and valuable advantage point of the IVIG supply scale. The distribution of these grams will span all sites of care--the home, the hospital and infusion offices.

At this time, I do not believe there is an overall shortage of IVIG. However, I do believe, and evidence strongly supports that it has become increasingly difficult to obtain IVIG at affordable prices. There is a new market reality--fewer suppliers and rising prices. The economic reality of plasma fractionation necessitates this increase in revenue for IVIG. I believe Julie Birkhofer will appear here to discuss fractionation and what has been referred to as last leader economics in more detail.

Today, seven years and nine days since Congress held hearings on the IVIG supply situation, we have an opportunity as an industry of healthcare professionals to avoid the problems of the past. If you are healthcare provider who treats Medicare beneficiaries in a Part B setting,

it is virtually impossible to obtain IVIG prices conducive to continuity of care. There are three reasons for this, modest price increases from the manufacturers; the implementation of the ASP plus 6 reimbursement methodology in Part B healthcare settings, and, not unlike the late '90s, we have increasing evidence of opportunistic pricing practices of the secondary channel distributors.

On this slide you can see our average selling prices from FFF, the price that appears on healthcare providers' invoices compared to the current Medicare reimbursement rate in Part B settings. This data shows how difficult it is for Part B providers to sustain continuity care for Medicare beneficiaries in a rising price marketplace. I believe the ASP, established from trailing six-month manufacturing average price data, was designed in anticipation of steadily decreasing prices. It simply does not provide adequate reimbursement in the rising price marketplace.

In this view we have broken down our

average selling price over the past three years and one quarter, the first quarter of 2005. We use the same non-lyophilized and lyophilized designations CMS created in bifurcating the rates earlier this year. The rising price trend is clearly eliminated from 2003 to 2005 data points from approximately 34 percent of the grams distributed in the United States. Please pay close attention to the pricing trend in 2003. We began to notify our largest customers of a tightened supply trend around October of that year.

When you consider this data you may begin to see what was happening with our inventory levels at FFF over the past three years. Around this same time, May of 2003, we had approximately 1.6 million grams of IVIG in our inventory. From that point forward, our ability to replenish our inventory began to diminish. Supply was gradually, almost imperceptibly starting to tighten. Take a look at the green bars that represent our 2005 inventory level data where we have around half a million grams of inventory in stock.

This is a more crystallized image of the situation we have today. We are only able to maintain 7 percent of our normal 30-day increasing

demand rate. There is virtually no inventory slack in the system and we are extremely dependent on timely lot releases and shipments, and we had between three-quarters to a million consumers that did not notice when we experienced delays in lot releases and manufacturer shipments. Right now, we believe we are as close to equilibrium as I have seen in 17 years of doing this. I can offer but one guarantee. This situation will change. How gradual and how manageable that change will be may be decided here today. I believe the inventory data on the previous slide and on this one mirror almost identically what was reported in the PPTA data.

Let's take a look at a specific product example. As you can see, our inventory for this product since the fall of 2004 has steadily declined. This is panglobulin. Panglobulin is one of the more affordable products in the marketplace

today. Despite what is generally spoken about doctors' business acumen, they know a bargain when they see it. Customers always gravitate to the lowest priced products.

We have seen a clear pattern of inventory depletion based on the product's price. The lowest priced product went on allocation first, followed by the higher priced products second. The highest priced product in the primary channel is also the latest entrant to the U.S. market, Octagam, manufactured by Octapharma. Coming up in a few images, you will see that we began importing the first commercial quantities of Octagam in July of 2004.

By September of 2004, all the lyophilized inexpensive products were on allocation to the manufacturers. In the non-lyophilized or liquid brands there was limited availability because at that time we were still building Octagam inventories.

Here is a graph of our Octagam receipts during the last six months of 2004 and the

beginning of 2005. I think it is important to note that IVIG must not come to us in one-twelfth increments. These are our receipts.

This slide depicts the growth in inventory of Octagam over the same period of time. Keep in mind that our overall inventory is plummeting while Octagam grows. Suddenly, in February we noticed a dramatic change. While our well trained sales force has done an outstanding job in introducing Octagam, I have never seen demand take off like this. We sold as much in January, 5000 grams, as we had in all of 2004.

In February demand for Octagam jumped to 117,000 grams. In March our biggest IVIG demand month ever in the last 17 years saw Octagam spike at 177,000 grams. In April, on the far right, because we could not sustain that rate of distribution, our sales for this product dropped. These numbers become even more meaningful when you realize that Octagam is sold through a very clearly defined channel. Only two distributors in the United States handle Octagam, FFF and ASD. If you

consider the March distribution data collectively between ASD and FFF, we distributed 350,000 grams of Octagam into the marketplace. This is an unsustainable rate. Octapharma cannot keep pace with this level of demand. Something very interesting is taking place.

Again, look back to the April data on the right. Distribution declines, as I said earlier, because our inventory cannot support the demand. If we had had 200,000 grams of Octagam in April we would have sold it easily into the marketplace. We cannot meet the existing demand.

Everything is now on allocation and we have more demand for Octagam than we can sustain. This is a graph from our popular buyer supply trends that we publish electronically twice a month. It is our IVIG supply index. We have less than 30 days inventory on hand on all products. We are the only distributor who provides this data publicly.

Now into the strong influence of the secondary channel, indicated in grey on the left

side of the slide. The primary channel distributors are in blue on the right side. The pricing behavior of the secondary channel is also very indicative of what is happening in the overall supply situation. They are a constant, destabilizing influence in this business. How big a force is it? By our estimates, 24 percent of the nation's supply is vulnerable to the pricing practices of the open market. That is over six million grams annually. Some people refer to this as the spot market.

Let me show you first a recent invoice reprint from a primary channel with a contracted price. Ironically, it is from FFF. You can see this being sold at \$40 per gram. If this product was purchased through the Medicare beneficiary the provider would still be having a loss because the current rate is \$39.14.

Here is a scanned image of a secondary channel distributor for the same product. These are recent invoices, 4/27/05. This was sold to a physician office that was unable to purchase enough

IVIG from a primary channel distributor to meet their patients' needs. As you can see, \$714 for a 12-gram vial is approximately \$59.60--I didn't do the exact math--or close to 50 percent higher than a primary channel distributor would charge. This type of behavior was tempered somewhat while we were able to supply Octagam in the \$56-\$57 range, and Octagam is a liquid product.

As our ability to meet this demand diminishes, surely this type of behavior will increase. Here is a recent price quotation from a secondary distributor who has a contingent liability with the U.S. government of \$45 million for alleged Medicaid fraud, with a clear pattern of opportunistic pricing behavior emerging. This is when the safety of these products becomes threatened.

As you can see, it wasn't just a price quotation from this company. Here is an actual invoice, a recent invoice from the same distributor, charging \$75 for Gammagard. You only pay these prices when you can't find it some place

else cheaper. It doesn't mean there is not IVIG but you only pay this price when you can't find it some place else cheaper.

I believe you will find this most fascinating. Frankly, it frightens me. This is a price quotation from a healthcare provider selling their IVIG supply. The current reimbursement and supply environment has made it sadly more lucrative to sell IVIG than to use it for a Medicare beneficiary. Perhaps even scarier is the language above the price table that shows panglobulin and polygene in the \$90 range in manufacturer's original packaging. What else would it be in? Heaven help us!

For my remaining time, I am just going to page through some recent examples of dozens of customers' testimonials that we have collected in the past few weeks. I will remain silent and allow you to read some of these testimonials as I page through them.

This is an interesting slide because this shows the transition for patients in a physician

office into a hospital. These are experiences of a hospital Tri-City Medical Center in San Diego, California. They indicate more bio. time, increased pharmacy staff time to increase the demand load of disenfranchised Medicare beneficiaries. There is a shortage of nationwide pharmacists, and also increased nursing time. There is also nationwide shortage of nurses.

Dr. Holmberg, can I have a few minutes for wrap-up? Just to conclude, manufacturer inventory levels have decreased. Primary distribution channel inventory levels have decreased. Demand continues to grow steadily, and we are in a declining reimbursement trend environment. For the first time, public payers can go to a web site and click on to see the manufacturers' average selling price. We will see declines in reimbursement in the private pay market. Before January 1 of 2004 that was not available to private payers. Medicare beneficiaries increasingly are being denied care and setting of choice. Opportunistic pricing from secondary distributors are impacting affordable

care in all settings. And, I believe we have a potential healthcare crisis on our hands and lives are negatively being affected.

An immediate action plan, if I can be so bold as to make some recommendations--we need grams placed in the trust of a responsible channel--perhaps the idea of a safety net. There must be a quick interim fix to the Medicare Part B reimbursement methodology, and the total industry, I believe, has to collaborate on a more permanent solution.

This may be a little controversial but I believe we need to ask FDA to assist in education of safe and appropriate use of albumin. Appropriate utilization of albumin and any possible decrease in demand will help produce additional affordable IVIG. And, we need primary channel distributors to supply inventory and distribution data. To that end, I commit to having our company be a part of the solution to this problem and we volunteer our data to be used to help assess the overall supply situation. Thank you very much for

your time, I very much appreciate it.

DR. BRECHER: We have time for one or two questions. Susan?

DR. ROSEFF: I have a question about the allocation method. You talked about the lyophilized products being allocated early on, and that changes the way other products get distributed. Can you explain that to me, please?

MR. SCHMIDT: Well, at first all the lyophilized products went on allocation. I think you are referring to the slide where the liquid products were not on allocation at that time. It is because we had plenty of Octagam in inventory, and we had plenty of liquid product at the time. On the earlier slide that I showed, it was almost as if there was a spotlight on each product and people would want to acquire the lowest priced product first. So that got tight to the next more expensive product and right down the line. At that time, in 2004, we still had excess grams of IVIG in our inventory so we could take up any slack, and if a healthcare provider had an allocation of

panglobulin, let's say, and they needed 200 grams and that was their allocation because that was their purchasing history from us, and they had some need for 300 grams we could provide them with liquid product. Maybe we could not provide them with the product of their choice but we had enough product in our inventories to provide them with another product choice. Today we don't have that benefit anymore. We don't have additional grams to augment anyone's existing allocation. Granted, it is not constant; they do not have a 200 gram demand per month. It is 250 a month, 300 a month and you have to be able to provide inventory at the time to meet the fluctuations in their demand. You know, we can't get patients to show up in one-twelfth increments.

DR. ROSEFF: So, are the products then distributed on a first come, first serve type of basis? Whoever gets there first gets the product they want and the others--?

MR. SCHMIDT: On the allocation system or in terms of what is available?

DR. ROSEFF: On the allocation system.

MR. SCHMIDT: On the allocation system we try and make sure that we have those--if you have

an allocation, for instance, and we get the product in we will contact you and say your allocation is 200 grams. Do you need 200 grams? And, if you don't need those 200 grams we try to move those to another location and interactively allocate. So, those grams should be there for you, for customers who buy from us on a regular basis. So, if you have an allocation the intent is to make sure that those grams will be there for you.

DR. BIANCO: Patrick, I hope you can help me understand where does the product in the secondary market come from? And, why do people choose to buy it in the secondary market instead from a reliable distributor?

MR. SCHMIDT: Well, that is a difficult question to answer. Where the product comes from, sometimes--often the manufacturer will sell directly to those secondary channels and they have various business practices to acquire the product

either from healthcare providers--and, we see this activity. As the inventory becomes short in the U.S., we see this inventory increasing. Most people will come to a primary supplier first, and if we can't meet their demands they are forced to go to a secondary supplier. The way the distribution system in the U.S. has been, in a long marketplace the customers look for the lowest price. In a short marketplace they look for product.

DR. BIANCO: So, did I hear you correctly that manufacturers themselves sell it to secondary?

MR. SCHMIDT: You did. They may not consider themselves secondary suppliers.

DR. BIANCO: None of us considers ourselves secondary anything.

[Laughter]

DR. BRECHER: Let me just make one quick comment, I would take issue--I don't want to speak for the FDA but I don't know that it is the FDA's role to provide education on the safe and appropriate use of albumin. Jay?

DR. EPSTEIN: Well, the FDA had posted a web notice after the publication that Cochrane report on albumin safety in the British Journal of

Medicine, alerting physicians to the need to consider those data which had called safety into question. Since that time, the meta-analysis that was in that publication had been criticized and a large prospective, blinded, controlled trial was done in Australia, the so-called SAFE study, which did not find safety problems with albumin with the potential caveat about concomitant brain injury.

So, I believe--Dot, help me out here--FDA has already posted a revised notice on its web site, or will do so soon, recognizing that more recent data have, in fact, reversed the previous thinking. We know that sales of albumin did decrease in wake of the Cochrane meta-analysis study and that there is the potential for decreased use of albumin to change the funding situation for the fractionators, so-called "reimbursement per liter fractionated." But, you know, we are neutral on the clinical practice. We just wanted to

promote truth to physicians and understanding of the current safety assessments.

DR. BRECHER: Thank you, Jay.

MR. SCHMIDT: Forgive me if that wasn't the right agency. The Cochrane report was devastating to the albumin market. Dr. Scott, if you will let me know when that is posted, I will get that to the committee members. Thank you very much for your time.

DR. BRECHER: Thank you. Our next speaker is Julie Birkhofer, who is executive director for the North American Plasma Protein Therapy Association.

Plasma Protein Therapeutics Association

MS. BIRKHOFFER: Thank you, Dr. Brecher, Dr. Holmberg, members of the committee. It is a pleasure to be before you again. I am Julie Birkhofer, on behalf of the Plasma Protein Therapeutics Association, PPTA. We represent the manufacturers of life-saving therapies, including intravenous immune globulin to treat individuals with primary immune deficiency, blood clotting factor that treats individuals with bleeding disorders, and

alpha-1 proteinase inhibitors that treat individuals with alpha-1 antitrypsin deficiency, as well as albumin and other specialty hyperimmunes.

Today I am here to talk about IVIG supply and reimbursement. Supply is linked to capacity, production and demand. PPTA member companies are committed to producing life-saving therapies. The industry has consistently demonstrated its commitment to invest in the IVIG community. Plasma fractionation results in the production of multiple proteins and the patient demand for IVIG has increased.

Access is linked to reimbursement. I have been before you in the past to speak about that. Methodologies are applied unilaterally and fail to recognize the unique nature of plasma protein therapies. These are unique life-saving therapies, very different from traditional pharmaceuticals. So, again, when a methodology is applied as one-size-fits-all, it doesn't work for our therapies. We have discussed that in the past.

ASP plus 6 percent, as implemented by CMS

does not reflect market dynamics. Provider and consumer organizations have been reporting that changes in reimbursement methodology are negatively impacting access to IVIG. This is an overview of what is going on currently. The main point here is to differentiate and to separate out supply from access.

With regard to supply, the goal of our companies is to manufacture life-saving therapies in a manner that assures the long-term viability of the industry. PPTA and its member companies work with stakeholders to support access to the therapies. Our March, 2005 data is in yellow, as it has been in January and February. However, this does not support a shortage scenario. As demand shifts over time the companies are responding, and have responded as you will see, by increasing supply to meet demand. IVIG production increases must be in balance with the market demand for other therapies.

Some possible issues that impact supply and demand balance--new entrants into the U.S.

market. As Dot Scott said, we have had four new IVIG entrants in the past year and a half. We have companies that are seeking FDA certification and licensure for their plants. There is increased use of IVIG. The companies have implemented yield improving technologies. There are scheduled maintenance shutdowns and order assessment, and I will talk a little bit more about order assessment in one of the following slides.

With regard to U.S. IVIG supply, since 1998 we have seen an 80 percent increase in supply, 15,000 kg to approximately 27,000 kg. PPTA is committed to keeping its commitment to stakeholders. We administer a data-gathering program where we report the industry aggregated data out to the stakeholders. Again, because it is aggregated it is averaged by a third party. PPTA and staff do not involve themselves in the hard data. This is a useful system for approximating available IVIG but, again, it is based on 12-month average distribution. Our companies report data monthly to the third party, Georgetown Economic

Services.

If there is a yellow or red light scenario PPTA sends letters to stakeholders informing them of the situation, giving them the ratio and directing them to the web site where we have a web-based traffic light style system. If you go to PPTA's web site you will see these icons. You click on them and it will give you the 12-month average distribution as well as the inventory. That is currently what we have on the left-hand side of our web site, if you go there, publicly displayed.

In the yellow light scenario, you can see January, February, March inventory now is in balance with the 12-month average distribution. The industry has taken responsible action since 1998 when there was a shortage. Congress found there was stockpiling and price gouging in the distribution chain. The companies individually put in place order assessment where manufacturers assess IVIG distribution to avoid speculation, to avoid stockpiling, price arbitrage and to make sure

that orders that are filled are in line with historical practices. Again, it is important to stress from an association's perspective that this is an individual company's decision based on their production planning and inventory status.

Very clearly, order assessment should not be confused with shortage. It is a consistent business practice when you have a yellow light scenario. IVIG is available but access is impaired. What I mean by access is impaired is that providers, physicians, cannot get the brand of therapy they want at the price they want to pay. They are not making their margins. It is impacting what they are buying and what they are making available. This is a provider issue and a consumer issue. Access is not as a result of a manufacturer's business practice.

If you look at this slide you see that reimbursement goes to providers and the role where we have spoken, the uncertainty in the middle, the distribution chain, the actions of secondary distributors versus primary, this is where we

believe the problem lies.

With regard to access, congress passed and the President signed, in December 2003, landmark legislation, the Medicare Modernization Prescription Drug and Improvement Act, known inside the Beltway as the MMA. It legislated major changes in reimbursement methodology. Among the changes was a shift from AWP to ASP. Whenever you have this sea change in methodology one can expect access issues down the road. PPTA, in January, 2005, in our comments, crystallized a little into the future and made the following comment: We believe that the transition to a new payment system for these therapies has the potential to create access problems.

PPTA, working with stakeholders and other interested parties, has put together the following list of short-term administrative remedies that we feel are within CMS' discretion, implementing the statute, classifying IVIG as a biologic response modifier; debundling the HCPCS codes to provide for an add-on payment to cover the cost of services and

supplies. Stakeholders have suggested classifying IVIG as a blood product for reimbursement purposes, and to conduct a demonstration project similar to what is currently done for chemotherapy infusions. Again, these are short-term options that we would like CMS to consider. The Association is working on a long-term legislative solution but, absent the fact that Congress will open up the Medicare Bill this session, this is the list we have come up with in the short term.

With regard to the ASP methodology, what has caused access problems is the fact that the rate ASP plus 6 percent is based on sales and all sites of service, including hospitals, with the exception of the DoD, VA and the Public Health Service. Hospitals generally use larger amounts of IVIG than Part B providers, are able to negotiate lower prices. You have on the flip side of that that the reimbursement rate applies only to the physician office and other Part B providers, and that results in the fact that ASP rates are brought down by sales to hospitals.

Some limitations of the ASP methodology--and, again, this is already clearly laid out in statute--are the six-month lag time

from the time data is collected from the manufacturers to the time it is published. It does not recognize the cyclical dynamic nature of the IVIG market. There are individual company price fluctuations that can and do occur within a six-month period. And, we believe that a CMS calculated ASP may not reflect actual ASPs by the time the rate is published.

PPTA has proposed that CMS fund a third-party auditor to assure the accuracy of these rates before they are published because we all have seen, and will hear, the impact on fragile populations.

The impact of ASP plus 6 percent on access--so far it has been reported from providers and consumers that there is a negative impact. It is restricting the physician and patient freedom of choice. Providers are reporting that ASP plus 6 percent is not a sustainable business model. Some

providers reportedly are shutting down their infusion suites. This is causing disruptions in site of service.

CMS responded with a band-aid approach in April, 2005 to separate the liquid versus the lyophilized forms of IVIG. It is not a complete solution. This is a complex issue. The long-term solution is to debundle each brand within the HCPCS code so that all the brands will have their separate code. The arbitrary split of liquid versus lyophilized or powdered fails to recognize individual therapeutic values. The result--access problems still exist. The therapies are still bundled and we have the same reported inadequacy issues with ASP plus 6 percent.

We would like to recommend that CMS take appropriate action. Failure to do so may result in continued patient access to care problems for IVIG. Patients may be forced to receive treatment in the hospitals, which is not the optimal site of service. Patients with primary immune deficiency disorders receiving treatment in the hospitals

exposes them to increased risk, as well as there could be increased cost to the Medicare system.

In conclusion, PPTA urges CMS to establish a long-term strategy on reimbursement of plasma protein therapies, including intravenous immune globulin. The committee, back in August of 2003, discussed the problem of access to IVIG and, again, the committee made a recommendation that CMS be directed to utilize validated cost data available from not just manufacturers, as is the case with ASP, but also from distributors. Plasma protein therapies, including intravenous immune globulin, are unique and a one-size-fits-all reimbursement formula does not work.

PPTA member companies are in the business of producing life-saving therapies. They have demonstrated their commitment and will continue to do so. PPTA has long demonstrated its commitment to patient access and will continue to work with CMS, Congress, the advisory committee, policy makers and consumer organizations to assure patient access to care. Thank you.

DR. BRECHER: Thank you, Julie. We have time for one or two questions or comments. If there are no questions or comments we will move on

to the next speaker. Thank you, Julie.

MS. BIRKHOFER: You are welcome.

DR. BRECHER: Amy Bassano, Director of the Division of Ambulatory Services, Center for Medicare and Medicaid Services. Any is an analyst in the Healthcare Financing Administration's Office of Legislation working on Medicare Part B policies.

Center for Medicare and Medicaid Services

MS. BASSANO: Hi. Thank you for the opportunity to speak to you today. I have no slides but I am happy to provide you with any additional information you may need. I will start with giving you a little background about Medicare Part B drugs in general and then I can talk to you more about IVIG.

Medicare Part B has a limited drug benefit. There are approximately 450 drugs that Medicare does pay for. These are primarily oncology drugs and other drugs furnished in service

such as IVIG. Inhalation and other drugs are furnished under the doable medical equipment benefit, certain oral anti-cancer drugs and oral immunosuppressive drugs. Medicare spends about ten billion dollars a year on these particular drugs, and the rate of growth is far faster than the rate of growth of Medicare in general, and it is faster than the rate of inflation as well.

Prior to 1994, Medicare Part B drugs were paid at 95 percent of the average wholesale price. Average wholesale price is similar to a sticker price, a list price that is reported and not necessarily related to exactly the prices that providers were accessing the drugs at. There are numerous reports from the OIG, the Office of the Inspector General, and the General Accounting Office that Medicare was overpaying for these drugs and needed to have a new payment system. The Medicare Modernization Act changed the way Medicare paid for these drugs towards a market oriented system that pays more accurately for the drug and also for the drug administration, or the issues of

chemotherapy administration with the doctor not being paid enough to administer the drug. So, it tends to end the cross subsidization between the drug price and the drug administration.

As we have already heard, beginning January 1st of this year Medicare began to pay based upon something called the average sales price. That is data that is submitted to CMS from the manufacturers on a quarterly basis 30 days after the end of the quarter. So, we are now in the process of analyzing the average sales price for the first quarter of 2005 that was due to us on May 2nd, so I guess two weeks ago.

As we also heard, ASP is for drugs based on all U.S. sales except for a couple of exemptions that are based in the law. The first is sales exempted from the Medicare rebate calculation, such as sales to VA and Department of Defense and then nominal sales, which are very small sales. Manufacturers also need to take into account volume discounts, property discounts, any other charge-backs and rebates other than Medicaid

rebates. So, at CMS we gather this information and we take a weighted average of all the drug codes and come up with the average sales price. Then we make that public and update it on a quarterly basis, and we pay 106 percent of the average sales price. That was all included in the Medicare Modernization Act and we are following the requirements of the law.

IVIG specifically is mentioned in the law as being included in the ASP. Unlike blood and blood products, other than blood clotting factors, they are excluded from ASP and continue to be paid under the average wholesale price. Just as a note, also on the blood clotting factor we also pay furnishing fee, which is a fee for the administration of the clotting factor, and that is 14 cents per unit.

The law doesn't give us the authority to use an alternative methodology. The wholesale acquisition cost, instead of ASP, in cases of a public health emergency but the way the law is written, it is a pretty high threshold that the

Secretary would have to determine and it is something that has not generally been triggered.

IVIG, specifically it is the number ten of the list of drugs that Medicare Part B pays for in terms of dollars spent on a product. In 2003 Medicare spent 182 million dollars on it and in 2004 Medicare spent 300 million dollars on the product. So, it is increasing dramatically even though the payment rate in 2003 was 95 percent in AWP and in 2004 it was 85 percent so we saw this enormous increase even with the payment rate decreasing.

As we have already heard, when we first put out the ASP methodology at the beginning of this year there was one code for IVIG. After discussions with the community, we split the codes, beginning with the second quarter, April 1 of this year, for a separate payment for liquid and lyophilized products. This was about the same time we started to hear reports of access and problems with providers being able to acquire the product with the Medicare payment rate. We have been

having a series of discussions with the community, with the FDA, with manufacturers, providers and patient community to get a better sense of what is going on in the market, and concur with what we have heard today. You know, there are many forces at work here that I think go beyond the Medicare payment rate.

So, one of the things we did do is we have talked to manufacturers about the submission of their ASP data because we are looking at areas where we would have control over some of these issues, and what we have authority to do, and because the ASP was so new we wanted to make sure--and we have done this with all other manufacturers as well, to make sure that they aren't missing anything; that they are doing it correctly, and we have found no issues there.

We have also increased our surveillance of IVIG issues through our 1-800-Medicare number where beneficiaries may call in if they are having a problem accessing a product through regional offices, there are ten regional offices across the

country, and through the local carriers who are contractors who process the claims. And, we have been getting reports of issues, mostly from providers, of the payment rate, although some beneficiaries but these reports do seem to be localized into particular areas of the country.

As I mentioned, we are also currently looking at the ASP submission for the first quarter and, given the discussion we have been hearing about price increases, we would hope that we will see that reflected in the ASP, although the data is lagged. This would be data from the first quarter that we use for the July 1st payment. It should be reflected if the prices are increasing as we have been told. It should be reflected in the ASP data.

One other point I would like to make is that we are very concerned about this issue and looking at what we can do but, given that there are multiple issues going on in the market, we are, you know, concerned that we don't want to take any step that would have any inadvertent effects or somehow further exacerbate any problems of beneficiary

access. I will be happy to take any questions.

DR. BRECHER: Thank you. We have time for one or two questions or comments. Jay?

DR. EPSTEIN: Thank you, Amy. Do you have precedents for other Part B drugs where the ASP is categorized or segmented according to the care setting? Because what we seem to have heard here is that there was, in fact, a lower cost of providing immune globulin in the hospital setting but driving reimbursement down to the hospital level has caused the dislocation because it is no longer affordable at home or in the infusion center. So, it seems as if we are creating sort of a circular problem because if you are force the patients into the hospital and they start receiving product at the lower cost and you continue to reimburse it at that cost when, in fact, what you have done is shift the care setting. So, the question is whether under the existing law the option exists to define the reimbursement level as care setting specific.

MS. BASSANO: Well, to answer your first

question, I guess the closest analogy would be chemotherapy treatment and we have heard that oncologists were saying that they would have to shift care to the hospital setting, although that was before beginning of this year, and we haven't heard real reports of that actually occurring and, again, we have very close monitoring of that going on as well because of the way the payment systems work, whether in the physician's office or the hospital.

So, the point to make is IVIG I think is unique. We heard that there were going to be lots of problems with ASP before it was implemented and now that it has been implemented IVIG is one of the few drugs that we have been hearing issues with. Most other providers can access the drugs with the Medicare payment rate.

DR. EPSTEIN: The second question was whether under the existing law you have the ability to stratify reimbursement based on the care setting. Your central point was that ASP averages all pricing, giving some weighting rate, but is

that the right model if, in fact, the cost of providing the product is different in different settings?

MS. BASSANO: Right. Well, that is something that we wouldn't have the authority to make the change. The law is clear about what is included in ASP and, you know, that it is all settings. It is all purchasers including institutional purchasers, and Congress specifically said ASP was to be the payment rate for these physician-administered products.

DR. BRECHER: Jerry?

DR. HOLMBERG: Amy, thanks. As far as IVIG being a biological product, would that require a legislative change or is that within the purview of the CMS?

MS. BASSANO: It would be a legislative change because it is specifically mentioned in the law as being paid under ASP.

DR. BRECHER: Two quick questions, why is there an administration fee for clotting factors and not for IVIG? You would think that they would

be similar. Two, I imagine the reason why CMS would be reluctant to debundle is because when you bundle you actually put pressure to use the cheapest product.

MS. BASSANO: Right. The first issue, the physicians can bill for the administration of the IVIG. The clotting factor is specifically mentioned in the law and my understanding--and you all probably know this better than I do--is that clotting factor is traditionally not administered in a doctor's office; it would be through home care or a special hemophilia service center.

DR. BRECHER: And the debundling?

MS. BASSANO: You are right, it is a weighted average so if you take it apart then you could force to the more expensive product.

MR. SKINNER: I am not quite sure how to ask the question but you made a comment in the middle of your testimony that there are many forces that go beyond the Medicare reimbursement rate that are affecting the access. Do I interpret that correctly to say that increasing the reimbursement

rate would not resolve the access problem? And, can you be specific about what those other forces are that you are referring to?

MS. BASSANO: Sure. We don't know what would happen but, given the testimony that was presented earlier on secondary markets and potential opportunistic pricing, we would be I think concerned that if we had authority and could somehow raise the reimbursement rate all that would happen is that there still would be supply issues, and there still would be the concern about, you know, the secondary market coming in and just raising the price to match what the Medicare rate is, and it wouldn't do anything to get the care and services necessary to beneficiaries. This is all speculation.

MR. SKINNER: So, the notion that industry or the manufacturers aren't producing additional supply isn't profitable--keeping in mind what I think was PPTA's comment that I think what they stated as their first goal was long-term sustainability of industry to supply not only IVIG

but all the plasma-derived products and, IVIG being an important part of that, they are not going to produce it if, in fact, there is a loss for them to do so. If the reimbursement rates go up, then it perhaps gives them incentive them to meet the supply needs. So, I am just trying to figure out, you know, how the pricing in the first instance that goes to the manufacturer isn't part of the solution.

MS. BASSANO: Yes, it is not clear which comes first and how it would work. But I can tell you that the agency is doing everything we can given our authority, and we are very concerned about this issue but, unfortunately, the law is relatively prescriptive and we can only do so many things.

DR. BRECHER: We are running out of time, maybe if it is a quick question, Art?

DR. BRACEY: Yes, one quick question, and that is a lot of the use is off-label. Is there information in terms of how much that is dollar-wise, and are there data on efficacy in

terms of the off-label use?

MS. BASSANO: I don't have the data. It is something that we are beginning to look into in the sense of, you know, we are spending a lot of money on these products and want to know who is getting it and what it is used for. It is generally at the local contractor discretion as to whether or not they are going to pay for it if it is for off-label use. There is a fair number of uses that are off-label that they are paying for, but I haven't heard of anything that they aren't paying for.

DR. BRECHER: Thank you, Amy.

MS. BASSANO: You are welcome.

Public Comment

DR. BRECHER: We will move into the public comment period. Michelle Vogel, Vice President of Government Affairs, Immune Deficiency Foundation will go first. I would ask that each of the public comments be limited to five minutes as we are already running behind.

MS. VOGEL: Thank you, Dr. Brecher and Dr.

Holmberg for holding this important meeting today, especially taking the time out to really talk about IVIG reimbursement.

Before I get into my talk, I want to first respond to a few issues that were brought up by some of the participants before me. The issue that Amy Bassano brought up on responding to a need to fix some of the other issues that are going on with the distribution marketplace, and especially the secondary market, and should we take care of reimbursement and would those numbers increase and actually take care of access to care--I have to say yes because when we first looked at the numbers and we saw the drop in reimbursement on January 1st to \$40/gram and all the patients were being dropped, and we brought it back up to \$56.72 we saw some patients being picked up again. On April 1st, when we saw the codes switch and break down again we saw all patients shifted.

So, although there are problems in the secondary market, which I think can be worked out within the industry and are being worked out, I

think we cannot wait anymore time before we fix the reimbursement numbers.

With that, I will take this really fast so we get back on schedule. IDF has received over 300 calls from Medicare patients. At the most, we have about 7000 patients primary immune deficient patients that are on Medicare right now, 300 calls from Medicare patients on January 1st is a lot of calls coming in, who cannot receive their IVIG infusions at their physicians' offices, outpatient infusion centers or home care settings, or even in the hospitals at this point. Some patients have been shifted to the hospitals and have been admitted for 23 hours for their infusions.

But I also have to say when Julie gave her presentation about patients being shifted to hospitals, we don't have that option anymore. Many hospitals are not taking patients at this point. We have a lot of patients who have not been treated as of January 1st, and some were taken back and now we have a whole crop of patients that have not been treated since April 1st and we can't wait any

longer because we are going to start losing lives. Every day that goes by treatment of IVIG is one more day that can't continue before we lose patients. We haven't had a report yet but I am sure we have lost patients at this point.

We have infusion centers that have shut down. Outpatient hospital clinics have shut down or are in the process of shutting down--Ohio State University, now Sinai Medical Center in New York City, a big infusion center, is talking about shutting down their IVIG clinic. It is crazy. Ambulatory Care in Texarkana, Arkansas, North Ridge Hospital Medical Center in Los Angeles--the numbers keep on increasing.

Right now, just going very quickly through data, I said we have 7000 Medicare patients. According to our data, 67 percent receive it in non-hospital settings; 32 percent, which we thought were being taken care of infusion and outpatient hospital settings and we assumed were under the hospital outpatient prospective payment system--it is not accurate. Many of those patients are in

infusion clinics located in hospitals but those infusion centers are actually owned by physicians and are billed under the physician payment fee schedule. So, the number of providers billing under the physician fee schedule is higher than that. So, we have a serious, serious problem.

I just broke this down to show you where CMS did a great job in bringing the reimbursement up on January 14th. We saw a drop again on April 1st with separating these new codes into lyophilized and liquid categories. So, right now we have products that cannot be purchased at the reimbursable rates and patients lose access of live-saving therapies at most, if not all, sites of care.

I am going to use my pointer for this chart just to show you the statistics. I take a typical primary immune deficient patient. Here is your rate last year, \$66; here is your rate under the liquid product reimbursement; here is your administration fees. When Amy talked about what the Congress intent was, to reduce the profits on

the drugs but increase reimbursement rates on the administration side it went down for these physicians that are treating with IVIG. So, here you saw a big drop in total for an average patient who receives 30 grams for 3.5 hours. Most of these Medicare patients are longer than that. Some of them are up to 8 hours administration. You have a decrease of almost 16 percent in the doctor's office. Home care, you have a huge blank here because they don't even get coverage for administering the product.

It is worse for the powdered products, the lyophilized. If you look here and look at the drop, almost 40 percent reduction so huge, huge decreases.

I had to put this slide up because I really do feel like I am being bounced around at this point. I do feel that everybody is very sympathetic and realizes there is a problem but nobody has been able to fix it at this point. Everybody at CMS has been extremely receptive and I have to thank Amy Bassano because she has been

fantastic in taking my calls at this point and working with us closely. They know that there is a serious problem but at this point we have no solution. I have met with all the members of Congress and the key staff on the key committees and we know that the Medicare Bill needs to be fixed. Will it be reopened this year? It is still a big question mark. It has to be but in the meantime we have problems. We have met with the FDA because there are reported concerns that reimbursement may not be the only problem occurring, and they are looking to see if there are supply issues.

So, I am here today with a number of patients that are not being treated increasing every day, and not knowing what to tell them when they get sicker, and knowing that time is running out before we start losing them when they call in and say the hospital won't take me and they try every single hospital in the area that a doctor has privileges at and no hospital will take them, and the hospitals are using every excuse, saying that

these patients have adverse effects and they need to be monitored in ICU units, or they don't treat with IVIG.

So, what we can do right now to get the patients treated--I know Amy said it is very hard to declare a public health crisis but I have to say we have a public health crisis. We have patients that are not being treated with a life-saving therapy that is approved for these communities. So, I say either declare a public health crisis or reimburse IVIG as a blood product. We need to go back right now into the old reimbursement system of AWP because we know that we can get the patients treated under this system right now.

Is it a perfect long-term solution? No. Will this get patients treated right now? Yes. Does it have to be as high as 95 percent? Absolutely not; that is high. But can it be equal to where the hospitals are being reimbursed? I would say yes. At 83 percent of the AWP, I would say that would get patients back into the doctor's office and the home care setting.

I also want to remind the committee that as of January 1st the hospitals dropped to where the physician offices and home care settings are

now. At that point, access completely for IVIG will be eliminated so the hospitals must be stabilized and cannot be switched over to the new reimbursement methodology.

So, what I really propose for the next two years is to freeze everything; get the physician payment fee schedule back to where it was under AWP; put it at 83 percent; keep the hospitals where they are; and let's get a study going on where we can really look at what needs to be done for the best payment methodology for this. Let's put together CMS and Congress with the manufacturers, the distributors, the providers and the patient groups because the goal needs to be to ensure access to all brands of IVIG in all sites of care. And, we need to develop a surveillance system. We have to ensure that the reimbursement never eliminates access to life-saving products.

For long-term recommendations, we could

look at unbundling the codes because, again, there should be no push to treat with the cheapest product; it should be the best product for the patient. But if you unbundle these codes right now without an add-on payment we will see what happened with separating liquid and lyophilized but even in a worse scenario. So, you have to have an add-on payment with that.

We also have to get the IV administration codes covered for all sites of care. Right now, the IVIG has dropped in the administration offices to a level that is equal to administering saline solution and IV antibiotics. The chemotherapy code included administration for biologic response modifier therapies and monoclonal antibody therapies. IVIG was meant to be in there but CMS doesn't recognize what a biologic response modifier therapy is. I am asking them to look at the definition and see what IVIG does, and recognize that because that will bring the reimbursement up by 20 percent so physicians aren't losing money by administering the product anymore.

We also need to set up a fee schedule really for IVIG specifically for all sites of care, for physician offices, for the home care setting

and in the hospital. I really feel that needs to be developed through a study.

That is really my presentation. If there are any questions I would be more than happy to answer them.

DR. BRECHER: Questions? Comments? If not, we are going to move on.

MS. VOGEL: Great! Thank you.

DR. BRECHER: Thank you, Michelle. The next public comment comes from William Larkin, Senior Vice President, Pharmacy Division, Greater New York Hospital Association.

MR. LARKIN: My thanks to Dr. Holmberg and the committee for inviting me here today to make some public comments. The good news is I have no slides, just comments. We had two presentations this morning, one from FFF Enterprises that supported a product shortage, and the other from Julie Birkhofer from PPTA that said that production was

in harmony with demand. From my members' perspective and, by the way, let me just go over my organization and whom we represent. The Greater New York Hospital Association is a hospital trade organization. It represents 175 acute and long-term care facilities in 14 counties in the greater metropolitan New York and New Jersey area.

My members' concerns are around availability of product, product integrity and price. There has been significant market consolidation in the last 18-24 months. Aventis-Behring, Alpha Therapeutics, Bayer Biologics and now the American Red Cross as a supplier all gone. ZLB acquired Aventis and moved production to Switzerland. Alpha has been acquired and moved production to Spain. Talecris bought Bayer Biologics and, thankfully, are remaining here, in the U.S., and ARC no longer market finished products that Baxter had made for them under an agreement. So, Baxter now will control all of that plasma supply.

So, it is our feeling that there has been

market consolidation due to an oversupply situation in 2002-2003 that has caused this rate of consolidation and now the manufacturers are emerging a little stronger. Pricing is starting to go up to support the manufacturing efforts, which is good; we need them to be strong suppliers, but we don't think that the supply is adequate to meet the demand.

Every one of my members experiences product shortages. They are all on allocation. Daily I get calls from my members about IVIG problems. I don't know which I answer more questions on, flu vaccine or IVIG but it is a continuing problem and I would advocate that manufacturers look a little more closely to the ebbs and flow of the demand curve. I know that they want to keep pricing at a certain level to support their efforts but the demand is out there in the marketplace, as you have seen from the PPTA slides. Their production has increased in response to demand but we don't think it is where it needs to be at this time.

Those are my comments. Thank you very much for the opportunity. I appreciate it.

DR. BRECHER: Thank you. Are there any

other public comments on the topic of IVIG?

MS. SCHWEITZER: My name is Melissa Schweitzer. I would like to also thank you for bringing this important concern to the committee today. I am the Director of Patient Advocacy for the Immune Deficiency Foundation and I talk with literally thousands of patients with primary immune deficiency diseases on an annual basis. I am also a patient with common variable immune deficiency and have been on IVIG every four weeks for the last 18 years. So, I personally understand the plight that many of our patients have faced in getting a diagnosis and dealing with the frequent--excuse me, this is very true to my heart--and serious infections that characterize this type of chronic condition.

I also understand the relief in having an effective therapy for this diagnosis and others treated with IGIV. Equally, I understand the fear

and the worry or knowing if this therapy that has allowed me and others to lead a normal and productive life will be accessible to me in the near and distant future because of the current reimbursement crisis.

While I have not yet been personally affected by this crisis that has hit our community, I have talked with numerous patients who have been, and I am here to represent those patients who couldn't be here to tell their stories. I would like to share just a couple of stories with you today. I have not used their real names.

In late March, Brooke was told that she would no longer be able to receive her regular IGIV infusions in her immunologist's office where she has been receiving them for more than 15 years to treat her primary immune deficiency disease. With her immunologist's assistance she began her search to try and find a hospital to treat her. Of the two closest to her in eastern Florida, one did not carry her preferred IGIV product and the other informed her that they would only provide IGIV to a

patient with an acute illness who needed it. She has had numerous reactions to other products and, therefore, is dependent on her specific brand so, therefore, a search for another hospital.

A hospital 30 miles from her home was able to treat her, however, she recently had her first infusion there and it didn't go well. Besides having to drive the distance, Brooke, who is in her 70s, explained that she had put cream on her hand where she usually receives her infusion to reduce the pain of the needle insertion. The nurse gave her a difficult time about using the cream and informed her that she would give her IV wherever she wanted. Most concerning, Brooke's infusions typically last about eight hours because of her previous reactions. In the hospital she was told that she would have to receive her IGIV in four hours because that was their protocol.

At the end of her four-hour completed infusion, Brooke developed shaking and was shrugged off by the treating nurse when she told her. She had to then drive home in this condition.

Additional adverse effects, including confusion and a headache, developed later that evening, lasting into the next day. Her next infusion is next week and she is very concerned about going back to this same hospital but has no other choice.

Linda is another patient. She lives in Texas and her last IGIV infusion was on March 29th. She has common variable immune deficiency and began receiving IGIV therapy in '96. Until March she had been receiving her infusions in her immunologist's office. Because of the reduced reimbursement of IGIV, her immunologist can no longer treat her and two local hospitals have refused to treat her because they do not want to take on the responsibility.

Linda explains: Before I began my IGIV treatments my condition was so severe that I was in bed all the time. I could not do anything for myself. It was terrible. Once I was finally diagnosed and started treatment it still took a long time for the treatment to work because I had been so sick. Now I need my treatments to stay

healthy and I would go to the hospital but I am also fearful because of exposure to infections but now they won't even take me. We are very sick people and they are denying life-saving treatment. It would be like taking insulin away from a diabetes patient or taking chemotherapy away from a cancer patient, though they wouldn't do this to a cancer patient. But they can get away with taking our treatments away because so few people know anything about our diseases.

Linda goes on to explain that we should be able to continue to get the treatments in our doctor's office. He monitors us to make sure we don't have side effects. They know what to look for and they keep us away from other patients with infections that can make us sick.

She also says I am afraid I will end up back in the same condition I was in before I started by IGIV therapy. I will get infections and not be able to fight them. I won't be able to care for myself or provide for myself. I don't know what I am going to do.

So, now you have heard the fear and worry that is spreading across our community. This has started with Medicare patients but we have also

received calls from patients with private insurance who can't get their infusions because the insurance companies have dropped their reimbursement rates to match Medicare. The patients preferred sites of service, such as some home infusion companies, can't afford to treat them. After finding this out, I too called my home infusion company to determine the status of my infusions because, obviously, this has become very alarming and scary for me. I was reassured for now that there are no problems with the supply or reimbursement of my product.

So, in closing, I would just like to reiterate that IGIV is a life-saving therapy for me and so many other patients with primary immune deficiency diseases. It allows most of us to live nearly normal lives with a manageable number of infections. Without it we will again face the serious recurrent and even life-threatening

infections that plagued all of us before our diagnoses. This is what is starting to happen and will happen to more and more patients if the reimbursement of IGIV continues at the current rates. On behalf of the Primary Immune Deficiency community, I urge the committee to help save the lives of our patients by working with us to help solve the reimbursement crisis. Thank you.

DR. BRECHER: Thank you. Any other comments, if they can try to keep their comments to five minutes or less?

MR. STEIN: I will probably do less. My name is Gary Stein. I am Director of Regulatory Affairs for the American Society of Health System Pharmacists. We have 30,000 members who are pharmacists working in hospitals, inpatient and outpatient clinics, home care and long-term care and other components of healthcare systems.

We are very pleased to see the strong recommendations that were made by the committee in its January meeting regarding adequate

reimbursement for plasma-derived products. We are very disappointed that CMS has not yet responded to those recommendations. We think that the committee should continue making similar recommendations until they hear a response from the agency.

Our members have told us that hospitals are already stressed because of the number of patients that have been transferred into hospitals from outpatient clinics where they have been receiving these therapies. We are also concerned about the higher cost. The higher demand, the higher cost make it very attractive for what we are calling the grey market to get into this, and we are not only concerned about the higher prices, this is a safety issue. We have seen with other drugs that when the grey market secondary and tertiary suppliers get into it we have a problem with diverted drugs, counterfeit product and, because of the storage conditions necessary to produce products, we see a significant safety concern. Thank you very much.

MS. BOYLE: Hello, my name is Marcia

Boyle. I am the Chairman, CEO and founder of the Immune Deficiency Foundation. I want to thank the committee for having this meeting and for focusing attention on IGIV reimbursement. It has become an unnecessary and avoidable public health crisis for the primary immune deficiency community, as well as for the many others who rely on IGIV for their life-saving therapy.

A key role of IDF, the Immune Deficiency Foundation, is to immediately react to the needs of our community and implement programs to meet those needs. Now the biggest threat to our community is the IGIV reimbursement practices. As a parent of an immunodeficient son--and you have certainly heard the testimony of Melissa Schweitzer--let me tell you there is nothing more frightening than to learn that patients can't obtain the therapy that keeps them healthy and ultimately alive.

IDF will immediately begin surveying the Medicare patients and physicians who treat our community to assess the impact that reimbursements have on access to care, as well as negative health

outcomes due to delays in treatment, reductions in dosages and changes in product of choice. As you have heard, IDF has received over 300 phone calls from Medicare patients and physicians since the change in reimbursement since January 1st, and the calls are increasing weekly. We have also received reports of potential product supply issues. We understand that data needs to be collected to determine whether or not the issue lies deeper than reimbursement and if there actually is a supply issue.

In the late '90s IDF was able to quantify the IGIV shortage and implement the safety net program for physicians and pharmacists to be able to get products for their patients. Due to requests that we are receiving from physicians who are having problems accessing products, we are actively evaluating the need to restart the safety net program. We can't stress enough the need to increase the reimbursement of IGIV immediately to ensure access to all brands of product and all sites of care for our community.

IDF will share the results of our surveys with this committee as well as CMS, FDA and Congress but we can't wait for the outcomes to

implement the type of relief that our patients need that are going without treatment. They need to get their infusions immediately. We can't allow patients to become sick, be hospitalized unnecessarily, and some to die when we have an FDA approved therapy that is the only life-saving therapy for primary immune deficient patients that cannot be affordable due to reimbursement. When Congress enacted the Medicare Modernization Act last year it was shortsighted in understanding this particular product and the impact that changes would have on patients who depend on it.

A public health crisis has been created and patients are suffering unnecessarily. Tomorrow is too long to wait for a solution. IDF respectfully urges this committee to rectify this appalling and unacceptable situation immediately. Thank you very much for your attention.

DR. BRECHER: Thank you.

MR. DONOHUE: My name is Chris Donohue and I suffer with two chronic illnesses, a chronic immune demyelinating polyneuropathy and a chronic immune deficiency. I will try to be very short here.

I would like to start out by contrasting

my physical condition prior to the onset of my condition in 1990 and what my condition is today. I was a very active, physically fit, healthy 25 year-old. I was employed full time, working up to 50 hours a week, and enjoyed a happy and fulfilling social life. I engaged in many sport activities, exercised and ran five miles a day but, weighing 200 lbs, I carried very little fat.

Within a two- to three-month period from the onset of the disease, my physical and emotional state deteriorated significantly. Simple daily activities I once took for granted and did with little effort or concentration became difficult or impossible to perform. I was unable to continue to work at all. I could not engage in any sport activities. No longer could the five mile runs and

exercise that I looked forward to each day be a part of my life. Most social events that occurred with friends or family I could not take part in because of pain, pressure flare-up paralysis, fatigue and lethargy. From muscle wasting and gastrointestinal complications, my weight dropped from 200-160 lbs.

Other than the limitations I already described, I experienced the following, I needed assistance getting up out of bed and from a chair. When dressing, I was unable to do buttons or zippers. Simple hygiene, showers, shaving, raising arms, grasping to brush teeth and shave was difficult and at times impossible. I was unable to prepare my own meals. I had difficulty eating due to problems of raising my arm and grasping.

In 1991 I was diagnosed with chronic immune demyelating polyneuropathy. Initially the illness affected me by causing partial muscular paralysis and sensory paresthesia. Plus, I incurred the following deficits, significant loss of muscle mass and motor coordination; inability to

sustain physical activity, work or sport activities; severe systemic chronic pain; sweats, fevers, sleep disturbances, irritability, chronic lethargy and depression; frequent and repetitive sinus and respiratory infections that were treated with courses of antibiotics. I was later given a secondary diagnosis of the chronic immune deficiency by my physician, Dr. Draker.

I initially was treated with steroids and plasmapheresis. The steroids did not help at all. In fact, they caused physical and psychological side effects. The steroids were gradually eliminated. The plasmapheresis was effective in that it marginally improved muscular motor function. However, it became less effective, requiring treatments weekly and, on occasion, more than once a week. Sometime in the mid '90s, after IVIG was proven to be a beneficial therapy for my conditions, my doctor, Dr. Draker, began to give me infusions. These infusions noticeably improved my condition in a matter of three to four months. The simple activities of daily living--shaving,

showering, dressing, eating, raising and lowering myself, rocking, balancing, steadying myself all improved. As important was the fact that the chronic infections that I had, treated with antibiotics, were no longer laying me low, and I have not experienced one of these infections nor have I had antibiotics since this time period.

Although I still battle with many challenges of living with this disease on a daily basis, there is no question regarding the efficacy of IVIG therapy that I have been receiving. In May, 2004 I had a complete neurological evaluation, muscle testing, nerve conduction study. These studies, when compared to those before I was receiving IVIG infusions, show an overall improvement with the transmission velocity of motor nerves and, furthermore, the muscle testing improved as well.

The changes in the Medicare reimbursement formula for IVIG have had an effect on my treatment and condition. One of these changes was in the brand of IVIG that I had been receiving was

changed. This new brand caused a reaction with me. That is, my skin broke out in hives. Besides that, I experienced light-headedness and weakness. The reaction went from bad to worse why airway started to restrict. Thankfully, because of Dr. Draker, his expertise and professionalism of his staff, I was quickly administered medications which altered this potentially fatal situation. I also experienced severe burning and inflammation in my vein from the access point of my arm and into the shoulder.

In 2005, the reimbursement formula interrupted my prescribed treatment schedule. I was three weeks overdue on two different occasions. This meant I have lost two treatments in total. I began to have symptoms of deterioration in both my upper and lower extremities, with significant increase in tingling, prickling and numbness. I also experienced some muscular deficits. My muscles fatigued more quickly and I have experienced unsteadiness which continues now.

These treatment interruptions cannot

continue. Without IVIG I will deteriorate to the condition I was in prior to receiving IVIG or worse. The higher level of exacerbation caused by treatment interruption can result in nerve axon damage in my body. Nerve axon does not regenerate. This could lead to deficits that can't be reversed, which would be very tragic for me.

Though I have had treatment interruptions, thankfully, due to the compassion and tireless efforts of my physician, Dr. Draker, I have not had the misfortune of being without IVIG as others have since January of 2005. There are some people, as we have heard here today, who haven't been able to have treatment at all.

In closing, I would just like to thank you for the opportunity to present my treatment history and the deep concern I have that the treatments will continue as in the past not only for myself but for all of us who suffer with these crippling diseases. I am grateful to have been invited and know that you care enough to listen to someone who has benefitted from IGIV's life-saving treatment.

Thank you very much.

DR. BRECHER: Thank you. Please?

DR. DAVIS-FUJI: Hi. My name is Dr. Davis Fuji. I am a neuromuscular specialist in private practice and also on faculty at UTMB, in Texas. I would like to bring to this committee's attention that my patients cannot get adequate access to IVIG since the Medicare has changed its funding. I have to send all my Medicare patients to the hospital. The hospital doesn't have the drug; they don't have the nurses that know how to administer it; they don't have the space, and their condition is deteriorating. In fact, I have a patient here that has come all the way from Texas to express her concern as well.

I would also like to reiterate that all IVIG products are not equivalent. You would use one brand for a patient with congestive heart failure or with chronic renal insufficiency, whereas you would not consider using one of the other ones. I would also like to support what Ms. Vogel said as well. Thank you.

DR. BRECHER: Thank you.

PARTICIPANT: Hi. I am one of Dr. Fuji's patients from Texas, and I am the local

representative for the Myositis Association. I have myositis and I am alive today because of IVIG. I will die without it. Here is one of Dr. Fuji's patients. She is one of the people, this is her face. I would like someone to explain to us and to her why we are expendable. She will die and she will die very soon without this treatment. The quality, the limited quality of life she has now is as a result of this specific brand of IVIG. We thank you for hearing us.

PARTICIPANT: This is not easy for any of the patients. Without IVIG our life will deteriorate. I have a quality of life with it. If I don't have this treatment, like I said, I will eventually die. We need somebody to stand up and look at us and know that we are people; we aren't just numbers, we are people and we need your help. Please help us, the thousands of people who couldn't be here. Please try. That is all I can

say. Thank you.

DR. BRECHER: Thank you.

PARTICIPANT: Good morning, Mr. Chairman, members of the committee. I am with the Committee of 10,000. We are not unknown to the committee. It was our work with Sen. Kennedy's office and Sen. Graham's office that led to the Institute of Medicine report whose recommendations led to the establishment of this committee.

I think it is important to remember that what was in those recommendations and what you are hearing today is that this issue cries out for leadership and coordination at the federal level between agencies, CMS, FDA, CDC, HHS, and we are concerned that that coordination isn't happening and, as a result, people who are in dire need of immune globulins are on a roller coaster similar to one we have seen in the past. Our experience with immune globulins became firsthand in the age of AIDS because many persons with hemophilia surviving with HIV came to depend on immune globulins for various off-label usages and problems they were

having and that is still going on.

I am a person with HIV and hepatitis C. I know what that roller coaster is like. The downward pressures to a less safe product are really frightening when you are on this side of the table. Unfortunately, we believe with what we have seen with IVIG today is that the gains we made in the 1990s that were pretty strong and took a lot of effort and death of a number of people are at risk now due to the pressures of economics, not the pressures of supply at this point, not the pressures of safety because we have safe products available, but the pressures of economics.

We all know that we are dealing with limited resources. The issue then, it seems to us, becomes one of leadership. How do we use those resources, not bankrupt the system, and try to ensure the greatest degree of safety and efficacy in a large landscape where coordination with federal agencies is absolutely critical? Frankly, from my perspective, we don't see that coordination. We see it in some areas. Obviously,

we are very glad to see the participation of CMS at the table. We have had some discussions with CMS in recent times. But we think a lot more leadership is necessary.

I don't mean to repeat what Marcia Boyle said but the kind of things you are hearing today are critical when you listen because I think the problem is going to grow and I think we are all facing the situation where that leadership has to come here.

As I said a moment ago, the gains we made in the '90s we see being eroded. The last thing I would like to say is we are glad to see CMS at the table but we think it is absolutely unconscionable that the hepatitis C epidemic is not being addressed in a more concrete way. The leadership is not coming and we are having trouble getting co-infection on the table and treatment for so many people with immune deficient problems you are talking about today.

In closing, I would like to say we believe that the Committee of 10,000, an we are meeting

this week to discuss just this--that the committee needs to reinvigorate itself and be aggressive about the federal response which is what the IOM recommendations were all about, and what the committee has done at varying times very well. Thank you for the opportunity to address you today.

DR. BRECHER: Thank you.

PARTICIPANT: Good morning. I am the President of PPTA. One of the reasons that I work for this industry is because I am concerned about patients. Though I didn't finish my medical school, I believe in my position I can make a contribution. And, one of the contributions that I can make is to correct some statements that were made today that would lead to a false assumption.

I think it is clear from the patient testimonies what is at stake here. The reimbursement issue is causing tremendous problems and is putting the health of patients at risk. One other individual, I think it was from the Hospital Association, made a comment about the enormous consolidation that we have seen, also alluding to

the fact that some companies have shifted their fractionation to other parts of the world. The way it was presented it looks negative but it is very positive. By shifting your manufacturing capacity you are able to use better technologies that lead to higher yields so more therapies become available and, given the economic pressures that we have been dealing with, it is very important that we manufacture as much as we can.

So, I just want to make sure that people understand that the issue today is not a matter of supply. The data that Julie Birkhofer has presented today clearly indicates that we do have inventories. There is not a shortage scenario but there is a big availability problem, an availability problem because the physician is not able to provide treatment in the physician's office. That is the main problem.

I have one request for the committee. You have heard the statements. You have heard the testimonies of patients. You started this meeting by saying that you could not agree on the

recommendations from the previous meeting because the minutes were not approved as a result of change of administration. You cannot wait for one more month. Something needs to be done.

DR. DRAKER: I am Dr. Draker. I have the honor of caring for patients like Chris and others who trust me with their care. I have had patients like Chris who have been placed on ventilators and have come very close to dying. I am here because I am very angry. I became a physician to care for people, not to be handcuffed by bureaucracy. It is unconscionable that my ability to care for patients has been limited by the bureaucracy that we are a part of. I am also just disgusted that despite the number of calls I make--I visited Washington to meet with senators and congressmen, on my own time two weeks ago. I received no response.

Chris has received care, as my other patients, because I have been financing their care. I have been buying my product. By the way, I receive \$93 total for infusions that last anywhere from 2-8 hours. I cannot continue to do this. I

cannot continue to see my patients deteriorate and not have answers for them.

This is not something that can be dealt with at the next quarter. It cannot be something that we just assume is not a healthcare crisis. This is a crisis. I cannot stand by and watch my patients deteriorate any longer. I just don't know what else to do. I have always been idealistic; I have always had a positive outlook and been able to help patients with whatever healthcare need they have. I have no other options available to me. I need people to just respond appropriately to the needs of my own profession, my own patients. Thank you.

DR. BRECHER: Thank you. We are going to take just a quick ten-minute break and then we are going to come back and we are going to fix this. Right?

[Brief recess]

Committee Discussion

DR. BRECHER: All right, we have heard the problems of the intravenous immune globulin use in

community this morning. We have addressed some of these issues in the past, or at least similar issues in the past. The problem remains. We don't have resolution to this problem. So, the question is what can we as an advisory committee to the Secretary of Health and the Assistant Secretary recommend to try to fix this problem?

Just to remind people where we were, to remind you what we said at the last meeting--and we are still waiting for a response--about reimbursement for plasma-derived products and recombinant analogs, for those of you who can't see this, it says the committee found that current reimbursement schedules for plasma-derived products and recombinant analogs for treatment of chronic conditions are not adequate to support optimal care of individual patients. Additionally, shortages in supply of these needed therapeutics have impacted the healthcare of these life-long disorders. The committee, therefore, recommends the Secretary take steps to augment reimbursement for plasma-derived products and recombinant analogs.

The committee endorses the following principles to guide such effects: One, plasma-derived products and recombinant analogs

shall be reimbursed at rates consistent with the true costs, including costs of distribution and administration. Reimbursement should be sufficient to ensure an adequate supply of these therapies. Individual products within product class should be recognized as therapeutically unique. Equivalent reimbursement should be provided in different care settings and the life-long cost of treatment to the individual patient should be addressed in any pricing structure, including the extraordinary impact of co-payments.

So, this topic is now open to discussion among the committee. Art?

DR. BRACEY: There was some discussion and I think it is pertinent, this was pointed out today as an emergency. Clearly, we have to fix it but it appears that the options that are available to us will be slow, and in order to allow these people to have access to their needed therapies I would

suggest that we recommend to the Secretary that it uses the option to address the public health emergency. We did hear that there is an option from the CMS staff to address this sort of issue, and I would encourage that in order to, again, facilitate access that we would recommend that the Secretary use that option and then we would think about other strategies that would fix it over the long term. I am a little bit concerned about the ability to correct it with the mechanisms that are existent.

DR. BRECHER: Celso?

DR. BIANCO: It was a very difficult morning here in the sense that we hear from the outside--the presentations from the patients were really very touching. We have the manufacturers. We have their issues in terms of manufacturing and having their profit. We have distributors. We have secondary distributors--we didn't hear any. We have the pharmacists and we have CMS stuck to a law that doesn't seem to be responding to those needs.

So, one, I want to support what Art just proposed, that this is a public health emergency that should be addressed as such. Second, I think

that to wait for a legislative response is something unrealistic considering the urgency out there. I think that CMS has been creative on other occasions, and I think that they can be creative here and find additional ways by which they can reimburse the costs of administering these products in different settings that would balance out everything.

DR. BRECHER: Karen?

DR. SHOOS LIPTON: I am very much in support of everything that Celso and Art said. I think we have an urgent situation. It is not quite clear to me what path, and whether we can request that the Secretary deal with this as a public health crisis but at least we should do that. I think that it is very important that we put some sort of time on this in any kind of motion because I think we want to make sure that it is dealt with as soon as possible.

DR. BRECHER: We seem to have lost three months since our last meeting where nothing happened.

DR. ANGELBECK: I fully support everything that has been said, and I think the time is an issue here and at least one thing I thought I

heard, although I am far from understanding all the options here, is that there may be the ability for CMS to do a demonstration project that would not require regulation or legislation. If we knew more about that option, perhaps that is one thing that could be explored to address this more immediately.

DR. BRECHER: Mark?

MR. SKINNER: I don't see it in our materials but I am recalling PPTA's presentation where they identified what I think were about four regulatory or administrative options, one of which was the demonstration project that wouldn't require legislation. I think the other specific suggestion was perhaps from Michelle, looking back at average sale price or freezing, and I don't think that can occur regulatorily. So, I am wondering if we could

take a look again at PPTA's four regulatory options and perhaps discuss whether they could be a framework for a recommendation.

I agree completely about declaring a public health crisis. What is occurring is, in fact, tragic and it is only going to get worse. Time is of the essence so the regulatory and administrative options seem to be the only course of action that we can pursue. But if we can get a copy of them or have them, it would be helpful.

MS. VOGEL: I just want to respond to that. I did meet with CMS about a demonstration project. If it costs any money they will not do it. So, we approached them with something similar to the oncology chemotherapy with a survey so we can kind of get a handle of where all the patients have been shifted to, which patients haven't been treated, about adverse events with switching products, these type of things, and came up with a cost of, I would say, about 12 million dollars associated with that if we were treating all the Medicare patients, and what the add-on fee would be

to get all patients back into either the home care settings or physicians' offices or outpatient clinics, and access to all brands. And, they said absolutely not. So, we addressed that.

We looked at a number of other areas such as adding up to 15 percent if there is an access to care issue, and that would have to go through a whole rule-making process which would be very difficult to do. So, we have gone back and forth with every option possible that CMS can do, and that is really where it led to the issue of could we do either a declaration of a public health crisis or in terms of recognizing it as a blood product, which it is. Amy Bassano said they did actually define IVIG under the ASP formula, which makes it very difficult.

DR. BRECHER: Gerry?

DR. SANDLER: The committee is very much in support of an urgent emergency action. The one differing position that I might have is to make sure that we put into this document that this should be funded with new money. Very

specifically, if we have a budget and one part of the budget is under-funded, the quickest way, it seems, in an emergency to find a solution is to take something from somewhere over there and move it over. That is just going to cause another committee that advises the government to have to have some crisis. So, I think we want to make it very clear that this has to come from new money to fund this and not from some other budget within the healthcare system.

DR. BRECHER: Celso?

DR. BIANCO: Just very quickly to add to the comments that were made, I don't think it is our role to find the exact solution because we don't understand the system as well as CMS and others. Our role I think is to recommend to the Secretary that it is an emergency and that the solution is within CMS, period, and they have to find it.

DR. BRECHER: Paul?

DR. HAAS: I don't want to lose the second part of what Art said right in the beginning.

There is a long-term issue here also and I think we are right in looking at the immediate problem but we don't want to lose sight that we need to come back to the longer-term problem.

DR. BRECHER: I think it is probably not going to work to draft a recommendation at this moment, but maybe we could have a small working group to work on drafting some preliminary recommendations, say, over lunch or overnight. So, I am looking for volunteers to work on drafting this recommendation from the committee members.

DR. HOLMBERG: I think this is the slide that Mark Skinner was asking about.

DR. BRECHER: Jay?

DR. EPSTEIN: Could I just ask whether those mechanisms would require any rule-making or guidance? Because I think that the issue here is the time line, whereas the solution may lie with CMS, it is not at all clear to me that rapid intervention lies in the power of CMS. So, if this can be done by administrative fiat, fine, but if this requires administrative procedure at any

level, we are looking at, you know, months at a minimum.

So, I support the statement that what we have learned is that there is a crisis now and what we are looking for is feasible corrective action now. It will be a band-aid. No one should think that whatever can be done now is going to fix the long-term situation, and that will require deeper level of insight and, you know, more creativity and constructive problem solving. But what we are looking for is just something that will bring the situation under control now. So, I hope, again, we have given you enough time to figure out if you can possibly guide us on whether these would be administrative actions that could be done summarily or whether they would require some kind of more time consuming procedure.

DR. BOWMAN: For the four bullet points on the slide, the first one, classifying or categorizing IVIG as a biological response modifier, biological response modifier are the words used in the statute. It doesn't actually say

in the statute whether IVIG is or is not a biological responsive modifier. So, there is some interpretation left open in the statute for that. What the intent of the statute was and whether it was intended to include IVIG is a separate consideration and, certainly, CMS would have to explore that in making that sort of change. I don't think that would necessarily require a proposed rule though.

The debundling, as it is termed in the HCPCS codes, basically is requesting to make a product specific HCPCS code for every IVIG product. Again, it would not require a rule because HCPCS codes are internally created by CMS for internal programmatic needs, which is separate from the regular HCPCS annual coding cycle process. So, that would not require a rule per se or a regulation.

Again, it remains to be seen whether or not just debundling and making product specific HCPCS codes in and of itself would solve the problem because the problem appears to be, from

what we understand today, a price gouging problem by so-called secondary, non-primary distributors. So, I am not sure that that addresses the so-called distribution or supply chain problem that we see today. Somehow secondary distributors are getting a hold of product from the manufacturers and they are price gouging it, as we have been told today. So, whether that would solve the problem or not I don't know.

Now, the third bullet is classifying IVIG as a blood product and, of course, reimbursing according to the way blood products are reimbursed. Again, I don't think that would require a separate proposed rule. Let me just preface that by saying I don't work in the exact section that drafts the physician fee schedule rule each year. That rule is drafted each year. It comes out as a proposed rule and then comes out as a final after comments. I may be mistaken and it may be required, but recategorizing IVIG as a blood product and paying it on a physician fee schedule as a blood product would have to be in the proposed and final

physician fee rules. The physician fee rule is under consideration right now and the final physician rule usually comes out around late October the first of November each year. So, that is certainly one solution or fix, if you will, a short-term fix that might require a proposed rule.

Finally, to conduct an IVIG demonstration, there is a whole host of issues involved with that because in CMS' world demonstration in and of itself has a very specific connotation under the statutes and under its authority, and there is a certain limited amount of funding for demonstrations in general each year. Many of the demonstrations actually ongoing right now were required by previous statutes, including most recently the MMA statute. So, I don't think a pure demonstration, in and of itself, would be a fix. Though the way demonstration is used in this bullet point means a survey and an add-on payment to the physician fee schedule, in the oncology sector was to get some increased payments for their chemotherapy infusions, and we are all aware from

last year's physician fee schedule there was actually a proposed and final rule. So, that would require some regulation.

DR. BRECHER: Julie, did you want to make a few comments?

MS. BIRKHOFFER: I don't know, Dr. Epstein, if you wanted additional comments that Dr. Bowman provided, from the CMS perspective. I am quoting from a memo from Hogan and Hartson PPTA's reimbursement counsel and, according to this memo with regard to biologic response modifiers, IVIG is being billed using codes for intravenous therapeutic or diagnostic infusions. The agency's CMS codes specify that IVIG should be considered a biologic response modifier for purposes of determining the appropriate code to bill for the administrative service. When CMS created the new drug administration codes it indicated that the chemotherapy administration codes also apply to "monoclonal antibody agents and other biologic response modifiers," 69 Federal Register, 66236, November 15, 2004. The special status for biologic

response modifiers was created by CMS and the agency did not define the phrase clearly. As a result, it remains for the agency to determine what products are to be considered a biologic response modifier. CMS has the authority to consider IVIG a biologic response modifier and instruct physicians that they may bill for administering it using a chemotherapy administration code.

DR. ANGELBECK: Jim, does CMS have a mechanism to respond to a public health crisis like that, for example, what has just been described as changing the classification of a biologic response modifier?

DR. BOWMAN: Well, I think we have seen this morning that CMS does have a mechanism to respond to concerns that are addressed by all the stakeholders, whether they are beneficiaries, patients, providers, suppliers, or whoever else is involved. So, there are a lot of mechanisms available. There are certain Secretary discretionary authorities within the statutes that can be invoked and used. There is nothing

specific, of course, about biologic response modifiers.

DR. BIRKHOFER: Can I make a comment about the public health emergency? The ASP statute provides CMS with the authority to use an alternative payment methodology in response to a "public health emergency." The public health emergency would have to exist under Section 319 of the Public Health Service Act, and there would have to be a documented inability to access the product and an increase in the price that is not reflected in the manufacturer's ASP data. In such circumstances, the statute permits CMS to use wholesale acquisition cost or some other reasonable measure of drug price to set the payment rate until price and availability have stabilized. Accordingly, to the extent CMS is able to make the documented findings to trigger this provision with regard to IVIG, CMS could revise the payment rate for IVIG.

DR. BRECHER: So, it sounds like as a consequence of current CMS reimbursement policies there is an urgent need to rectify the

reimbursement because, as it is currently structured, there is a negative impact on both availability and access. Specific recommendations--I think we can list a couple of examples of what might happen, such as reclassifying it from a biologic response modifier as a blood product. We would have to leave it to CMS to figure out how.

MS. VOGEL: Dr. Brecher, if I may address the committee, I just want to say a few things. In terms of the biologic response modifier, I just want to say a few things. One is that this is something that needs to be done but this is not a solution by itself. In terms of that, AMA, when they were working on the G codes for the administration of IVIG for the new ASP, when Congress looked to reduce the profits in the drug margin and they put the G codes together for the chemotherapy or non-chemotherapy codes for administration, AMA made the recommendation to the RUC committee and they put together their wording to include, besides chemotherapy drugs, the

monoclonal antibodies, and they included the terminology "biologic response modifier therapy" for which they didn't use examples but they put that in to use IVIG, and in talking to AMA, that is what they told me.

So, that would bring the reimbursement on the administration side up where the doctors weren't taking a loss anymore in the administration. But if you look at the overall situation, you are still not going to have physicians buying products at a loss so you will get the administration side up to where it needs to be, and that is adequate, but you are still going to have a problem with the pricing. So, in your recommendations you say that CMS needs to rectify the situation on cost of IVIG as a biologic response modifier, or at least understanding that it is, and be in touch with the AMA RUC committee or the CPT committee, and I am trying to get the two to discuss it with each other and I have been trying to break down whatever barrier there is there.

But in terms of the other side of the coin, and that is on the pricing, and getting the reimbursement of the drug itself, IVIG, to a point

where patients can have access to that product, there need to be specific recommendations on that and, if you decide to go down the road of a public health crisis, I think what may be helpful to CMS is even having invoices coming in from the providers, showing what they are purchasing the products at, and we can help to facilitate that.

The other issue I just wanted to address is in terms of the second distributors and the price gouging that is going on. I don't look at that as the whole problem and I don't look at that as once reimbursement is fixed and we get it to a reasonable number where the patients can get access to it--I don't think that it is just an issue that there is a grey market area where physicians are having to just purchase in that area. I also look at this issue as a problem with opening up the allocations and allowing physicians, once they are able to buy product at a reasonable price, they can

then purchase the products that they had allocations for and be able to fulfill their contracts. So, that is an issue.

Right now, when they can't buy the product at those contracted prices, and you are shifting the patients to the hospitals, the hospitals that are taking them can't receive them because it is also above those contracted prices and then you are going into the open market. There have to be ways to try to discourage the open market from growing, and there are ways within the industry I think to do that.

But I just wanted to clarify that whole thing with biologic response modifiers. The other thing, if you look at number two that PPTA put up there about debundling the HCPCS codes, I just want to say also that you can't do that without doing the add-on payment because if you just debundle without an add-on payment you are going to have the same situation we have now. You are just going to have a whole bunch of products with one code, with each with its own code, but you will have nothing

covering that added price. I don't know if Dr. Bowman can answer this or not, if CMS has authority to extend what the hemophilia committee has with the clotting factor add-on, if they can do that with IVIG or is that something that has to be done legislatively?

DR. BOWMAN: I can answer the last part of your question, and that is definitely a legislative problem. The clotting so-called furnishing fee, the way that is termed, right now, as Amy Bassano mentioned, it is 14 cents per unit. It is by statute. The furnishing fee is by statute. The determination of 14 cents per unit was determined within CMS.

DR. HEATON: Mr. Chairman, as I listened to the statements made this morning, it seems to me that the recent crisis is driven primarily by recent changes, the administrative payment schedule which now reimburses on the average sales price, the ASP, which lags the average wholesale price. The plasma industry--those of us who have been in the business a long time--there is a classic boom

in the industry with pricing rising, followed by very rapid discounting with a periodicity of some two or three years.

So, as I look at the potential for immediate corrective action, I believe that we should focus on a mechanism which allows a focus on the average wholesale price and provides for a better periodicity in the assessment of the cost of the products that need to be reimbursed. I do believe there is a need for a long-term fix but I propose that we focus on the AWP and maybe a temporary change to the switching regulation to ASP, and go back to the AWP for a period until we work out a more comprehensive response.

DR. BRECHER: Jerry?

DR. HOLMBERG: Not to belabor the point, but I think that if the IVIG were labeled as a biological product, a blood product, then they would be under an AWP mechanism. Is that correct, Jim?

DR. BOWMAN: No. Categorization of a biological response modifier provides an additional

infusion payment to the physicians under the physician fee schedule. That is my understanding.

DR. HOLMBERG: That is not what I am asking. The question was if it were classified as a blood product, a biological blood product, would it be under AWP versus ASP?

DR. BOWMAN: The question of classifying it as specifically a blood product as opposed to, say, a drug or a biological response modifier would take it completely out of the so-called drugs and biologics statutory payment mechanism, and it would be paid just like blood or fresh-frozen plasma and it would be in that same category. Under the physicians fee schedule it is basically a cost-based reimbursement system. Under the OPPS outpatient hospital system it is based on claims data that is utilized to set the payment rates each year. As we have seen really in the last three years or so, there were some problems with the claims data and so there were initially some proposed reductions in payment for blood and blood products. Those reductions had to either be

dampened or they were actually fixed at the previous year's payment rates based on a lot of reports that the data was either inaccurate or insufficiently submitted on cost reports and claims data. So, that would take the IVIG out of the statutory payment as a drug or biologic, to answer your question.

DR. BRECHER: We are behind schedule so we are just going to have a few more comments and then I think we are going to break for lunch. Karen?

DR. SHOOS LIPTON: I just had a quick question. If we use this public health emergency, can they then go back and say under this they could revert to the AWP? So, is that the simplest way to achieve this quickly?

DR. BOWMAN: You are asking the wrong person. That is way above me--invoke the public health emergency context as a solution to this problem.

DR. HEATON: I think Jim's comments relate very well to the observations that I made, which is that this is a cyclical product with a cyclical

price. So, if you focus on the average wholesale price, then the accuracy of your cost reporting becomes paramount. I do believe that industry could be induced to report its average wholesale price much more accurately. In the past that information has not been available to CMS because of alleged competitive problems. But when there is such a significant difficulty with getting reimbursement, I imagine that could be overcome. CMS could be provided with cost information on a timely basis and we then wouldn't face these crises as we begin to focus on ASPs that go out of date very rapidly.

DR. BRECHER: Jay?

DR. EPSTEIN: I think I agree with the earlier remark by Celso that we are not in a position to come up with a technical fix. I think that the three elements of our message need to be, first, that we recognize that there is a current crisis in the availability of IGIV which is affecting patient care. Secondly, that there is a need for rapid measures to protect the life and

health of patients, pending stabilization of the current marketing situation. Third, that we would advise the Secretary to consider declaring a public health emergency in order to enable CMS to consider alternative mechanisms of reimbursement as an interim strategy.

DR. BIANCO: You don't have to write anything, Mark; it is written.

DR. BRECHER: No, it is dictated; it is not written.

DR. EPSTEIN: I don't think that would preclude CMS from coming up with other strategies if they are rapid and, you know, administratively feasible, but it would create the almost immediate option for CMS to exercise existing authority to use alternative reimbursement strategies.

I would just comment that the remarks by Julie Birkhofer were very helpful, that under Section 319 the determination rests on the finding that the product is not available and that the price is not reflected in the manufacturers' ASP data. I think the testimony that we heard earlier today speaks to

both those things. I mean, we heard many patients and professionals declare that patients cannot get their products, and we have also heard that the market price is not accurately reflective of the sales price by the product manufacturer and that there is a lot going on with intermediary distributors. So at least at a superficial level it sounds as if the criteria are met and, certainly, I think we have heard enough to suggest that the Secretary might, therefore, consider that mechanism.

DR. BRECHER: Julie?

MS. BIRKHOFER: Mr. Chairman, can I address Ms. Lipton's question? If there is a public health emergency declared, in such circumstances the statute permits CMS to use wholesale acquisition costs or some other reasonable measure of drug price to set the payment rate until price and availability are stabilized.

DR. BRECHER: Right, and, Jay, you are going to write down your suggestion. All right, we are going to take a one-hour break for lunch. We

are behind already. We will come back at 1:10.

[Whereupon, at 12:14 the proceedings were adjourned for lunch, to reconvene at 1:15 p.m.]

A F T E R N O O N P R O C E E D I N G S

DR. BRECHER: We are going to start. We are going to try to make up some time. Jeanne Linden is going to briefly review the January, 2005 discussion on emerging risks. Then we are going to forego the committee discussion and just move into our public health topics. So, Jeanne?

Strategic Actions for Emerging Infectious Diseases
to Reduce the Risk of Transfusion Transmitted
Diseases and its Impact on Availability
Review of January 2005 Discussion

DR. LINDEN: Thank you, Mr. Chairman. I will try to be very brief and just hit the high points. During the discussion a number of issues emerged, some of which really were brought to our attention by the IOM report. One was the need for a coordinated public health response within agencies, among federal agencies and also including other partners, including coordinating with state agencies and other countries because many of these pathogens are global issues.

An issue arose regarding how effective

surveillance could best be accomplished, looking for new agents that may be on the horizon as they start to emerge, and the emergence known agents or those previously identified but changing, as well as agents that are not presently sufficiently addressed, such as Chagas disease as an example.

There was also discussion of so-called phase 4 surveillance that is assessing the impact of products and their safety profiles.

Another big issue was prioritization of issues. What is on the list? Who works on issues? What do they do? Who does what? And what resources are devoted?

Another big issue focused on the research agenda and the need for coordination of efforts and funding to match the priorities of the issues that have been identified, especially in a timely fashion.

Risk communication was another big issue, getting the information to physicians and recipients and potential recipients. The issues regarding transparency of communications,

timeliness, especially when insufficient scientific data are known, what does one say when one has insufficient information, and at what time does one communicate that? And, also accountability in communications.

Another issue that emerged from discussion was technology development. What incentives could there be to drive the development of technologies for diagnosis, identification of the diseases, as well as potentially pathogen reduction came up as an issue. The issues of technology development and research especially were of concern with regard to infections or orphan agents where there would not be expected to be a large profit motive and what other incentives could be provided to get some of these technologies developed.

Another big issue was about scientific uncertainty and having a process developed to be adaptable to particular situations because they are going to be different. We could have a general framework but it has to be flexible to be tailored to the individual situation. And, at what point is

there need for action? And, what players need to be at the table, and the interaction of the different players in terms of new infections. Many people may need to be involved, the blood banks and also the clinicians and the patients, of course, the users. There was also discussion of whether HPCs should be included in this discussion and also mention of the fact that tissues and organs share many of the same issues.

So, overall the general discussion by my reading is that there is need to develop a coherent approach, utilizing all of the available resources and the strengths of the different agencies and organizations and players in a coordinated way, building on the strengths of those partners.

DR. BRECHER: Thank you, Jeanne. That is good lead-in to hearing about some of the coordination in the public health sector so we are going to go to our first speaker, Dr. Benjamin Schwartz. He is a senior scient advisor to the National Vaccine Program Office within the Office of Public Health and Science, HHS.

Public Health Coordination

HHS Pandemic Action

DR. SCHWARTZ: Thank you very much. It is

a pleasure to be here today. I am passing around a handout that will help you follow the slides. I made copies for all the committee members and they will be posted I guess on the web site after this meeting so that those who are in the audience can have copies as well.

I have been working on pandemic influenza, planning and preparedness, for about the past three years or so. It is interesting, until several weeks ago I hadn't thought at all about the impact of a pandemic on blood supply and safety issues. So, this has been a good opportunity to develop a little bit of familiarity with this aspect of pandemic planning and preparedness, and I look forward to the discussion of this committee and to the specific steps that might be undertaken to better understand the potential impact of pandemic on blood supply and safety issues.

My favorite quotation about pandemic

influenza is on the title slide that comes from Ed Marcuse, who is an ACIP member from the University of Washington. He said the pandemic influenza clock is ticking and we just don't know what time it is. I think that is a pretty good characterization of what the situation is going to be. We know that a pandemic is inevitable. We don't know when it will occur but certainly planning and preparedness are important so that when it does occur we are ready.

In this presentation I would like to do four things. First, I would like to briefly describe some background on the influenza pandemics and on the avian influenza threat; secondly, talk a little bit about what is being done at HHS for pandemic planning and preparedness, describe several of the key response components in a pandemic and briefly touch on blood safety and availability issues from my perspective which, admittedly, is one pretty much of ignorance about blood safety issues.

In influenza pandemic occurs with the

emergence and spread of a novel influenza A virus. This would be a virus that has a hemagglutinin and antigen or both hemagglutinin and neuraminidase antigens that are derived from animal viruses. It would be a subtype that would be new within the human population and, therefore, most or all of that population would be susceptible. If the strain underwent sustained and efficient person-to-person transmission a pandemic could ensue.

It would be characterized by a near simultaneous global outbreak associated with elevated rates of illness and death, and be the start of a new viral era with this strain then circulating and causing annual influenza outbreaks.

This slide shows the time-line of emergence of influenza A viruses in the human population in the 20th century. The first pandemic of the century occurred in 1918 with the Spanish influenza pandemic, which was the most fatal pandemic in our recorded history. In 1957 an H2 strain was introduced with Asian influenza, and in

1968 Hong Kong influenza represented the emergence of H3 and 2. In 1977 H1 re-emerged with the appearance of Russian influenza.

It is interesting. When they looked at this particular strain in 1977, they saw that it was very similar to the H1 strain that had disappeared from the human population a number of years previously, suggesting that this was the strain that emerged from a laboratory rather than representing continued evolution and mutation of a virus. Why that is interesting and perhaps relevant is because recently we saw the distribution of an H2 strain as part of laboratory proficiency testing accidentally, of course, and this has some echoes with what happened with the emergence of H1 in 1977.

More recently we have seen sporadic cases of novel influenza strains of H5, H7 and H9 but, fortunately, none of these has spread effectively between people and there has not been a pandemic.

Of the three pandemics that occurred during the 20th century, the most fatal, the most

severe was in 1918. It is estimated that there are at least 20 million deaths worldwide attributed to that pandemic, and most experts think that is more along the lines of 40-50 million deaths associated with that pandemic.

In the United States the 675,000 deaths that occurred in 1918 and 1919 make it the most fatal event in all of U.S. history. In 1957, by contrast, there were only about 70,000 U.S. deaths, and in 1968 the Hong Kong flu was only about half as fatal as that.

So, one of the things that we have seen from the three 20th century pandemics is that when you have seen one pandemic you have seen one pandemic, and that the magnitude and impact on health and on society of these pandemics has differed markedly.

I would like to provide a little bit more information about a couple of the pandemics to help you envision how pandemic disease may spread across the country and what impact it may have on health, on society, as well as on blood supply,

availability and safety.

This slide shows the spread of the first wave of the pandemic in 1918 between September and October. The legend on the slide is not clear, but you can see that from all of the different patterns--the hatching and the different colors--basically disease spread across the entire United States within a one-month period. So, in a month, in this time between September and October, the entire country was facing pandemic disease.

This slide shows the attack rate of clinical illness. The overall attack rate was about 30 percent in the population, about one out of three people becoming ill during the pandemic wave. But, as you can see, there is an age distribution of influenza illness, with the highest rates of illness occurring in children and young adults and decreasing with increasing age.

The outbreaks of disease within communities generally lasted between five and eight weeks. Shown on this slide are data from three cities, from Boston, from Washington and from San

Francisco. You can see that the mortality rates in each of these cities were pretty similar. The time course of the outbreaks was pretty similar, and the peaks were only separated by a couple of weeks, again making the point that this is disease that spreads rapidly across the country and involves all areas simultaneously, and that the idea that you can take resources from one area that is not affected and transfer them to an area that is affected just doesn't work in a pandemic.

Also you can see from this slide that there was a second wave of disease that followed the first wave by a couple of months. So, instead of having a year to recover like with annual influenza, it is possible that this recovery period may only be several months before a second wave of pandemic disease hits.

This is shown as well with the 1957 pandemic. The first wave of pandemic disease began when children went back to school in the fall of 1957. The peak of disease was in October, in mid-October of that year and the entire first wave

of the pandemic lasted for about three months. However, you can see that a second pandemic wave then occurred about three months later, with a peak in February of 1958. This slide is a little bit confusing. The dotted line shows mortality in the United Kingdom and the solid line shows mortality within the United States.

Well, the pandemics of 1957 and 1968 may provide a lower end estimate for the potential severity of the next pandemic, whereas the pandemic of 1918 may provide a higher end estimate of what the impact might be. This slide shows an extrapolation from the populations at those times to the current U.S. population, and suggests that a pandemic with a 35 percent attack rate of clinical illness--something that we have seen in all previous pandemics--may result in about 243,000 deaths as a low estimate and as many as 2.2 million U.S. deaths as a high estimate, with rates of hospitalization and disease as shown on this slide.

It is interesting to point out again that the rates of clinical illness are likely to be very

similar, and that really where the difference lies is in the severity of the disease in the pandemic, the number of hospitalizations and the number of deaths that may occur.

Well, there are several viruses that may be viewed as pandemic threats. Clearly, the greatest pandemic threat at this time is the avian H5N1 influenza virus that has spread across Asia. H5N1 is not new. It emerged first in southern China in 1996, but first came to our attention in 1997 with an outbreak in Honk Kong where there were 18 infections among people, 6 of whom died.

Epidemiological studies at that time identified exposure to domestic poultry as the risk factor for disease and the outbreak was stopped with massive culling of poultry in Hong Kong. As we lost sight of this infection disease continued to occur throughout China between 1997 and 2003. Then, in 2003 widespread outbreaks in poultry were identified in eight different countries and deaths among people occurred in three countries.

Shown on this slide are the countries that

were affected. In yellow are the countries that were still having disease in 2005 and in green are the countries that have eradicated their poultry infections. Shown in orange are the districts where human cases have occurred, and you can see that human cases have occurred in Thailand, in Cambodia and in Vietnam.

As of mid-April of this year a total of 88 human cases have been identified, of which 51, or 58 percent, had ended fatally. Clearly, our surveillance is detecting the most severe cases and we don't expect that this 58 percent case fatality rate is the true case fatality rate of all H5N1 infection, but it is also very clear that this is a serious disease and that the clinical picture associated with sepsis, as well as with respiratory infection and primary viral pneumonia, is one that is particularly severe for influenza viruses and calls to mind the situation that we experienced in 1918.

Now, since mid-April there has been a single additional case diagnosed and a single

additional death. However, before we congratulate ourselves on the effectiveness of the public health response in culling poultry, it is worth pointing out that avian influenza, just like human influenza, is a seasonal disease with a winter/spring seasonality so that what we might be seeing is the seasonal decline in disease rather than the success of our control efforts.

To summarize the avian influenza situation, certainly this epizootic has been of unprecedented scope. We believe there are limited prospects to eradicate H5N1 because of asymptomatic infection in wild bird species. While massive poultry culling can be successful in eliminating or controlling hot spots and decreasing human exposure, it doesn't seem like we will be able to eradicate this strain from the avian population, nor to eliminate exposure of humans to avian influenza.

Now, for a pandemic to occur it would require that this avian strain either mutates or reassorts with the human strain and, therefore,

acquires the ability to be transmitted between people, and it is unclear what the likelihood of this mutation or reassortment event might be. It is also worth pointing out that there are other pandemic threats. For example, several years ago there was an outbreak of avian H7N7 influenza in The Netherlands with associated human cases, and in 2003 there was an H7N3 outbreak in British Columbia, both in domestic poultry as well as in humans in contact with those poultry. So, we don't know whether H5N1, H7 or some other strain may be responsible for the next pandemic.

Well, one can come up with a number of different potential solutions for the pandemic problem, and one of the responses that was proposed in 1957 was to avoid influenza by gargling daily. Now, as far as policy, the Department of Health and Human Services believes that planning and preparedness might be a better solution so we have been involved in a number of planning and preparedness activities.

In August of 2004 a draft HHS pandemic

influenza preparedness and response plan was released, being published in the Federal Register and also posted on the National Vaccine Program Office web site. Our goal is to finalize this draft plan by this summer, and there are several things that we need to do in order to finalize the plan.

There are several critical issues that have not yet been resolved that we need a decision on. We need to improve the guidance provided in this plan in several different areas, for example, in terms of public health measures that may be taken to control the spread of influenza disease and in healthcare surge capacity. After the publication of the draft plan we received over 70 different public comments and we need to consider each of those comments and respond to them as needed. Finally, the guidance provided in the plan is based on the phases of a pandemic as defined by a 1999 World Health Organization document and in January WHO published revised pandemic phases. So, now we need to revise our plan to correspond with

those new phases.

The issues that must be resolved by the Department include the public or private sector vaccine purchase and distribution, or some combination of the two. It includes defining priority groups for receipt of vaccine and for antiviral chemo prophylaxis and therapy, and an approach to indemnification, liability protection and compensation. All of these issues currently are being addressed, primarily through the formation primarily through the formation of a pandemic influenza working group under the auspices of the National Vaccine Advisory Committee, which is composed of a variety of stakeholder organizations within the public and private sectors.

In addition to planning, a number of preparedness activities are being undertaken. They include enhanced surveillance with CDC establishing cooperative agreements with ten different Asian countries this past year. There have been a number of contracts that have been completed to improve

that same security and supply, including a contract that will assure the year round of egg availability, eggs providing the substrate in which influenza vaccine is produced; and to expand and diversify U.S. based influenza vaccine production. In addition, a pilot lot of H5N1 vaccine has been acquired by the National Institutes of Health and clinical trials are being undertaken, and a small stockpile of this vaccine also exists.

We have also established a small antiviral drug stockpile as part of the strategic national stockpile, and there are ongoing state and local preparedness efforts, both through the state and local health departments as well as with the healthcare system. Finally, there is active, ongoing research and development through several key breakthrough technologies that may markedly improve our ability to respond to an influenza pandemic such as, for example, antigens bearing vaccination strategies that would allow us to take the current vaccine production capacity and to extend it over a much greater number of doses,

allowing us to protect more people in the event of a pandemic.

I would like to very briefly summarize several of the key interventions that would be implemented to decrease the pandemic health impacts. These include vaccination, antiviral drugs and quality medical care. In this presentation I am not going to talk about public health or community interventions which may be implemented to decrease disease spread as these activities are currently being considered by CDC, and recommendations on the types of activities that would be undertaken are still being developed.

If we thought the last year's situation with the influenza vaccine supply was a problem, I think in a pandemic it is likely to be a much greater problem than we saw last year. We make several assumptions about the availability and need for vaccine in a pandemic. We assume first that imported vaccine will not be available; that a country that manufactures vaccine will retain whatever product in that country to protect their

own domestic population. Therefore, we will rely on vaccine produced in the United States.

Secondly, we assume that two doses of vaccine will be needed for protection to a strain which nobody has had prior experience with. The current U.S. manufacturing capacity for influenza vaccine is estimated at between 12-20 million monovalent doses produced per month. The implications of this are that we will be able to protect about one percent of our population per week of pandemic vaccine production once the vaccine began to roll off the production line.

Because of this limited production we, therefore, need to target defined groups to receive this early vaccine supply. So, who might these groups be that would be targeted for early vaccination? One group would be those who were at increased risk for severe disease and death in the pandemic, and this might be extrapolated by the risk groups that are recommended to receive vaccine on an annual basis which represent about 80 million people, or almost 30 percent of the U.S.

population. This includes persons greater than or equal to 65 years of age, those who have underlying diseases, pregnant women and young children between 6-23 months of age.

As a caveat, however, one has to recognize that risk groups in a pandemic may differ, with 36 percent of the mortality in 1957 and 1968 occurring in those less than age 65, and in the 1918 pandemic a characteristic W-shaped mortality curve with high rates of mortality among infants, among young adults as well as the elderly. In fact, most of the excess mortality in 1918 occurred in young and previously healthy adults.

In addition to those groups who would be at most risk for severe or fatal disease, we may need to preserve the healthcare system by vaccinating healthcare workers and to preserve other essential community services by vaccinating other occupational groups. Healthcare workers, as designated by the Bureau of Labor statistics, make up about 12.6 million individuals, or 4.3 percent of the population. Emergency service providers

include ambulance and EMS services. Public safety includes police, fire and corrections. There are about three-quarters of a million people who work on utilities; five million in transportation and over a million in other services such as state and local governments, sanitation, waste disposal, mortuaries and other potential important services.

Turning to antiviral drugs, because vaccines may not be available at the beginning of a pandemic the antiviral drugs we have in our national stockpile may be the first specific intervention that will be available to protect people from pandemic disease. There are two classes of antiviral drugs that are effective for influenza. They include the adamantines, amantadine and rimantadine and the neuraminidase inhibitors oseltamivir and zanamivir. We currently have about four million courses of rimantadine in the stockpile which were acquired because of the vaccine shortage last year and not as a pandemic preparedness measure. Oseltamivir has been acquired for pandemic preparedness. There are

about two million courses, and this will be the mainstay of our stockpile of antiviral drugs and I will tell you why in just a second.

In terms of the impact of these different drugs, both the adamantine and neuraminidase inhibitors tend to be 70-90 percent effective when used as prophylaxis, but only the neuraminidase inhibitors have been proven to decrease severe complications from influenza, including pneumonia and hospitalization. The reason why we are not stockpiling the adamantine for a pandemic is because the development of resistance is common, with about 30 percent of individuals shedding resistant isolates within three days of beginning therapy. By contrast, resistance with a neuraminidase inhibitor is uncommon. In addition, adverse events of the adamantine tend to be more frequent, particularly with amantadine where there are several severe neurological sequelae that are possible.

The issues with pandemic antiviral drug availability are similar to those for vaccine

availability. We need to define priority groups because the amount of antivirals available in the stockpile will not be equivalent to the amount that would be needed. We also need to develop appropriate drug use and distribution strategies, with treatment generally being preferred over prophylaxis give the limitations in drug supply and, because early treatment is most effective, we need to develop our plans so that the delivery site will be the point of care. You can imagine that if we had the antiviral drugs available in hospital settings everybody who had influenza would go to the hospital because of the possibility that they could get these antiviral drugs, and there would be some pretty overwhelming demand in hospitals and emergency rooms. So, we need to come out with what is the best plan for making these drugs available.

In addition, we need to define what the total antiviral supply should be and additional stockpile purchases, we hope, will occur following definition of the priority groups and the antiviral strategies by this working group that I mentioned

earlier.

Quality healthcare is going to be important in a pandemic regardless of whether we have antiviral drugs and vaccines. Shown on this slide is an example for the demand of healthcare in a mild pandemic, modeled by CDC after the 1957 and 1968 pandemics, and the flu surge software that was used to generate this curve is available on the NVPO web site.

What this shows is the demand for hospital beds, for ICU beds and for ventilators that would occur in Atlanta in a pandemic, again a mild pandemic modeled after '58 and '68. You can see in red that during the peak weeks of the pandemic about a quarter of all hospital beds would be taken up with influenza patients, over 40 percent of intensive care unit beds, and about 30 percent of ventilator needs.

There are substantial challenges to maintain quality medical care in the face of the increased demand that will occur in a pandemic. We need to assure the ability to effectively triage

patients to manage who comes into the hospital and who does not. We need to be able to effectively care for ill outpatients, which includes the delivery of medical care perhaps as well as medications and food to those who are in their houses. Given the high demand for inpatient services in a context of staff absenteeism and limited availability of critical resources, we need to define how we can best care for those who require hospitalization, and how we can provide the surge capacity to manage all of the patients who will be seeking care and requiring care.

So, I would like to end this presentation by briefly talking about what I think may be some of the potential issues regarding blood safety and availability, but I will look forward to a discussion and your thoughts about what the situation during a pandemic might be, and I would like to specifically consider pandemic impacts on blood donation, on blood safety, on the need for blood, as well as on the capabilities to obtain that blood supply.

Before doing so, however, I would like to briefly describe influenza illness. The duration of illness generally is 5-7 days, with additional

time required for recovery. Illness tends to be characterized by fever, which is one of the first symptoms, malaise, myalgias and respiratory symptoms which generally only occur later. Viral shedding occurs one day before symptom onset and some people have infection which is asymptomatic throughout its duration.

For annual influenza, viremia is seldom documented and is thought not to occur widely, For example, zanamivir is an inhalational product and it works well because influenza, seasonal influenza is not a systemic disease but tends to be limited to the respiratory tract. However, this situation may not be the same for H5N1 influenza. In February of this year there was a report in the New England Journal of Medicine of a four year-old child in Vietnam who had overwhelming H5N1 disease, who died from that infection and was documented to have influenza in serum specimens and detected by

PCR in the cerebrospinal fluid. However, it is worth pointing out that this child was also very sick and clearly would not be donating blood.

In addition, it is important to point out that we estimate that about a third of the population will become ill during a pandemic and, obviously, many others will be anticipating either becoming ill or having to take care of ill relatives.

So, what are the implications of this disease then, the blood safety and supply issues? I would suggest first that blood donation will be markedly decreased either because people are sick, because they are febrile and are therefore deferred from giving blood, or because in the context of a pandemic they just won't feel like giving blood.

With respect to blood safety, I think that it is unlikely that safety will be affected in part because influenza associated viremia appears to be uncommon, and primarily because if viremia does occur it will be associated with fever and severe illness so it is unlikely that these folks are

going to be donating blood.

What about the need for blood? I think that it is likely to be decreased with elective surgeries being canceled, although I have to say I don't know how much of the blood supply is used in elective surgeries. However, it is possible that the need for cardiothoracic surgery may increase because one of the main causes of death in influenza outbreaks is from cardiac disease. Nevertheless, the capacity to do such surgery may be limited so I am not sure that there will really be an increase in cardiothoracic surgery during a pandemic.

Finally, in terms of the capacity to obtain blood, it will likely be decreased because of illness and possibly the need to move the staff who currently draw blood to other healthcare services during a pandemic.

So, my conclusions would be that in a pandemic there will be a decrease in blood supply; there will be a decrease in the demand for blood and in blood drawing capacity; and I don't think

that there will be a major impact on the safety of the blood supply.

However, I think there are several questions that we do need to consider further. First, given the assumptions on the attack rate of pandemic disease and on the need for blood, what might be the magnitude of a gap between supply and demand? I think that that is something that can be estimated.

Secondly, what options should we as pandemic planners and in implementing preparedness--what should we consider in order to close that gap if it, indeed, exists?

Finally, will the lack of blood drawing capacity limit supply, and should donation center staff be a target group for pandemic vaccine or antivirals, or would these individuals already fall within a target group by being healthcare workers who would perhaps have other healthcare activities as well?

So, I would like to conclude here and look forward to any questions, any discussion, and

certainly any ongoing collaboration and communications as we improve our planning and preparedness for a pandemic.

DR. BRECHER: We are falling behind so two quick questions and then we are going to move on. Celso?

DR. BIANCO: It is clarification that will be very important for us here, you said that 30 percent attack rate. That is total? So, 70 percent is not going to get it, at least from the models that you have?

DR. SCHWARTZ: The attack rate would be about 30 percent for illness--

DR. BIANCO: It is not a continuing 30 percent of the population that are sick; it diminishes?

DR. SCHWARTZ: Right, although in subsequent ways additional people--

DR. BIANCO: The second thing is that Dr. Epstein is here. He is the head of Blood at FDA. If you want to defer someone in a city where the epidemic is raging for exposure to flu, would you

defer somebody from donating blood or not?

DR. SCHWARTZ: In a pandemic exposure is going to be widespread and universal. I think that if you were to consider household exposures versus community exposures, you know, it would be a very difficult situation. It would be difficult to define who is exposed and who is not exposed. I think household exposures are going to be incredibly common. The incubation period before which clinical symptoms may occur would generally be on the order of a couple of days.

DR. BIANCO: And finally the issue of healthcare workers, in the last exercise or attempt to vaccinate first responders, our phlebotomists, the people that draw blood, were not considered first responders so that you have touched on a very important issue here.

Well, I said finally--the one issue that you didn't put in the list is not so much that our staff would be sick; our donors will be afraid of coming to a public place to donate. That is probably what happened--kids didn't go to school

and all those things.

DR. SCHWARTZ: Yes, I think there are a lot of potential barriers to blood donation. In terms of staff being identified as first responders, I think I would be more interested in whether they would be included in that healthcare worker category, whether they also have other healthcare worker tasks, for example, whether there are nurses who would be providing other services. You know, it is interesting, we were trying to define these priority groups and we called the Red Cross and we were told that they don't tell the number of volunteers that they have. So, you know, we do need to do a little more work to try and identify the population and its size.

DR. BIANCO: We will help you.

DR. BRECHER: We need to move on. Karen, one quick question.

DR. SHOOS LIPTON: I just wanted to comment that there is a subgroup of the AABB, an organizational task force on disasters, and we have actually convened to talk about these issues. We

think that the biggest issue is going to be the effect actually on the fear of donating and going out, and then also on healthcare workers. The answer is that most of our people are not included as other healthcare workers so we recognize the need to work with the local and state officers to make sure that we are included in some kind of plan. So, we are trying to put together a white paper which we would share with this group and certainly with the Public Health Service.

DR. SCHWARTZ: The ACIP, the Advisory Committee on Immunization Practices, and the National Vaccine Advisory Committee are making recommendations for priority groups. Those recommendations are going to be presented to those committees at the end of June and mid-July. So, it would be most helpful if we could talk before then and if these thoughts could be considered in the deliberations of those groups.

DR. SHOOS LIPTON: We could do that.

DR. BRECHER: We need to move on. Our next speaker is Dr. Fernando Guerra. He is

currently Director of Health and Director of Center for Environmental Health for the San Antonio Metropolitan Health District. He serves on a variety of advisory committees.

National Association of County and
City Health Officials

DR. GUERRA: Thank you very much, Dr. Brecher and members of the committee for the opportunity to visit with you this afternoon. It is like coming home for a while. I served on this committee a few years ago and have certainly benefited from my time on the committee and the discussions that took place. I think you have some important relevance in public health, and what I would like to do is just to take what Dr. Schwartz has shared with you that is really the big picture and, certainly in the instance of specific conditions of major proportions, such as pandemic flu, I would really like to establish a context for you of what goes on every day in a local health department in a large urban center and the relationships that must be maintained with the

local blood center because of the important public health considerations that need to be a part of it.

This was put together on rather short notice, at the end of last week, and I certainly commend Jerry Holmberg for guiding us in the process. I think it is good to kind of give you a broad overview of what goes on in a local health department by just very quickly highlighting some of the essential public health functions that I think have relevance to issues of blood safety and the work that the committee such as yours is doing.

Certainly, local public health monitors on an ongoing basis the overall health status and specifically investigates health problems in the community whether it is an outbreak of flu, respiratory illnesses or food-borne illness, or something that puts the population at risk. Certainly, there are systems in place for maintaining surveillance of a variety of diseases, in particular infectious diseases and a variety of chronic diseases and a number of other areas related to community partnerships and health

policy. But one of the major functions of local health departments is enforcing the health codes and regulations, including any number of, for example, blood collection centers or the plasma centers where, again, we have to monitor those operations; and supporting public health research and innovation that relates to any number of activities that have to do with the handling of blood.

For example, in our community that has 20 large hospitals and some smaller hospitals we are talking about over 6000 beds with a varying level of utilization. But in the background is always the system for surveillance 24 hours a day, 7 days a week, and it is on issues related to response for threats real or perceived of biological agents, chemical agents, bioterrorism that has to be in place in a system for surveillance that is coordinated through the medical system, doctors' offices and clinics' emergency departments, local hospital laboratories that report to us on a regular basis, reporting any unusual or clustering

of pathogens to the health department and then, of course, the backup of the state health department that coordinates any number of the specific diagnoses of a variety of agents where we do not have the capacity in the laboratory when we need confirmatory testing.

An important area for your consideration is one that has to do with communication and coordination. In the instance of outbreaks, it is the health department's surveillance system and activities that can give a local blood bank some idea of when, where and to what degree an outbreak is occurring--tremendously important, and it works both ways. For example, if in their screening they find that for some reason there is an increase in individual screening for a particular viral or infectious disease, that is certainly reported and, of course, investigations are done.

The surveillance system that we have in terms of blood banks, for example at the end of or beginning of the flu season, we have sentinel sites collecting samples at the beginning of the season

so that we have an idea of when the flu virus is entering the community and then begin to take steps and monitor more closely, including school-based and emergency department-based surveillance systems. Of course, the blood bank relies to a great extent on the prevalence data that we have for a variety of infectious agents that potentially could contaminate the blood supply. In an instance where there might be an outbreak, as I think all of us have certainly recognized in recent years--community outbreaks of hepatitis A, and right now we are in the midst of various significant outbreaks or community acquired resistant Staph., and whether or not these are going to have some implication in blood drawing and would be safe for the blood supply.

Because of our proximity to the border and, in fact, rabies is endemic in many of the border counties, rabies is very common and, again, we certainly recognize that on occasion will enter into the tissue donation consideration. So we are at least maintaining some tracking of the incidence

of rabies. Then, because San Antonio is an area where many military personnel are deployed from, or come back from, or spend time in different training functions, we also know that that is a group that at times has to be monitored for a variety of diseases that they might have been exposed to and that does have some impact on the blood supply.

Then, obviously, the changing patterns of disease, you know, something like Dengue that does occur on a seasonal basis, or as we have witnessed in recent months, an increase in the number of individuals infected with syphilis, again, these are important considerations for us to share our information with the blood and tissue centers.

Another role for public health is being able to map out in the clustering and/or the observations that we make where there might be certain diseases. For example, if they are being reported to us and we are able to map them out with a GIS mapping capability that might provide some important clues again for diseases that need to be tracked in the instance of blood donors, and we can

do that very quickly by zip code, census tracking, even individual neighborhood blocks.

Another area is obviously maintaining information about the supply and high risk patients, and also population demographics that go along with that. We don't have so many international flights in and out of San Antonio but there are a lot of people that travel into the city via connecting flights that have been in many different parts of the world, again, where there have been a variety of disease outbreaks. In the instance of the outbreak of SARS of a year and a half ago, again, there are some special systems that were set up for surveillance of passengers arriving from that part of the world where they might have been exposed.

We also have the capability for assessing supply and demand for blood and blood products because of the close work that we do for the hospitals and the trauma centers. Then, the public health department has a very important role in promoting and/or at times hosting in some of our

clinical settings local blood drives. That is something that, again, the directors of the blood and tissue centers will come to us and say they are having an unanticipated shortage and because of the close working relationship that we have with the media, and the different media outlets in the instance of community-based public health concerns we are certainly able to generate the support from the community.

We have a refugee population that we serve, again, coming from parts of the world where they potentially are at risk for spreading diseases. Certainly, our local blood bank has been closely involved with disaster planning activities and serving on committees. The health department is a member of the regional medical operation response plan and this is something that coordinates many different activities for the hospitals within the region and management of city-wide hospital divisions which is a significant problem at times; the bed usage and the capacity of medications, ventilators, all of these things that

are so important in the instance of response and preparedness, and this is coordinated, of course, through the city's emergency operation center.

Recent federal legislation for public health preparedness has certainly helped expand some of the capacity whether it is having a stockpile which is tremendously important in the instance of pandemic influenza, and/or setting up the capacity for mass vaccination clinics if there is a threat, and some of the infectious agents that potentially could be prevented with vaccination, and then setting up the laboratory response network that is a real-time way to communicate across the country with any number of different emerging pathogens.

Within our own community the funding has given us the capacity for developing a level 3 bio safety lab, which gives us additional capability for rapid diagnosis of a variety of organisms. Some of the strengths that we think public health in its relationships with blood centers has certainly is at the heart of community involvement.

There is no question that it has an important leadership role in overall disaster planning and in public health today certainly one of the members of a team first responders and, again, the close working relationship that we have with blood and tissue centers certainly positions that very well within the network of response. This also facilitates the communication. You know, ordinarily a blood center is not linked to police, fire or EMS in those instances but I think with the capability that we have been developing as part of the overall preparedness of the community has really enhanced the system for communications with wireless technology, and there are certain key members on the response team that have blackberries available to stay in constant touch, but also has not just the electronic transfer but also cellular telephones.

Some of the weaknesses that continue to exist and we have been observed that I think are important just to keep in mind are that unless the department has really been able to generate the

kind of support that it needs to continue to build capacity, it sometimes falls a bit short whenever there is a need for surge capacity, and we certainly have experienced that in some instances. We have had major flooding in parts of the community and have had to deploy a significant number of staff to deal with the many different environmental impact issues--spread of infectious disease, etc.

Usually though there is limited local funding to support many of those activities. The issue of staff turnover which I think certainly affects not just on the health department but certainly blood centers; also keeping up with changing technology, and a lot of the technology that relates to rapid testing is not yet in place in many instances and I think that we need to have the capability for rapid diagnosis of some of the emergent strains of influenza viruses. Then, again, we still need the capacity, which I know this committee has been very involved in, in discussions in the past, and I am sure are

currently and will be in the future, and that is the window period of safety and infectivity of the donor pool and whether or not we can narrow that window to an extent to give us more absolute assurance of the safety of the blood supply.

Just a quick case study, South Texas Regional Blood and Tissue Center performed about 138,000 donations in 2004 and so far this year 35,000. Of that number, there were 2,262 that were not used for transfusion because of a variety of contamination issues. There is a deferral period for a number of live virus vaccines in the instance where we were doing some of the broader community-based vaccination with the smallpox virus and/or some of the other vaccines and, again, being able to track that population so that they can be deferred for a period of time. There is still the concern for those who have traveled to various parts of the world where variant Creutzfeldt-Jakob disease has been prevalent and, again because of the sizeable military population in San Antonio there are many who are not eligible to serve as

donors and that has certainly affected the overall prospective pool of donors for the blood center.

Then, just a quick listing of some of those that were screened out in the past year that they have reported to us--HIV, HTLVII, hepatitis B, hepatitis B core antibody, hepatitis C. We have a fairly high prevalence rate of hepatitis C-infected individuals. I mentioned syphilis before, West Nile virus and then ALT.

So, those are just some thoughts about how a local health department can work closely with the blood and tissue centers to give the greatest level of assurance for the safety of the blood supply. Thank you very much.

DR. BRECHER: Thank you. We are open for questions. Merlyn?

DR. SAYERS: Thanks. Can we just have that last slide on again? You know, I don't want this to be an opportunity to exaggerate the prevalence of disease in the donor population, but those HIVI/IIIs presumably are the reactives, not the true positives.

DR. GUERRA: That is right.

DR. BRACEY: I have a question, not so much about the window of infectivity but the window

of notification. At what point did you set your threshold for notifying the blood center about, you know, a given epidemic? Have you established that level?

DR. GUERRA: I guess it depends very much on the organism and what one is dealing with. For hepatitis C, for example, right now we are carrying a case count of those that are screened out on community-based screening programs and we have probably a little over 7000 infected individuals. We certainly consider that, at least in the background, of an almost epidemic proportion but because this has been so pervasive over and extended period of time, we are not going to label it as an epidemic but, rather, just make sure that we have in place the systems for screening, and those individuals who are screened out are referred into the health department for trying to give them definitive testing through limited community-based

resources and/or to protect those individuals also in those instances where there is a possibility for protecting against hepatitis A and hepatitis B. For some of the others--West Nile virus, and some of the population's lifestyle and a few cases--there was one death from encephalitis--but I think one really has to keep things in context.

DR. BRECHER: In the interest of time, I think we are going to move on to the next speaker. Thank you. The next speaker is Dr. Richard Raymond. Dr. Raymond is Director of Department of Health and Human Services, Regulation and Licensure, Nebraska Health and Human Services System. He is Nebraska's Chief Medical Officer and is President of the Association of State and Territorial Health Officials.

Association of State and Territorial
Health Officials

DR. RAYMOND: Thank you. I will try to get you back on time by being brief. A lot of what Fernando just got done telling you is not going to be a whole lot different at the state level.

Fernando has a health department that has more people in San Antonio than I have in the whole State of Nebraska. In the State of Nebraska we have 93 counties. Two counties comprise 50 percent of our population. Those two health departments do a pretty good job of exactly what you just heard. The other 91 counties are very dependent upon the state to do the epidemiology surveillance, etc. So, we are all just a little bit different.

But I want to tell you a little bit about ASTHO is, Association of State and Territorial Health Officials. This is an organization of 57 men and women representing the 50 states, 6 territories and the District of Columbia, whose mission is to formulate and influence sound national public health policy, and to assist the state health agencies in the development and implementation of programs and policies to promote health and prevent disease. It does include working with our community foundations like the Red Cross.

ASTHO has been very active in pandemic flu

activities, which I won't repeat because you heard Ben Schwartz already tell you in great detail about pandemic flu, probably as much as you want to know for the day. We have been very involved with him. I do serve on the National Vaccine Advisory Committee and also on their subcommittee for pandemic flu planning. Then, we also have participation in the CDC work groups that Ben mentioned that is gathering information on prioritization for the antivirals, for the vaccines, etc.

ASTHO will assume a major role, we believe, at the time that there is any emerging new infectious disease, and the main thing that we do, and we think we do well, is to help coordinate the response with federal, state and local public health agencies. Last winter, when it was announced on October 5th, that we would not be getting about one-half of our flu vaccine supply that we had anticipated, immediately there was a surge of phone calls set up every Tuesday and Thursday afternoon coordinating the CDC with ASTHO,

with the city county health officials, with the Society of State and Territorial Epidemiologists and with the public health labs. There were three members of each one of these organizations on these regular calls that very few people ever missed, they were so important, and they what was so important is that we were able to gather input from our members and give it back to the CDC. The CDC was able to give us feedback on what they had been hearing across the country. And, it was an ongoing give and take of information sharing and changing of policy rapidly and on the fly.

I have heard sometimes in our meetings criticism that CDC kept changing what they said, and that is true because they changed what they said based on the input that they were getting. I don't think there has ever been that much cooperation of the major public health agencies in any one effort as there was in trying to make sure we get that vaccine to groups that needed it the most, the high priority groups. It took a lot of work and a lot of time--nothing compared with

pandemic flu, but I think we set the baseline and that we can work through cooperation with those agencies. We need to include more agencies such as the blood and tissue, Red Cross, etc., to be involved in dialogue when it does involve their groups.

This sharing of information is vital to a response to public health emergencies, and I would suggest that this sharing of information needs to begin now; that you can't wait until pandemic influenza or the next infectious disease outbreak that we hadn't anticipated. We must begin now. We must know who the players are, and we must begin those preparations.

One of the things a state health agency will do across the 57 state and territories, and also sometimes the larger local health departments will do, with any infectious disease outbreak is surveillance, investigation, response and intervention. I am going to spend just a little bit of time telling you about those things to make sure you know what we do.

Since September 11th and since anthrax attacks we have been receiving a large amount of money from the federal government on an annual

basis to help prepare for public health emergencies. Those dollars have been used to prepare for all public health emergencies, not just bioterrorism but any Mother Nature; also infectious outbreaks we have seen standard SARS and monkeypox. We have seen it with the vaccine shortage. A few things that have helped with surveillance, the epidemiology staffs have really improved in the local and state health offices because of extra funding. The public health laboratories have dramatically improved their capacity to rapidly detect diseases, some of them special pathogens, and also to detect chemicals of mass destruction. I understand that next year will be radiological and dirty bomb detection. The response time to any new information has been cut manyfold by the health network system, which was in the process of being developed prior to September 11th and took on an extra added sense of urgency after September 11th

and now state and local health departments can communicate via fax, telephone, e-mail, etc. almost instantaneously to all local health providers, local health departments, the labs, community and sister agencies, law enforcement--you name it. The state can design it who they want to communicate with and they can pick and choose.

When I communicate in Nebraska, I can communicate with physicians in one county, physicians in the whole state, or just infectious disease physicians, or just the county sheriffs. It takes about three minutes to set up who I want to send it to. It also can be used not just to communicate and disseminate information, it can be used to gather information. We have used it extensively for the last two years with vaccine shortage to find out where the vaccine was at and help reallocate it to places of priority. Then the intervention, to either get either mass prophylaxis with antibiotics or mass vaccination, or quarantine or isolation--those are all areas that are being practiced and exercised on a regular basis by state

and local and federal agencies to make sure that when the event does happen we would be prepared to respond to it.

We are also in charge of coordinating response with other local public health agencies, the medical community, the privates, and also community organizations such as the Red Cross.

Then, lastly, ongoing public communication and education of the public is something that cannot be overlooked. Any time something new comes along, like Fernando mentioned with the one case of West Nile virus and death from meningitis, the newspapers tried to make it an epidemic. That does happen when it is new. When three people are killed in a car rollover it doesn't make the front page. So, the public will get their information from the media and we need to make sure the communication received from the media is on time, is current and, most importantly, is correct and I look at public health as the persons being responsible for that.

What can we learn from past events, recent

past events? One, September 11th underscored the need for coordinated messages coming from all providers and all entities. The ticker kept coming across TV to "go down and give blood; go down and give blood" and people continued to go down and give blood even after the public health and emergency management agencies said we are not going to be needing blood; there are no survivors, and you all know that story and the waste and the overload.

The smallpox vaccination program that went throughout the country--Fernando briefly mentioned that, but also certainly one thing I wish we would have followed in Nebraska--we actually had about 2500 people and, of course, they could not give blood. It would have been really nice to say if you want to be part of this program you might want to consider going down and giving a pint of blood the day before you get your smallpox vaccine so we don't lose that resource. And, if we ever had to do mass vaccination for something like smallpox, which is a live vaccine, it would be different than

if we had to do it for influenza for pandemic. That would really be a disruption to the blood supply. We really need to think about that beforehand and how do we build up that blood supply prior to the vaccination program.

West Nile virus I want to talk about just a little bit because we really got hammered in Nebraska with West Nile virus two years ago. We had the second most cases in the country and we aren't that populated. We had the second most per capita. The Red Cross began screening for West Nile virus for persons donating. We did not know they were doing that until it was announced in the paper and we had several dozen positive donors who weren't ill. Now, that is good news because that helps get into the safety of the blood supply. We appreciate that. We had over 500 individuals identified that year going to give blood and finding out they had the virus before they became ill. That is the good news. The bad news is it was considered sometimes proprietary information and we needed to find the locales. We needed to

know where the epidemic was the worst. The fact is it got so bad in a couple of the smaller counties, the Red Cross just quit going out to run the blood mobiles because they were going to turn down 20 percent of the population and it just wasn't worth it. But that is important to us as public health officials to know so we can respond to the public out there.

One of the things we are going to see with the pandemic flu obviously is the disruption. Now, the other two speakers have already talked about that and I am not going to talk to you too much about that, other than about the question that was raised, and I believe it was to Ben. Since we may not have the way to test for the virus when someone comes to give blood the day before they become symptomatic, what we need to do is have a communication system already in place with the agencies that are collecting blood. We should have a list of who gave blood so the next day when we see a list of who is positive for flu we can work together to get that bit of blood out of the supply

line, or vice versa, like we did with West Nile virus. That information can be shared. Obviously, you have all thought about this, you donate blood and wait 48 hours before that blood gets put into the pipeline to make sure that person is not symptomatic. But you are going to have to have a call-back system and that is where the state and the locals, with the epidemiology staff and surveillance center, I believe could be a big asset to the blood community.

Then, the priorities of where you get the antivirals or where you get the vaccine--I don't have a whole lot of confidence we are going to have enough antivirals. I mean, it is important but I don't look at that as a big way to save lives with this epidemic, unfortunately. Then the vaccine, and who is going to get it, there are many people who think they are top priority. We have an outfit in Omaha called First Data. If you use your credit card today for lunch there is a 30 percent chance it went through First Data in Omaha to get processed. So, they feel they should get

vaccinated because if they shut down the whole banking industry shuts down. So, it depends which chair you are sitting on who the priority is. Do you want to fly to D.C. without air traffic controllers? Do you want to go to hospital without nurses or doctors? It is going to be tough to decide those priorities.

One thing that I don't think Ben did mention is we probably aren't going to come up--our communities aren't going to come up with a concrete list of who gets it first and who gets it second because we are going to have eight to nine months of watching who is at greatest risk and who is dying from pandemic and this priority list is going to be a little bit flexible. It has to be flexible. We can't decide it is just the nursing home residents first. They may not still be with us if this pandemic is bad enough, for instance.

So, those are things that have to be addressed and we don't know yet whether they will be addressed at the federal level or the state level or the local level. With the vaccine

shortage this winter the federal government and ACIP did a good job of saying here are eight priority groups. Some states said we don't have enough vaccine to even do the eight groups; we have to narrow it down to four. Other states said we have the eight groups taken care of; we are going to broaden it and expand it. I don't know if we would be allowed to that with a pandemic. The vaccine may be very strictly controlled by the federal government and dispersed to the states, and it may not be. You know, those are issues that are still to be determined.

I will get out of here in just a minute. I think the thing we want to talk about just briefly is how to strengthen the relationship between the community blood center coordination efforts and the public health, particularly for pandemic influenza, and you need to know who is on your state planning committees. You need to get on the committees, the Red Cross and the blood collection centers.

In the property guidance agreement for

bioterrorism there is a statement, and I want to read this one by quote: The states must establish an advisory committee to include representatives from the Red Cross and other voluntary organizations--and it goes on to list a group of entities, but the Red Cross must be involved with the advisory committees for bioterrorism preparedness planning, with all those dollars we are getting from the federal government.

I want to tell you just a brief story about Nebraska that does frustrate me a bit. I thought I had the Red Cross. I called the local chapter, told them what we were doing and needed a representative. Of course, two months later after the first committee meeting I got chewed out by another Red Cross chapter and then I got chewed out by the private blood bank. So, we need a unified voice for blood. We need a unified voice. The GAO report from September, 2002 says both the Red Cross and ABC are independently pursuing their own plans to meet emergency and long-term needs. It also said this committee received a report from the AABB

task force calling for all blood banks to be designated suppliers of blood in an emergency and that the Assistant Secretary for Health serve as a spokesperson for all organizations involved in managing and transporting blood in an emergency. I don't know where you are at with that. It has been two years, almost three years. That I think, from a state health official standpoint, is critical. I don't have time to meet seven new friends if we are dealing with a potential disruption of the blood supply. We need a national spokesperson and that I think is the main message I want to leave today, to try to get that part worked out.

Lastly, we need to continue supporting state and local epidemiology laboratory infrastructure. It is coming along very nicely. We have made tremendous, tremendous strides in the last three years to improve our ability to respond and we just need to continue that. It wouldn't be fair if I didn't say publicly that we have come a long way but we still have a long way to go. It is a marathon, probably without a finish line in

sight.

I hope I have talked fast enough to get you back a little bit on schedule.

DR. BRECHER: And we do appreciate that. Is there a comment or a question?

DR. BIANCO: Maybe Karen wants to say a couple of words about the task force.

DR. BRECHER: But maybe not!

DR. SHOOS LIPTON: We do have a task force that was convened. It is an organizational task force for disasters and acts of terrorism. We do have one convening entity. We don't make decisions but AABB convenes all the parties. We have different layers of members who sit at the table. I think in the past two years we have worked very effectively to try to speak with one voice and make sure that we have a common message, to make sure that in the communities that we operate people understand who the players are. We have been involved in these TOPOFF 3 exercises and I think it is actually--I mean, we keep refining it but I think we are at a much better place than we were

several years ago, and I would hope you will be able to see that at some point.

DR. RAYMOND: Again, the TOPOFF exercise for instance, they are important. That is where you find out where your weaknesses are and now is the time to be exchanging those business cards, not when the stuff is really moving fast.

DR. SHOOS LIPTON: Each of our blood centers actually has a manual that we have given to them, and they can get access to all this information on our web site, and it does say that they should make best friends with their state and public health departments.

DR. RAYMOND: And I would echo that because the state and public health departments have this new money coming down for preparedness, and there may be ways that we could help the blood agencies, collecting agencies to expand or improve their services, such as mobile units to go out to more remote areas, things like that that I think need to be talked about.

DR. BRECHER: Thank you. We are going to

move on to our next speaker, who is Dr. Alfred DeMaria. He is Chief Medical Officer, Director of the Bureau of Communicable Disease Control and State Epidemiology with the Massachusetts Department of Public Health. He has served on a number of state and federal advisory committee panels and task forces.

Massachusetts Department of Public Health

DR. DEMARIA: I think I can go very quickly. Let me just start with the bottom line for all of the speakers today, that the days of the blood collection agencies and the blood distribution systems who are doing their thing in public health are over, and I think for a variety of reasons. And, I am here today basically representing the state epidemiologists, the Council of State and Territorial Epidemiologists which was founded in 1951 and basically serves the function of making recommendations to the Centers for Diseases Control about what diseases should be reportable or how they should be reportable and how surveillance should be done for them. Basically

the state epidemiologists in each state work to do the surveillance and to do the response and intervention at the state level, working very closely with the local health agencies as well, which over the United States differ very much in terms of size and organization. So, you go from New England and, actually in Massachusetts in particular there are 351 independent health jurisdictions and 12 percent of all local health departments in the United States are in the Commonwealth of Massachusetts. So, there is a lot of variability about how public health is organized across the country, and that is why I think that a lot of what the blood collection agencies and blood banks have to do is work with both local and state health departments because there is no sort of national fix to this in terms of dealing with the issues discussed today.

The history of notifiable diseases goes back a long way and there are a lot of things that we look at that related to what the blood banks and blood collection agencies do, and a lot of that has

to do with collection of information that is important from a public health standpoint as well, as well as from a transfusion and blood product standpoint. So, I think we need to recognize that a lot of the information that you have is important to us and a lot of the information we have is important to you because we use that information to track trends and identify clusters. We need that information for interventions, prevention and service planning, as well as to serve as education policy guidance, and then use that information for evaluation. I think the West Nile in particular suggests a way that we can share information that would be of value both in terms of feedback to the blood industry as well as sort of using sentinel information for us as we get more experience with West Nile.

This is sort of the traditional public health surveillance system, very charming with pictures and people reporting but, obviously, we have to go beyond that now and the trend now, over the last 15 years, has been electronic data trends

submission, particularly electronic laboratory reporting and you can see how that might relate to blood screening syndromic surveillance, linking illness rather than disease and diagnoses and laboratory results. There are administrative data sets to do that that are now available to identify illness in the community before diagnosis is even made, and look at pharmacy surveillance, put all of that together in geographic information systems, and we are also looking at antibiotic resistance and infection reporting, both because it is a good thing to do and obviously there is public demand for that now.

The other things that epidemiology programs at the state level do relate to public education, provider education, as well as surveillance and disease intervention, and frequently immunization is located in these epidemiology acute disease programs.

Also, with are involved with vital statistics, health promotion and disease prevention, as well as occupational and

environmental health where surveillance is done in epidemiologic analysis is necessary. So, in most states there is a variety of activities that go on under the rubric of surveillance and epidemiology.

I think from the standpoint of the state epidemiologists the important issues are disease reporting of reportable diseases. [?] Basically, it is sort of a collaborative relationship with the blood banks and blood collection agencies because there is always this concern that with the information we are generating the health department will show up on somebody's doorstep [?] but I think we have become much more sophisticated over the last 15-20 years so we have mechanisms to make sure that the interests of blood supply and the interests of disease control are sort of better meshed.

Also reporting clusters and outbreaks, I think as we look bacterial contamination and how you follow up on that and identify cases in the recipients of bacterial contaminating units, it is really going to have to involve both the hospital

infection control and healthcare infection control community, as well as the health departments. Frequently that is done on both the local and state level.

Vector-borne diseases are of particular concern in the part of the country where I work in terms of identifying both donors and recipients who might be infected by vector-borne diseases, in addition to West Nile virus or tick-borne diseases. [?] establish means of communication we have to be able to recognize those. Prion diseases aren't even mentioned. It is a big issue with the public. Transfusion-related [?] I didn't put on there because my attention is brought particularly because of concerns of legislators who are waiting to legislate how you would deal at the level of blood collection and distribution with transfusion-related acute lung injury. I tend to think there are probably better ways than individual legislation and individual states to deal with that issue. I think that is another reason why this closer working relationship between

blood collection agencies and blood banks and public health has to happen.

The particular issue is the immune globulin and blood supply issues [?] and there is going to be a move in some circumstances when it is really necessary to IVIG, raising issues of supply with that product.

Then, you know, we are all interested in maintaining the blood supply. So, working with some preparedness programs that state epidemiologists are involved in becomes very important. So, I think from my standpoint and from the standpoint of epidemiologists, what needs to be done is to build on existing relationships that have been established with West Nile virus in particular, as well as emergency preparedness, to develop guidelines we are all comfortable with in terms of reporting of screening results, laboratory results and outbreaks, and to develop this at the level of jurisdictions.

You know, it is almost shocking, I have to admit, how little the average public health worker

knows about blood collection, blood banking, screening and all the other aspects of what is done. People in public health don't know anymore than the general public, for the most part, about what it is all about. So, we really need to correct that because if we want to have an effective working relationship we have to be more educated about what the [?] and how it does it.

Then, I think the blood collection agencies and blood banks and transfusion services have to understand what public health does, and there has to be appropriate cross-participation across a variety of committees like this, and committees like the AABB has, and committees that public health has to address public health issues. It has to be adequate and cross-represented to foster that kind of communication.

We have heard a lot about pandemics and I can close my eyes and see this chart now because it demonstrates quite dramatically what happened in 1918, at least in Massachusetts, in terms of death. You can't see 1957 and 1968 on here because [?]

but whether it is ordinary influenza or 1918 influenza it is going to have a tremendous impact on everything that society does [?] on blood collection and the blood supply as well.

I am not going to repeat what has already been said, but all those things are of critical importance and need to be planned now, and on the state level we are sort of trying to slide into a national trend, because none of this is done in isolation, looking at prevention and control on a local basis to have a plan where everybody knows what they are supposed to be doing when the time comes, and also to have [?] across agencies. You know, most public health agencies now at least are at the point of developing plans and trying to think about these things. But we now have to go to other agencies within state government, and we have plans with the state police to provide security for our immunization clinics [?]

So, we need to have specific agency plans that cross both the public and private sectors, and then all the other things that I think are obvious

for preparedness, including having adequate influenza immunization programs to have a platform upon which to build for pandemic influenza vaccine clinics, as well as to make sure the general public and anybody who is a candidate for pneumococcal vaccine get that, and it is another area where we can work together to make sure that not only the general public understands but specifically blood donors understand what they can do now to help when the time comes and the pandemic occurs. I will just stop there.

DR. BRECHER: Thank you. Questions?
Merlyn?

DR. SAYERS: This is just a comment, not a question. But as blood bankers, one of our earlier relationships with health departments was in the establishment of alternative test sites at the time of the HIV emergence as an epidemic. That is not to say the same is going to happen with whatever the next pandemic is, but I think it is just worthwhile remembering that health departments do play an important role in ensuring that donors did

not donate out of test seeking behavior. So, thank you for what was done in the past and I am sure we will call on you to do the same should the need arise.

DR. BRECHER: Other questions or comments? If not, we will go to federal government. We will first hear from Dr. Michael Soucie, from the CDC.

Models for Disease Reporting and Adverse Event
Surveillance Universal Data Collection

DR. SOUCIE: I am passing out some handouts of my talk. I appreciate the opportunity to inform the committee about a public health surveillance system we set up at CDC to monitor advisory outcomes of blood product therapy in the bleeding disorders community.

I work in the Division of Hereditary Blood Disorders and our mission is to reduce or prevent the complications of hemophilia and other bleeding and clotting disorders and thalassemia. This work is funded by a mandate from Congress that arose from response to the bleeding disorders community who requested a monitoring system of the blood

supply so we would not have a repeat of the HIV epidemic that occurred, as you all know.

Approximately 18,000 people in the United States have hemophilia, which is a congenital lack of one or more proteins necessary for normal blood clotting. These patients will have bleeding, usually internal bleeding either in response to trauma or at times just spontaneously, bleeding into joints and cause chronic and debilitating joint disease. Treatment for the bleeding consists of infusions of biopharmaceutical products made largely from plasma donations. While, as you have all heard, there have been viral inactivation steps added to the manufacture of these products and extensive screening, and so on, for donors it still behooves us to continue to monitor these products to make sure that they do not contain any viruses. So, we have established a public health surveillance system for product safety in the bleeding disorders community.

Our target priorities with this prevention program are the same as those of the bleeding

disorders community, that is, blood product safety; the elimination or decrease of joint disease; addressing the special issues of women with bleeding disorders; and the detection of hereditary abnormalities associated with bleeding and clotting disorders.

We work on these priorities through a cooperative agreement with 135 hemophilia treatment centers which are specialty clinics set up in educational institutions throughout the United States and its territories. We provide funding to the centers so that they can participate in blood safety monitoring and surveillance efforts with us. We collaborate with lay organizations to deliver consistent prevention messages that result from the surveillance information that we obtain. And, we maintain a prevention evaluation network to assess the efficacy of these prevention services.

The blood drops on this map show the distribution of the 135 treatment centers which pretty much follow the population patterns in the United States. We also have a center in Puerto

Rico and Guam.

The Universal Data Collection System, or UDC, is the surveillance system that is designed to monitor blood safety among the recipients of blood products. We also monitor the extent and progression of joint disease and we use this system to help us to identify issues that require further study.

The UDC is a national protocol that is approved both by the CDC's IRB and each of the 135 institutions. We use standardized data collection forms to collect data on patients annually, and these forms were developed with input from experts and were extensively pilot tested. In addition, the patients donate a plasma specimen annually. A portion of this is stored in CDC's serum bank for use in the future for blood safety investigations as they become necessary. We also take a portion of the specimen and test it for hepatitis and HIV, and any new infections, new infections since the last time tested are investigated for any link with product.

The data collection elements consist of demographic information, clinical information such as hemophilia type and severity, treatment

information about the number of bleeds and infusion frequency. We collect information on all blood products used during the past year between visits. We collect information about the extent and treatment of liver disease and if any joint infections may have occurred. We collect information on the impact of joint disease on daily living, the number of days lost from work or school. And, we collect an objective measure of joint disease, joint range of motion measurements in ten joints.

To give you a little idea about the enrollment in the project. Since we began this project in May, 1998 we have had over 16,000 unique individuals with bleeding disorders who have been enrolled in this project. Once again, we ask patients to enroll in this project every year so that we can get serial specimens and, therefore, identify potential seroconversions that might need

to be investigated. So, there have been over 40,000 visits from which we have collected information, and the overall national refusal rate for enrolling in this project is 7.6 percent, which we believe indicates the measure of success or the acceptance of the community for this project.

We started out with this project in 1998 by paper forms that we are in the process now--all the HTC's are beginning to use the electronic clinical software data tool which is useful to them in the clinical practice and allows them to send the data to us electronically.

In terms of the blood safety monitoring we have done thus far, there have been no new infections with HIV or hepatitis due to blood products among any of the UDC participants. One of the benefits of the program is that many patients at risk for hepatitis A infection are receiving vaccinations. We believe that that is particularly important for those who are hepatitis C infected and don't need anymore liver injury. We believe that the system provides reassurance to the

bleeding disorder community of product safety and the serum bank has been established for future use in blood safety investigations. We now have over 40,000 blood specimens in the serum bank.

We have conducted a number of special investigations using material from the serum bank, one of which I will describe briefly for you. As you all know, there is evidence from the community of blood-borne transmission of West Nile virus. The products used by people with hemophilia were thought to be safe from West Nile virus because viral inactivation steps probably were effective. Nonetheless, we have tested over 5000 specimens in patients with hemophilia who had visits during the previous two mosquito seasons and, to date, there is no evidence of West Nile virus transmission through any of these blood products.

We have set up a similar system for patients with thalassemia who receive at times monthly blood transfusions. Since January of 2004 we have received data and plasma samples on 200 patients. We believe that this is a good adjunct

to the blood safety surveillance system because these patients, unlike the viral inactivated products that the hemophilia patients receive, are receiving straight blood transfusions. So, we are also storing and testing plasma specimens from these individuals and we are in the process of developing data collection tools to address some of the issues concerning this population, primarily transfusion reactions and complications of iron overload.

Just to mention that this system is flexible in terms of the kinds of things that we can do. We are starting a pilot study of inhibitors which are antibodies to factor products that make the normal products useless to treat a bleed for a patient. This, as you might expect, is a very serious event for the person that it happens to. Fortunately, it is quite rare but, given that it is rare, it is difficult to study. So, we are looking at the system to do post-marketing surveillance of treatment products, and looking at other risk factors for the development of

inhibitors.

The key features of this surveillance system are that we have clinical centers with dedicated staff who have access to the patient population. The number of patients that we have enrolled in the UDC, the hemophilia patients we believe represent about 80 percent of the patients with hemophilia who use these centers in the United States. The data collection tools must collect a minimum amount of data necessary because these are, again, busy clinicians that are collecting the data for us and it is important that we keep the data to a minimum. We also seek to collect data that is easily available.

We perform regular and frequent data analyses of these data and we make the results available to those who need to know, as well as those who collect the data, to actually make them understand its usefulness and help with the cooperation in data collection. In addition, patient understanding and acceptance is key to successful study recruitment which I believe we

have in this study.

We have an expert working group and I list them not necessarily just for their names but to show you that there is a multi-disciplinary group of physicians; we have consumers; we have regional coordinators, nurses, physical therapists and social workers--examples of all the disciplines who work in these clinics to make sure that the tools that we make and the data analyses that we perform are appropriate.

We report the results of our surveillance through routine surveillance reports that come out two, three, four times per year through published articles in journals, and we have a web site which lists up to the minute numbers for national, regional and HTC numbers of patients and characteristics, and so on.

We also provide an HTC specific annual report that summarizes each treatment center's patients, their characteristics, and puts it in the framework of the regional and national perspective.

Finally, this is our web site. It may be

easier just to go to CDC.gov and search for hemophilia and you can find any of our web sites. Thank you.

DR. BRECHER: Thank you. We have time for a question or two. Merlyn?

DR. SAYER: Thanks. I am curious about the consent that you get from the patients. Do they give a global consent to testing when they are giving their annual samples?

DR. SOUCIE: The testing is for blood safety issues only.

DR. SAYERS: But you don't specify what in your opinion is the blood safety pathogen of choice? I am just thinking in terms of what happens, say, when a screening test for prions becomes available. This might be an interesting group to look for the prevalence of a marker. Would you have to get specific consent for that particular screening test or do you have some global consent?

DR. SOUCIE: It is global as far as infectious diseases. It states specifically that

there is not genetic testing involved.

DR. BRECHER: Jerry?

DR. HOLMBERG: So, who has access to the serum samples?

DR. SOUCIE: Well, we, in our Division, have control over the specimens but, you know, if there were issues--for example, we did the West Nile virus. We have looked at parvovirus B19. If there were, for example, a test for prion disease or something like that, samples could be made available for that.

DR. WONG: Perhaps I can just clarify this. The consent basically is sort of future-looking in saying that there is the possibility that we will test for unknown pathogens so it covers everything. We do revisit it once a year.

DR. BRECHER: Art?

DR. BRACEY: One group that seems to be missing is the sickle cell group, particularly after the STOP trial. Transfusion is becoming a bigger part of the therapy of those patients.

Would you see any reason, or is there any chance of including that group?

DR. SOUCIE: There would be a chance if we were able to get funding to do that testing, yes.

DR. BRECHER: It doesn't seem to be part of their specific charge.

DR. BRACEY: As of the data that came out of the STOP trial, you know, the treaters of sickle cell disease were sort of loathe to transfuse at one point but now they are moving more towards transfusion. If you look at a large population of chronically transfused people, it is a great group.

DR. SOUCIE: Yes, the thalassemia population is very small compared to the sickle cell population. That is true.

DR. BRECHER: We are going to move on to our second CDC speaker, Teresa Horan.

National Hospital-Based Transfusion Reaction
Surveillance Using the NHSN

MS. HORAN: Thank you. It is tough being the speaker before the break so we will try to get you to the break here.

I was asked to speak to you today about some possibilities for a national surveillance for transfusion-related adverse events in the context

of the surveillance systems that we have in the Division of Healthcare Quality Promotion in the National Center for Infectious Diseases at CDC. So, just to tell you something already know, getting an estimate of the scope of the problem, we were able to find some data that there are about a million deaths and serious disabilities associated with hemolytic reactions due to incompatible blood or blood products, and if new misses are counted it is estimated to be about five million.

In contrast, the types of healthcare-associated infections that I most closely work with, we estimate that there are about two million hospital-associated infections annually, accounting for about eight million extra hospital days of stay, contributing to about 80,000 deaths per year and costing upwards of 4.5 billion dollars. So, it is clearly a problem that CDC has been interested in for a long time.

We have three major surveillance systems in the Division of Healthcare Quality Promotion that relate to healthcare surveillance. These have been designed to help infection control, dialysis and occupational health programs to promote patient and healthcare worker safety by providing them

tools to identify the problems that need to be addressed in their individual institutions, to monitor the success of the interventions that they have to try to prevent these infections, to trend their data over time to see how well they are doing, and to determine which events they should target to maximize their efficiency and impact.

Well, how do we do that? We do that by providing them with standardized protocols and definitions for the events of interest, and we help them to identify and monitor risk factors for adverse events or exposures in the healthcare setting. One of the hallmarks of our systems has been feeding back risk-adjusted aggregate rates for comparison. We publish these data on an annual basis, and even hospitals or institutions that do

not participate in our systems use those data to benchmark where they are in their processes of preventing infection. So, although our membership has been only about 300 hospitals in the U.S. for one of our systems, the data are used broadly across the U.S. Finally, we provide access to prevention guidelines and other prevention tools to the community.

The systems that we have in place are three, as I mentioned. The first is the National Nosocomial or Healthcare Associated Infection Surveillance system, known as NNIS. The second is the Dialysis Surveillance Network, and the third is NaSH, or the National Surveillance System for Healthcare workers.

Those three systems are summarized very briefly on this slide. The NNIS system is for monitoring healthcare-associated infections primarily in critical care and surgical patients. It started in 1970 and we just stopped collecting data at the end of 2004 because we have replaced it with our new system, which I will describe in a

minute.

The second system for dialysis surveillance is focused on bloodstream infections and vascular access infections in dialysis outpatients. It is a relatively new system. It started in 1999.

The third system, NaSH, is for healthcare workers. It is for exposure to blood-borne pathogens of healthcare workers after injury or needle stick events, tuberculosis, skin testing and exposure to TB, and also a way to monitor vaccine history and receipt of vaccine among healthcare workers and any adverse events associated with the receipt of vaccine. That has been ongoing since 1996.

These three systems are being consolidated and integrated into a new system, called the National Healthcare Safety Network, or HGSN. It is going to integrate the NNIS system, the NaSH system and the Dialysis Surveillance Network into one system because in the past each of those were distinct, disparate systems that didn't talk to one

another, had separate epidemiology and statistical and IT staff working on them, and they didn't talk to each other at all. Clearly, we needed to stop doing business that way and so we tried to integrate them into one system called the NHSN.

The NHSN has two components that I think are of interest to this group. One of them in particular is the patient safety component which has modules in it that are based on the NNIS and the dialysis surveillance system, but it can be extended to other areas. From our existing systems we will focus initially on events associated with the use of devices, procedures or medications in health care.

The second component is the healthcare personnel safety component, and those modules currently are based on our current NaSH system, focusing again on exposures, investigations and interventions among healthcare workers.

In the patient safety component I mentioned three modules, device associated, procedure associated and medication associated. In

the device-associated module we look primarily at device-associated bloodstream infections, urinary tract infections and pneumonia, and in dialysis patients what we describe as dialysis incidents.

In the procedure-associated module we look primarily surgical site infection and post-procedure pneumonia. It is in this grouping that I think were there to be some sort of broad safety monitoring in hospitals, it might fit into the procedure-associated module, and I will describe that in a minute.

In the medication-associated module currently we are looking at antimicrobial use and resistance in health care. I will skip the healthcare personnel safety slide so you can have coffee.

The premises upon which NHSN has been built are shown on the next couple of slides. One of them is to share data in a timely manner while maintaining data security, integrity and confidentiality--all very important to our systems. As you may or may not know, CDC is not a regulatory

agency so we have especially, I think, to keep the data that we get safe and secure, and our systems in our Division all have an assurance of confidentiality associated with them, which means that we do not share the data publicly; we need to keep it confidential for the institutions. They, of course, can share it if they choose.

So, we need to be able to keep the data secure but people have a need to share data and they want to share it sometimes with health departments and sometimes with other hospitals or entities within their systems, like if you have a multi-hospital system you might want to know what is going on in all of your institutions. So, there are plenty of reasons to share data. So, we have tried to develop some ways to do that within the NHSN without violating our need for confidentiality.

A couple of other problems are shown here: To minimize user burden and I think a couple of speakers earlier have touched on this. One of the ways that we have tried to do it in our domain is

to streamline the data reporting protocols. We have had plenty of experience collecting data in these arenas so we have learned a lot about how to do that from our user group, so we have tried to streamline the data collection protocols so that they only collect the data that they are going to use. Rather than trying to build a huge case, they are simply trying to collect the data that is going to be useful for them to compare rates with one another and characterize the epidemiology of the infections.

We also have paid particular attention to increasing capacity for including data from existing electronic sources and, again, someone alluded to this earlier. As we become more standardized across IT systems, it will be increasingly possible--in fact, it will be demanded to try to get data out of existing sources like laboratories, pharmacies, clinical and administrative databases so that the user burden of the data collector can be minimized.

We also wanted to be able to allow all

healthcare delivery entities to participate in our system. In the past we have had to restrict the membership because of certain attributes that we wanted to include in our system, but now we are very much interested in opening it up to all-comers.

So, how does this relate to the reason that you are here today? Well, one thing that we can think about in terms of national surveillance of transfusion-related adverse events is should you use an existing system or extend an existing system to collect the data that are required. As you know, and as I think you will hear later, there are several systems that the FDA operates, the AERS and MedWatch system, the BPD system, fatalities, and there is another system called MERS-TM for transfusion medicine. So, those systems potentially could be extended for transfusion-related adverse events. To speak about NHSN and the possibility there, we concluded that perhaps under the procedure-associated event module is where a surveillance system like this could fit.

So, what might that look like? Well, first of all, you would have to define your events, what are transfusion-related adverse events and

what do you want to know about them. So, there might be some numerator data that were collected which probably would have some patient data required, and the transfusion reaction data would need to be described and you would have to come to agreement on what that would look like and what types of events would be of interest. Then, what risk factors you might potentially want to know about.

In terms of denominator data, if rates are to be calculated, obviously, you are going to need some relevant information on each of the different types of blood product transfusions that are of interest, and some of those are mentioned on the slide.

I just looked at our new system, the National Healthcare Safety Network, and I said, well, if I were going to do something where would it fit here? This is just a screen shot of our

event data entry screen. So, it has patient demographic information. These demographic data were chosen for our systems but they could be modified as appropriate for what was needed for the transfusion group. Then I made up actually an event here and it is highlighted there in blue. So, the types of events that would be of interest could be shown in a drop-down screen and people would choose which ones they wanted to report as they occurred. Then, they could be linked to a particular procedure. In this case I just put blood transfusion but it could be a specific type of procedure. That would constitute the numerator data. You could add risk factors or specific event details you wanted to be captured, and information on organisms could also be captured.

In terms of denominator data, again you would define the types of blood transfusion procedures that you wanted to capture and enter the data for those at the procedure level to get a denominator.

So, issues to consider when trying to

decide what national surveillance might look like--these are just generic issues that others have raised, but are the data readily available? What data sources would be needed? Do you need both numerator and denominator data sources? And, do you have data collectors out there who are willing and able to access those sources of data and collect the data for you? In the case of healthcare-associated infections, we tap into existing infection control professionals who are in every institution in this country, and that is one of the things that is in their job description, to do surveillance. So, we tap into a group that already exists so we don't have to pay data collectors.

Another question to consider is what do you want to look at, which adverse events? Do you want to look at all of them or the common ones, or just sentinel events like deaths or serious adverse events? What about the patient populations? Are you interested in all of them who have transfusion, or would a sample of those patients be good enough?

What about confidentiality? Is that something that is needed or even wanted? If not, then that is a layer of complexity that can be eliminated.

Should reporting be voluntary or mandatory? Right now mandatory reporting of healthcare-associated infections is a very big deal. It has been looked at and mandated in many states already, and probably in the next few years it is going to be mandated in almost every state. I would suggest to be proactive here so if it is going to be mandatory you mandate what you want.

Do you need to link to other systems? Obviously, there are many other systems and if there is a desire to link those up, then there need to be data sharing agreements. Who is going to manage the different databases? How are they going to relate to one another? What about data analysis? How is that going to be done? Who is going to be responsible for it?

Obviously, the issue that is one of the most important is what kind of resources are available to do this kind of work. Questions?

DR. LINDEN: I have one question and one comment. The comment is just to point out, since we are talking about infectious diseases today,

that some of the things you mentioned, like TRALI, you would know that right away and those are relatively easy to capture. But infectious diseases, with the noted exception of bacterial contamination, are generally not things that you are not going to recognize right away. It might be six months or a year or more, unless there was some kind of error that you know was transfused. So, I think we need to maybe think out of the box in terms of different ways of trying to capture these because I think some of the systems we have relied on in the past will not work for your particular new pathogens. But certainly the infection control officers in hospitals are one resources to draw on, but most of these diseases that do develop down the line are not going to be in hospitalized patients so you are talking about local physicians in the community, and in my experience it is a group that is very difficult to get data from. That is just a

comment.

My question is on your second slide, could you please explain what these data are that you presented and where they came from?

MS. HORAN: These are data that were from Iowa report and also the National Quality form data. I think they are supposed to be estimates.

DR. LINDEN: In the U.S.?

MS. HORAN: Yes.

DR. LINDEN: I don't think so. I don't think these data are what the text says they are.

MS. HORAN: Fair enough.

DR. LINDEN: Incompatible transfusion I believe are in the range of 25/million and only half the people who get incompatible blood have any sort of reaction. Less than 5 percent are fatal. So, you know, U.S. maybe 150 and a handful of fatalities. I think the text on this is perhaps just not correct. I mean, I have no idea what this is but it is not what it says, I don't believe.

MS. HORAN: Okay.

DR. BRECHER: It might be all adverse

events, everything lumped together.

DR. LINDEN: It may be everything.

DR. BRECHER: Other comments or questions?
If not, looking around the room, I think everybody
is ready for a break. Ten minutes.

[Brief recess]

DR. BRECHER: My goal is that we will be
out of here by 5:30 at the latest. We are going to
continue with the federal presentations. We are
now going to hear from Theresa Smith, from CDC, on
models for disease reporting.

ArboNET

DR. SMITH: I appreciate being asked to
come and talk about West Nile virus and blood
safety. Basically, I am going to give you a little
bit of a story about what we have been doing over
the last few years as we have recognized this
problem and tried to move to improved blood safety.
I give you the caveat that West Nile virus has not
reached its ecologic niche in the United States.
That means that we don't really know what the
long-term balance of health problems is going to be

so some of this may be changing as we continue understanding this problem.

West Nile virus is a mosquito-borne flavivirus related to hepatitis C virus, which all of you are familiar with in blood safety. It was first seen in the United States in 1999. From studies in the United States and outside the United States, we know that roughly 70-80 percent of people who are infected with West Nile virus remain asymptomatic; 20-30 percent develop West Nile fever. They do so probably within 3-6 days of becoming first infected. Less than 1 percent of people develop West Nile neuroinvasive disease, which is what we have been, up to this year, tracking with our surveillance in the United States.

Even before finding West Nile virus in our blood supply we knew there was a potential for it to be a blood-borne transmission problem given that peak viremia occurs before illness onset, and that the duration of viremia is estimated to be about 6.5 days.

West Nile virus blood screening--excuse me, I tried to shorten my talk and it looks like I did too good of a job!

[Laughter]

DR. BRECHER: Well, that was fast. Thank you!

DR. SMITH: West Nile transfusion-associated transmission was first noted in 2002. A total of 17 confirmed West Nile virus transfusion-associated transmission infections were found, and you can find information about that in The New England Journal of Medicine, September 25, 2003. Fifteen of the people who developed an infection with West Nile virus through transfusion developed West Nile neuroinvasive disease and two developed West Nile fever. It appeared that 16 infectious units were implicated. They were donated between July 22 and October 6. Nine of those donors were symptomatic near their donation with either headache or fever. Overall red cells, plasma and platelets, each were implicated in at least one of the infections. Initial donations had

no West Nile virus IgM or neutralizing antibody present in them. The 2002 West Nile virus transmissions probably led to an organ transplant transmission as well, with the person who donated the organs actually receiving one of the implicated transfusion-associated transmissions prior to donation.

In response to this, the FDA and CDC worked together to see what we could do to continue to monitor the problem, as well as ameliorate the difficulty with blood safety. FDA called for more commercial screening tests to be available and two nucleic acid amplification tests appeared to be ready to be used for investigational purposes. They are both minipool formats, such as is used in HCV and HIV, and FDA offered investigational new drug protocols for these so they could be available as screening protocols.

There was rapid implementation during the summer of 2003 of these nucleic acid tests, and two goals that came out of the implementation were to see how effective they were, looking both at

potentially infectious donations that had been interdicted, as well as the breakthrough transmissions that may occur.

Here you can see the pattern of how these tests are used. In either a 6- or 16-donor minipool they are tested for nucleic acid. If they are not reactive the product is immediately released. If they are reactive the minipool is broken down into individual donations and retested. If those individual donations are non-reactive they are released. If they are reactive they are again retested individually using some other method. If they are again reactive that is reported to the health department. Whether they are reactive or not at this point, they have been reactive twice and the product is destroyed. The person who donated the blood is asked to come back in and is retested for IgM and IgG ELISA and another NAT test is used and that donor is deferred for a period, after which follow-up NAT and IgM/IgG ELISA will be used.

The reporting of these cases goes through

the states to what we call ArboNET, which is the National Electronic Arbovirus Surveillance that is used not for just West Nile but all of the arboviruses in the United States. It collects ecologic data on mosquitoes, birds and mammals and human data on the disease cases, and for West Nile virus alone on the presumptively viremic donors.

The blood banks report to the public health departments the gender, age, residence by zip code and donation date for the presumptive viremic donors, as has been described in the previous slide. The public health departments then follow-up on these patients and ultimately report to ArboNET with both demographics and clinical follow-up of how well they have done, whether they have remained asymptomatic, developed fever or neuroinvasive disease. Any blood donors who become ill shortly after donation are asked to be reported to us as well, and any recipients who become ill are also asked to be reported to us, and it is the state and local public health departments that do that.

Another method that we have for learning about presumptive viremic donors is what we have called AlterNET. It is a weekly AABB conference

call that includes the FDA, AABB, the Department of Defense and CDC. Recall that AABB accounts for approximately 90-95 percent of all U.S. donations so this gives us a fairly good sense of what is happening in the blood donations on a weekly basis. We discuss the recent presumptive viremic donor activity, the number of units screened and the PVDs found and, because of the way that the blood banks are set up, we can identify risks at a very close level, very fine level within the blood collection sites, and because they collect zip code data we can discover how possibly work is more a risk factor.

To give you an example, two areas that had a lot of activity last summer were in Arizona as well as in southern California. It was very clear in Arizona that home and work were approximately equal risks because of the way that the zip codes and the blood donation sites seemed to overlap. On

the contrary, in southern California it appeared that home alone appeared to be the risk because the zip codes of donors and the blood donation sites did not overlap.

In 2003 PVDs were reported again through ArboNET and AlterNET. In ArboNET 812 PVDs were reported. Because this requires going through the state health department that does clinical follow-up, we can tell you information about how those people did. One percent developed neuroinvasive disease; 15 percent developed West Nile fever; and 84 percent remained asymptomatic--slightly improved odds of remaining asymptomatic over what you would expect.

AlterNET was able to tell us how many donations had been screened, 6.2 million, and they have found 1027 presumptive viremic donors. We heard earlier that there was a problem with the question of how this information gets translated to the local health departments. You can see here that it wasn't getting translated to the local health departments and, therefore, wasn't getting

transferred on to ArboNET or the CDC. So, at this point, when we see this kind of data we can go back to our flow of information and our partners and make sure that the information is moving forward to the people who need to know.

The next thing that CDC needed to do was look at some of the screening effectiveness measures such as breakthrough cases.

Investigations into these cases were defined as probably, confirmed, non-case or inconclusive.

This is one of the slides I have made shorter for you. Probable has evidence of West Nile virus in the donor and infection in the recipient. A confirmed case essentially has more evidence to the same effect. A non-case shows no infection in the donor. An inconclusive case lacks samples so we can't tell where it might be.

In 2003 33 cases were investigated. Five were considered probable or confirmed; 14 were non-cases and 14 were inconclusive. The donations occurred in July through September, and the onset dates of West Nile neuroinvasive disease, which

occurred in 5 cases, were in August through October.

The Est Nile virus blood screening conclusions that one come to in 2003 include that overall West Nile virus blood screening was successful. It had rapid implementation of a new set of screening tests. Over 1000 potential infections were prevented. The 2003 West Nile virus transfusion-associated transmission infectious donor viral load was lower than in 2002, which tells you that at least some of them virus-laden donations were able to be found. But there were still infections that went through the blood system and it was felt that sensitivity could be improved. There was a sense that perhaps presumptive viremia donor density in an area could be used as a trigger to switch from pooled donation to individual donation testing.

In 2004 we had reports that would have reflected this new set of triggers where, instead of pooled donations being used, individual donations were being used at high densities. In

ArboNET we received 223 reports of presumptive viremic donors and their subsequent development of disease was very close to what you would expect out of a normal population, telling us we were getting close to the normal group that you would want to see. In AlterNET we learned that over 8.2 million donations had been screened and that 206 presumptive viremic donors had been found by this group which, again, represents roughly 90-95 percent of the blood banks and so we would expect the number in AlterNET to be smaller than ArboNET. So, now we have some evidence that our partners are beginning to do better at giving information to all the people that need to know.

In 2004 we had 14 case investigations. Only 1 case was considered a probable case. Eight were non-cases and five were inconclusive due to lack of donations to test. The donation occurred in June of 2004, just as the switch from pooled donation into individual donation testing was being turned on and was missed just at that cusp. This person developed West Nile neuroinvasive disease in

July of 2004.

So, if we compare 2003 to 2003, we see that in 2003 there were 5 transfusion-associated transmissions with a viral load of approximately 0.11 plaque forming units/mL. There were 821 presumptive viremic donors reported in ArboNET versus 1026 reported in AlterNET. There was about 1 transfusion-associated transmission for every 205 reported PVDs in AlterNET.

In 2004 a single transfusion-associated transmission had a viral load of 0.12 plaque forming units/mL, about the same as the year prior but, again there is only one so it is hard to say anything about what that means. There were 223 presumptive viremic donors reported in ArboNET versus 206 in AlterNET, and there was approximately 1 transfusion-associated transmission for every 205 AlterNET presumptive viremic donors reported.

Our conclusions for 2004 are, again that blood screening continues to be a success, with fewer investigations and cases found in the year; fewer presumptive viremic donors. On the other

hand, we do see that the viral loads between the two years are approximately the same. With only one case being found, that may not be meaningful. With the ratio of the transfusion-associated transmissions to PVDs being almost identical between the two years, it is unclear whether or not the sensitivity was improved by the triggers and we will probably require another year or two of surveillance outcome understand that.

So, in 2003 the fewer number of PVDs reported to ArboNET helped us to understand that there were communications problems, which have been resolved. But we definitely learned about the PVDs sooner when we were talking to the AlterNET version of our surveillance because we had a weekly conversation with them.

In 2004 it looked as if ArboNET and AlterNET had appropriate numbers of PVDs found in each, given that one only captures a portion of the other. But we still learned of PVDs much sooner through AlterNET.

Some of the limitations that we have

currently are the places where there are multiples of any aspect of the surveillance system. We have multiple test manufacturers. We have multiple blood collection agencies; multiple sites. All of these feed information into state health departments that, like ourselves, are receiving from multiple entities. Then we receive those state health department PVDs, forwarded to us on the basis of their own ability to follow-up each of those PVDs. And, we have the fact that these are experimental screening tests and that they have variations not only between manufacturers but even slightly from year to year on how they are being used.

MS. SMITH: All of these feed information into state health departments that, like ourselves, are receiving them from multiple entities, and then we receive those state health department PDDs forwarded to us on the basis of their own ability to follow up each of those PDDs.

And we have the fact that these are experimental screening tests and that they have

variations not only between manufacturers but even slightly from year to year on how they're being used.

We also have problems investigating possible transmission--associated transfusions. The sample availability is not a hundred percent, which is why we end up with inconclusive case, and sometimes people simply chose not to follow up, so we can't find out whether or not their second testing would have had an IgM or a neutralizing antibody available.

And last, a transfusion associated transmission recognition is very clinician dependent and maybe so insensitive as during 2002 as to yield tertiary cases through organ transplantation.

The benefits that we have of what is currently going on are that we have two systems that allow critical data to be shared quickly between blood banks and the Department of Health and Human Services. And I spread that to the Department as opposed to CDC, since FDA joins us on

these calls.

The information on asymptomatic human illness may be gained through this system because we have presumptive biremical [ph.] donors as you might call a case ascertainment method for asymptomatic donors, and this was used in 2003 and will again be used this summer as a method of trying to learn more about how people deal with this sort of infection.

Blood bank screening evaluations, linking to surveillance, can both improve the screening methods as well as the surveillance methods, and I think you see that with the fact that the screening method changed between 2003 and 2004, and so did the surveillance method.

Finally, we can see that improving blood safety can improve transplant safety, since people who are mortally ill often need blood. Thank you. What can I answer for you?

DR. BRECHER: Questions? Comments? Jay?

DR. EPSTEIN: If you could come back to your, I guess, 18th slide where you compared 2003

to 2004. I'm a little bit concerned about how one might interpret the bottom lines in each data set? In 2003, you had one transfusion associated transmission per 205 alternate PVDS.

MS. SMITH: Mm hmm.

DR. EPSTEIN: Because then in 2004, you had one transfusion associated transmission out of 206 alternate associated PVDs.

But the subtle inconsistency here is that in 2003 we didn't have individual donation testing, and in 2004, we did. The case that occurred in 2004 was one that antedated by a couple of days the use of individual donation testing.

So I think that the statistics, while accurate, don't get at the core question, which is have we eliminated the risk when we do individual donation testing.

And so can you state--I think it is the case that there have been no infections transmitted by units that were screened for IDT net.

MS. SMITH: We have found that's--

DR. EPSTEIN: And that's--and then

statement that one would make in 2003, where there were cases of transmission from units that were screened by mini pool but not individually net.

So that really the big question in 2005 and beyond is whether we will see any cases of transmission if the donation is screened by an individual donation.

DR. SMITH: I agree, and even if this actually had occurred when all system were in place, I still think that one may not be the answer at the beginning of a new system.

So I would not consider these particular statistics to be proof that changes did not work. I would consider them to be proof that we have to continue looking at how things work.

DR. BRECHER: If no other questions or comments? Thank you.

DR. SMITH: Thank you.

DR. BRECHER: Our last speaker of the day is Dr. Robert Wise from the FDA.

DR. WISE: I'm very happy to be with you this afternoon to describe the safety surveillance

system for blood and blood products.

The blood safety assurance and surveillance process encompasses the protection of blood, including components and products, donors, and recipients.

Multiple interconnected and overlapping safety domains and reporting systems are involved. This afternoon, I'm going to touch on the following five: deaths in donors or recipients; product failures, also known especially previously as errors and accidents; device malfunctions; adverse events in product recipients; and we'll briefly mention medical errors.

How do we protect the donors? This group is probably quite aware of the confidential interview, the elements of the health screen. There's rapid access to emergency care in case of need. There's a notification of donors with medical referrals upon referral for abnormal findings, including especially infectious disease test results.

How is blood made safe? There are five

layers of blood safety, together with current good manufacturing practices that always apply.

The five layers begin with the selection of suitable donors, donor education, extensive risk factor screens, including malaria and variant CJD, and a limited physical examination.

The second layer is the use of deferral registries to identify unsuitable donors. The third is infectious disease testing for multiple agents. The fourth is blood quarantine until test results and suitability have been determined. And the fifth layer of protection is the monitoring, investigating and corrective actions for errors, accidents, and adverse reactions.

And again, the current good manufacturing practices and product standards apply in all areas. These include staff training and certification, standard operating procedures, use of approved methods, pathogen reduction for plasma derivatives and bacterial contamination monitoring.

How are recipients protected? Well, first and foremost, of course, through safe blood,

including components and products with these five blood safety layers and GMPs.

We also use a lot of automated processes to try to reduce the risks and consequences of human errors. Blood and components are grouped and cross matched for compatibility with the recipient, and other safety systems, include the recipient's sample and unit identifiers, hospital practice standards, event investigation and reporting, and corrective actions.

Blood safety event reporting can be looked at in three main areas: mandatory, voluntary, and medical errors.

The mandatory health reporting from manufacturers encompasses deaths, whether donor or a product recipient, product failures, the errors and accidents, and these include biological product deviation reports, medical device reports and adverse events.

Voluntary reporting--I'm sorry. On the adverse events, I want to draw your attention to the asterisk. Mandatory reporting by manufacturers for

adverse events does not currently apply to manufacturers of blood and blood components.

We will come back to that point in a moment with an anticipated revision in the system.

Voluntary reporting of adverse events is principally the spontaneous adverse event reporting to FDA's adverse event reporting system, AIRS, also known as MedWatch and these reports can come from any source. It's not limited to the manufacturers.

And finally, medical errors are primarily reported not to FDA but rather through the hospital system. And so we'll have a little further to say about that at this stage.

The blood fatality surveillance for donations and transfusions applies whenever a blood donor or recipient expires with a possible relationship to the donation or transfusion.

The obligation is on the blood collecting or transfusing facility to notify the Center for Biologics at FDA Office of Compliance and Biologics Quality.

Leading fatality categories in the last

four years included TRALI, Transfusion-Related Acute Lung Injury--in about a fifth of cases, ABO and other hemolytic transfusion reactions, and bacterial contamination.

The 20 percent fraction related to TRALI is probably associated with stimulation of reporting through a 2001 FDA health alert.

Bacterial contamination is of special interest. It's rarely implicated in deaths, but it's frequently reported as a product deviation. It's of special concern for platelets because of the room temperature storage and their utilization before reliable culture results may be available.

Potential sources for bacteria include donor bacteremia, which may be asymptomatic or follow a medical procedure, inadequate skin disinfection, skin coring, and contaminated aphaeresis solution water baths, pack exteriors or failed sterile connections.

The biological product deviation or BPD reporting aims are basically to provide an early warning system and for surveillance. The early

warning is to detect possible problems prior to the scheduled routine inspections that normally occur every two years, and to provide an indicator of possible immediate problems or a need for a product or lot recall or a prompt directed inspection by FDA compliance people.

The surveillance aims are for training of investigators and industry and to develop guidance for investigators before and during the inspections and for the development of guidance documents and policies for the industry.

Who must report the biologic product deviations? Licensed manufacturers of blood and blood components, including source plasma, unlicensed registered blood establishments, and transfusion services.

And what is reportable? Any event associated with the manufacturing of blood or blood components whether or not licensed that deviates from good manufacturing practices, regulations, standards, or specifications that may affect the safety, purity, or potency or an event that's

unexpected or unforeseeable and may affect safety, purity, and potency and if the event involves a distributed biological product. So if a problem emerges during the manufacturing process but the product involved has not yet been released for sale or other distribution, it does not have to be reported through the system.

The leading category of biologic product deviation reports far and away was donor suitability issues, with more than three-fourths of the cases in 2004. These events were usually based on post-donation information, where the patient called back with additional information or at a subsequent donation additional information pertinent to the prior one was elicited.

Medical device reporting applies to manufacturers who must report a device-related death, serious injury, or malfunction within 30 days. Examples of these devices include in vitro diagnostic products, actual devices like aphaeresis collection devices, and computer software--blood bank programs that can give inaccurate results

through inadequate design and or validation.

Now adverse events in actual people, monitoring and reporting, starts with the AERS Program, the FDA safety information and reporting program. We receive mandatory reports from manufactures, and voluntary reports from anyone. Reports can be submitted to AERS by Internet, through batch electronic submissions for manufacturers, telephone, fax, mail.

Non-fatal adverse event reports are not currently required for blood and blood components. Blood collection and transfusion facilities are currently required to conduct investigations and maintain reports of all adverse events associated with either the collection or transfusion of blood or blood components.

Then these reports are reviewed during the FDA establishment inspection that normally occurs every two years. A submission of the adverse events to the AERS/MedWatch system is not currently required, but a propose rule would change this situation.

The proposal was published in the Federal Register in 2003. It introduces an obligation to report for a facility that's performing

compatibility testing for adverse events related to transfusion or for the collecting facility for an adverse event related to the blood collection procedure.

It would require a written report to the FDA Center for Biologics again, within 45 calendar days.

General surveillance systems strengths include the fact for AERS, for example, that anyone can file a report. We provide confidentiality for reporters and patients. The system is not punitive. We don't want to introduce reporting disincentives. It's open ended, allowing detection of previously unanticipated problems that might not appear if you limited reporting to a check list on a pre-printed page or something like that.

The scope is national so that there and very infrequent events have the capability to be reported, and we have a capacity for rapid

recognition of issues and appropriate responses to evaluate a tentative signal to control a verified problem and to learn from experience.

There are also limitations in surveillance systems including those at FDA. The systems for blood safety monitoring are fragmented. Passive surveillance systems suffer from underreporting which is pervasive in any voluntary system, and this underreporting opens the opportunity for biases and confounding factors that often at least require consideration to make intelligent, reasonable use of the data that does come in.

Adverse event reports in AERs may be causally or only coincidentally related to the product. Spontaneously submitted reports are frequently incomplete. We normally do not have control groups, and we frequently lack denominators.

To summarize, blood safety depends on multiple overlapping systems at every stage from assessing donors to identifying recipients.

Important limitations include

fragmentation of systems and incompleteness of event ascertainment, particularly for voluntary reporting systems.

Strengthened reporting requirements for serious adverse events may improve blood safety surveillance in the near future.

Do you have any questions?

DR. BIANCO: Dr. Wise, thank you, and I think you're addressing probably one of the most important aspects of FDA, and the problem, Dr. Wise, is that data gets in and doesn't get out. We report a lot. And we don't know what happens to the reports. The report on the BPDs appear once a year--huge, long tables.

We've got no interpretation or misinterpret it. And I say misinterpreted because the categories are not prioritized and 76 percent being post donation information that some people consider it a failure of this system, most of us consider it a success. A donor that paid attention to the question when home asked the wife, the girlfriend or looked at the passport to see when he

or she traveled and calls back and says, oh, God, I gave you the wrong answer.

There are no combined reports. You told us that many of the reports on bacterial contamination they come as BPDs. It would be so nice to have a report that will say we keep still fighting this since the CDC and the Bacum's [ph.] study in the early days, and Dr. Kunard studied it to know how many fatalities per event or something like that. You said it's not punitive, but if you have a fatality, you can count on an inspector being in your facility between 12 and 24 hours.

And so that's why we have even concern about the proposal addition of the non fatal reactions because it will be more data, without organization, without prioritization, you have a ton of data, but even fatality--that is, a small table--the last time we heard about the numbers, you gave us percentages not numbers today--was in a meeting in July 2004, when Dr. Haas [ph.] gave a presentation--he's sitting there--on TRALI to us at the Blood Products Advisory Committee.

So I wish--I see that you recognize some of these issues, but I wish there was a revamping of that so that we could have useful data that we

could use to improve what we do and to play it more into that system.

DR. WISE: I appreciate these comments, Dr. Bianco.

DR. KUEHNERT: I appreciate Dr. Bianco's comments. I never thought I'd hear the work I was involved with as the early days.

[Laughter.]

DR. KUEHNERT: I'll try to recover from that comment, but-

[Laughter.]

DR. KUEHNERT: I wanted to ask about validation of--have any of these systems ever been validated in any way where either clinical events or laboratory events were looked at the ground level, at the hospital level and then look to see what the sensitivity and specificity of the surveillance systems are?

DR. WISE: I'm only personally familiar

with one effort to independently evaluate one of the systems. For deaths related to transfusions in 1988, we did an independent check against the national mortality data based on death certificates and we cross referenced the individual cases and found a little bit of overlap. I don't remember the details, but most of the cases in one system were not in the other and vice versa.

We interpreted that in terms of the large numbers of Hepatitis B deaths, which would have a long latency period so that the transfusing facility would be unlikely to be aware of the event when it actually occurred.

I'm not familiar with validation for most of these other systems and even that one warrants updating and extension.

DR. KUEHNERT: I just make the point just because we--we don't really know how much of the iceberg we're seeing here, and if we're talking about using the data. I may well be overwhelming once we actually, you know, make the systems more robust. So we just have to consider that in trying

to figure out, you know, where these systems will plug into.

DR. BRECHER: Andy.

DR. HEATON: I'd very like to speak out in favor of the proposed reporting for blood components. And as you look at worldwide blood bank and one of the things that stands out with the U.S. is that there are reporting system for adverse outcomes is very fragmented. And so things that aren't of major event, that are connected either with a licensed product, for example, tend to get underreported. And so I think the approach that you've developed for a, you know, a non-punitive monitoring system for reporting discrepancies for recipients is an enormous step forward. And I think this committee should very much support that. There are other areas like the tissue industry, for example, which are badly in need of that type of information. And I think that blood banking could set the lead by launching such a reporting and surveillance system.

DR. BIANCO: But reporting with good

analysis. I think that New York State is a very good example of reporting of non-fatal events, but the data that is analyzed is discussed and published.

DR. BRECHER: For example, if we look at the data that goes into the FDA. For the last year, this country has largely been doing bacterial detection, which we'll talk about tomorrow. How has that impacted the fatalities from bacterially contaminated platelet? How many deaths were there in the last year compared to, say, the last five years? I think we'd love to hear those numbers. Yeah, Merlyn?

DR. SAYERS: Thanks. Is there any chance--or what is the future for wrapping into this surveillance evidence for when withholding transfusion is unsafe?

DR. WISE: I think you're asking about monitoring somehow the risks of non-useable product for fear of its risks, of its dangers.

DR. SAYERS: Or for whatever reason.

DR. WISE: I don't see FDA immediately

having a way to monitor fixed risk for blood and blood products more for drugs, but it's a risk that we're aware of and that we think about and discuss in the guidance documents that when you're developing a risk management plan for a product, you need to consider not only the direct risks of the product, but also the risks of under use of the product where it really is indicated.

DR. BRECHER: Okay. No other questions or comments? Thank you.

We're now going to move into a public comment period on this topic. And if there are no public comments, we can go even quicker.

All right. Well, let's move on to the committee's thoughts and potential recommendations. The way I see it is we need to finalize our thoughts from this morning on IGIV. The discussions that we've had this afternoon carry over into tomorrow morning, so I think it's premature to frame our thoughts for the emerging infections and transfusion transmitted diseases.

But I think we can finalize the IGIV and

perhaps, Jay, you've had a chance to write down your recommendation?

DR. EPSTEIN: Yes, I penned some thoughts and they were written in for a projection. I don't actually have my original copy at the moment, so.

Thank you.

DR. LIPTON: Could we possibly bold that and put it in 14 point or something? It's going to be hard to--

DR. BIANCO: Dr. Epstein is our official scribe, always.

DR. EPSTEIN: Thank you, Celso. What I have proposed is that whereas, the Committee finds that there is a present crisis in the availability of IGIV products that is affecting patient care--let's wait for that to clear--and that rapid interventions are needed to protect patient life and health--

DR. BRECHER: While they play with that, I ask a humble request. Maybe we could stay away from the word "whereas" this time around.

DR. EPSTEIN: Okay. We, therefore, advise

the Secretary to declare a public health emergency so as--that's not transcribed correctly so as to enable CMS to consider alternative mechanisms for determination of the reimbursement schedule for IGIV products and otherwise to assist CMS in identifying effective short- and long-term solutions to the problem of unavailability of IGIV products in some settings.

So the word enable is missing in the bullet, where you have the cursor.

So as to enable--enable CMS.

DR. BIANCO: So as to

DR. EPSTEIN: So as to enable. Right.

Okay. And then there's some debate whether we should advise the Secretary to declare it or to consider declaring it. That's something we can debate. But that's the gist of the proposal, Mark.

DR. BRECHER: Comments? Questions?

Jerry?

DR. SANDLER: I'd like to suggest that the language that affects patient care is quite muted I think from the threat of life to patients that we

heard today. I mean I think we heard people say people are going to die. And from what I know from clinical medicine, I really do believe that. And I'm wondering since, for reasons that we don't know, we got absolutely no response to previous recommendation. I think as representatives of the people who communicated to us this morning, we have a responsibility to turn the volume up, and as a minimum mention that it affects patient care and threatens the lives of person who's life depends upon this or some similar language.

I think the life and death aspect is missing from the document as it stands. Otherwise, I really commend you, Jay, for capturing everything else perfectly.

DR. EPSTEIN: What if we say critically threatens patient care instead of affects?

DR. SANDLER: I don't think it represents what we were told today. I think people told us that they're afraid they're going to die. And had we gotten a nice letter back saying thank you for sending us a letter. We appreciate the time that

you all put in, then I would feel, you know, we can send another polite letter back. But we were blown off for reasons that may be explainable. But we worked hard. They didn't even say, yes, we got your letter. I think we have to send something that reflects exactly what people told us today: they're afraid they're going to die.

DR. BRECHER: So this is a life threatening problem, currently is a life threatening problem?

DR. SANDLER: Well, life threatening still doesn't say death. I mean people are afraid they're going to die.

MS. PAHUJA: Mike, can we say critically affecting patients' lives. That way you kind of have the critical in there and instead of saying the word death, you have--

DR. BRECHER: Okay. That is affecting patients' lives, comma and that to--so take out patient care and substitute patient lives.

MR. SKINNER: Yeah. I think the concept--I'm struggling with the word availability,

which I think connotes both supply and access, and I don't know if we're saying both, but I mean it's--the thought maybe is there now when we talk about lives, but to me it's access to essential life saving therapies is in severe jeopardy or something to that effect. But I do think that we need to be stronger, and I'm not sure the notion of access is captured as well. I think we've heard that I mean there capacity to produce supply, but it's the access that is to the patients which is the problem in the end that affects their lives.

DR. BRECHER: So is it availability and access, John?

MR. WALSH: Yeah. I think availability and access. I'd keep availability in there because I'm not certain that we're convinced that there's not a supply issue. I mean we don't know. We monitor what's happening with the manufacturers through the PPTA, but we don't have a clue as to what's out there in the distribution channels. And there's--you know, it would be nice to be able to collect that data to find out exactly what the

inventory situation is at any one time, but we don't know.

And I'd just like to make another comment if I may. You know affecting patients lives could me you have another baby. You affect, you know, patients' lives. So I think that's not strong enough.

I think this is life threatening . It is a matter of life and death--access to these therapies.

So maybe we say access to essential life-saving therapies as my esteemed colleague just said.

DR. BRECHER: All right. Why don't we change availability to availability and access first in the number one. And then we'll get to the patient lives. Availability and access.

So that is threatening patients lives or how would you--

DR. BRACEY: Why not just say life threatening.

DR. BRECHER: Potential.

DR. BRACEY: I mean you can say affecting and potentially threatening because the issue is that it doesn't always threaten. It depends on

what disease you have. So I would say it's a potential threat.

DR. BRECHER: Potentially threatening patient lives?

DR. BRACEY: Yeah. Affecting potentially threatening is good.

DR. BRECHER: Affecting or potentially?

DR. BRACEY: Or you can say affecting and--

DR. BRECHER: Microphone. Use the microphone.

DR. BRACEY: Affecting and potentially threatening.

DR. BRECHER: Okay. You know, I think maybe it ought to be a little stronger that is currently putting patients' lives at risk.

DR. BRACEY: Yeah.

DR. BRECHER: So that we would--we could then say that is affecting and placing patients'

lives at risk.

DR. BIANCO: Actually, we could even specify some like immunodeficiency patients. Specify saying patients with immunodeficiencies--

DR. BRECHER: Okay. And we could do that. And patients with--okay. That is affecting and placing patients with immune deficiencies lives at risk.

DR. WONG: How about threatening the survival?

DR. BRECHER: So affecting and placing patients with immunodeficiencies lives at risk.

DR. BRACEY: One of the comments we had over here is that actually if you narrow it, then you ignore the CIDPs, the other categories of patients that--it is an example, but I don't know if we want to restrict it.

DR. BRECHER: Well, we could make it parenthetical e.g., immunodeficiencies.

DR. BRACEY: E.g., deficiencies. Yes.

DR. BRECHER: So placing patients lives at risk, then say parentheses e.g., patients with

immunodeficiencies--small, small letters. Space.
Patients with immunodeficiencies. Or shall we say
patients with gamma globulin deficiencies? Why
don't we just say patients with immunodeficiencies.
Patients--plural--with immunodeficiencies.

DR. WONG: Mark, how about jeopardizing
patients' lives.

DR. BRECHER: I'm sorry. Who's speaking?

DR. WONG: Jeopardizing patients lives.

DR. BRECHER: I think placing patients'
lives at risk is perhaps a little stronger than
jeopardizing myself, but I'm open to other
thoughts.

MS. LIPTON: Mark, could I ask if instead
of rapid could we put immediate interventions are
needed?

DR. BRECHER: Right. And also in number
one below, I'm not sure that we can tell the
Secretary to declare a public health. We can say
to consider declaring. Yeah, to consider
declaring. And then go back up to number two above
where you have rapid interventions and what did you

want to substitute there?

MS. LIPTON: I just wanted to say immediate. I mean just because I think it would--

DR. BRECHER: Oh, immediate rather than the word "rapid?"

Jerry?

DR. SANDLER: In that second line, it would patients' with the apostrophe after the plural lives--to protect the patient life--I would change that to protect patients' lives and health and then capitalize the Secretary--the "S" in Secretary.

Apostrophe would go after the "S" in patients.

DR. BRECHER: We can fix the plural. Apostrophe "S." Yeah. Okay.

DR. BIANCO: And then on the other number one, the second considers--to consider declaring a public health emergency so as to enable CMS to apply alternative mechanisms?

DR. BRECHER: Yeah. That's good. That takes one of the "considers" out. We have

unavailability at the end of number two again. Is it unavailability and access?

MS. LIPTON: It should be unavailability of and access to. I'm sorry.

DR. EPSTEIN: I knew somebody would say it. And we need that same fix in the first paragraph.

MS. LIPTON: Mark.

DR. BRECHER: Yeah, Karen.

MS. LIPTON: As a minor format thing, isn't number two about the immediate interventions something that the committee has also found? So shouldn't it be--I don't remember how it starts, but that the committee has found or something, and then one, two. Just trivial formatting.

DR. EPSTEIN: You're talking about in the first section?

MS. LIPTON: Yeah.

DR. EPSTEIN: Yeah. I agree. The committee finds that colon, one.

MS. LIPTON: Right. Exactly.

DR. EPSTEIN: I agree.

DR. BRECHER: Okay.

MS. LIPTON: Right. The committee finds that colon, one, there is et cetera, et cetera.

DR. BRECHER: Take the one out. That's it. Take the period out. Take the space out. Hit delete one more time. Delete. The committee finds colon--the committee finds that colon. Colon. Hit return. Make that number one. Capitalize there.

DR. LINDEN: We need to lose one of the "that's" in my opinion.

DR. EPSTEIN: At the end of--

DR. LINDEN: Yeah. Make it the end of number one.

DR. EPSTEIN: At the end of sub bullet one, take the word that out.

DR. LINDEN: Right.

DR. BRECHER: Leave the "that" there and go down. That's it. Get rid of that "that."

DR. EPSTEIN: For parallel structure, should we make in this item one availability of and access to?

DR. BRECHER: Yes. Availability of--and

the availability of--no, not after access, but after availability. Go back. Yeah. That's it. Of. Of. Jerry?

DR. SANDLER: Do we want to make reference to our prior recommendation by saying the committee finds that one, since our recommendation of date, there has been a deepening crisis in the availability.

DR. BRECHER: Is that the committee's pleasure?

MR. WALSH: Yeah. I think it's good. I think we need to put some teeth in it. I mean if he's not going to answer us, let's do a capital bold underline and hand deliver it.

DR. BRECHER: Well, maybe we should say the committee once again finds that.

[Laughter.]

DR. HAAS: Or consistent with the recommendation. You know.

DR. SAYERS: Would anybody be interested in having persistent crisis instead of present crisis?

DR. BRECHER: Yes. That would make a persistent change.

DR. SANDLER: We could say a worsening

crisis.

DR. HAAS: Worsening I think is more of the spirit.

DR. BRECHER: Okay worsening crisis. So get rid of the word "present" in number one and make it "worsening." There is a worsening crisis. Now does that? That doesn't really get to the fact that we've been here before.

DR. SANDLER: Why don't we just say "since our prior recommendation?" And put a date in.

DR. BRECHER: Okay. So number one would be "since our prior recommendation, there is a worsening crisis."

Oh. Okay. Go "since our prior recommendations of January 2005--of January." Yes. "Of January 2005," comma, space, with a small "T" for there.

DR. BIANCO: While she's sure talking about recommendations. In the "we, therefore,

advise the Secretary." We should recommend.

DR. BRECHER: Okay. We can do that. "We, therefore, recommend that the Secretary."

DR. BIANCO: It's stronger than "advise."

DR. BRECHER: To the Secretary. T-O.

DR. SANDLER: I'm not keen on having urge instead of recommend.

DR. BRECHER: Sorry.

DR. SANDLER: Isn't it time for an "urge." We, therefore, urge the Secretary.

DR. BIANCO: Yeah. That's--

DR. SANDLER: We didn't get anywhere with--let's have an urge.

DR. BRECHER: Is that like an itch? You're having an urge?

DR. BRACEY: Under the last number two, it's sort of weakens it to a degree because it suggests that there's not access--that the access is limited to a given setting, but what we actually heard is that there's an overlap so that patients actually can't even get it on an in-patient basis. So if you in essence just strike "in some

settings," it seems to strengthen it, because the reality is that they can't even get it in the hospital if they want it.

DR. BRECHER: Well, rather than saying in some settings, in certain settings?

DR. BRACEY: No. I'm just saying--access to IGIV products. Period.

DR. BRECHER: Well, I think that gives the Secretary a lead in to that there's a distinction between settings. But this is a little flag that they need to pay attention to that there's differences among different settings.

DR. BRACEY: Yeah. And I guess the only thing I was thinking of is if it is mind, he says, well, if they just go from the outpatient to the inpatient, then it's a non-issue. Why issue an emergent?

DR. BRECHER: Jay?

DR. EPSTEIN: What if it said in all settings instead of in some settings?

DR. BRECHER: Yes.

DR. BRACEY: Yeah. In all.

DR. BRECHER: That would do it. That's good. All right. Are we happy? Someone want to make a motion?

DR. BIANCO: Yes. We're happy.

DR. BRECHER: Celso, do you want to make motion? No?

DR. BIANCO: I'm happy.

DR. BRECHER: You're happy. Celso is happy. Everyone else happy?

Jerry?

DR. SANDLER: I don't know the sense of the committee, but I had the sense that some people were communicating to us that they felt the crisis was precipitated by a reimbursement policy; that, in other words, things were going along, stably. There was a change in the reimbursement policy, and, as a consequence of a change in the reimbursement policy, people's lives were put in risk. If other people sense that, it's not communicated in our recommendation that this is all happening since the change in the reimbursement policy.

MR. SKINNER: Mark? My thought was similar to what Jerry just said. The--we don't say anything in our findings about what's happening in terms of pricing or reimbursement. And I thought we heard earlier that at least a couple of the criteria for declaring a public health emergency

was the disconnect between the average sale price and the market price, which I think also relates to the reimbursement rate and the changes. And I didn't know if we needed to be a little more clear and lay out the one, two, threes, so that it's self-evident that the compelling case for a public health emergency in fact exists and in that vein, I'm not sure why we want to urge them to consider. I've just--perhaps we want to urge them to declare. I mean urging them to consider is kind of wishy washy. I mean if we really want to urge, I don't really want to urge him just to think about it.

DR. SANDLER: I agree. I support that. I think--no, I agree.

MR. SKINNER: I agree.

DR. BRECHER: To make it declare. We

still haven't addressed the sort of disconnect between the price and the reimbursement. Is that point three? That there's currently a disconnect between current--there's currently a disconnect between reimbursement and actual cost to products? Cost to products and service? Number three, at the top. At the top. Three.

DR. SANDLER: It's probably in number two and then the immediate interventions are needed would be the three.

DR. BRECHER: Yes. That's correct. Let's type it out first and then we'll move it up. There is currently a--well, that works, too. No. Make it this number two and bring the immediate down. It will be number three. Right. That's now number three. Now go up to number two. There currently exists a disconnect between reimbursement and product costs--product and administrative costs. Reimbursement and product costs and administration. Jay?

DR. EPSTEIN: Would it be helpful to start that point by noting the changes in reimbursement

of IGIV products under MMA since January 2005 have resulted in a disconnect.

DR. BRECHER: Yes.

DR. SANDLER: That's it.

DR. BRECHER: That's certainly better. So that's good.

DR. EPSTEIN: So it would say changes in reimbursement. Of reimbursement. Singular. Oh, that's okay. Of IGIV products or for IGIV products. Under MMA, and, Jim, maybe you can tell us the correct wording. Medicare.

DR. BOWMAN: It's the Department of HHS has an approved abbreviation.

DR. EPSTEIN: As an approved abbreviation. Okay. Under MMA since January 2005 have resulted in disconnects. Make that plural. Disconnects between reimbursement and product costs. Okay, product and administration costs. It's product and administration costs.

DR. SANDLER: How about reimbursement for product and administration costs?

DR. LINDEN: No, because it's where the

disconnects are between. It's got to be between two things.

DR. BIANCO: You know, even if it doesn't sound like good English, I would put a comma after reimbursement to show that that's where the disconnect is or something like that.

DR. LINDEN: Well, or say in the cost of the product and its administration. The disconnects are between the reimbursement.

DR. BIANCO: That's good, Jeanne. And the costs of products--yeah.

DR. LINDEN: Yeah. And their.

DR. SAYERS: Anybody interested in shortfall instead of disconnects? Okay. That killed that conversation.

DR. EPSTEIN: No. I think that's a good point.

DR. BIANCO: Shortfall is good because it shows the direction. Yeah.

DR. LINDEN: Or you even want to say--

DR. EPSTEIN: And then it should be a shortfall--

DR. LINDEN: I'm sorry. I was just--I mean what we're saying is the cost of reimbursement is less than the actual cost. Right? Or you could

turn it the other way around.

DR. EPSTEIN: You could say a shortfall of reimbursement compared with.

DR. BRECHER: Well, you could just say have resulted in insufficient reimbursement for the cost of the product and the administration costs. But is that better? Insufficient or shortfall?

DR. LINDEN: I think insufficient could be interpreted as meaning what people aren't able to make enough of a profit off it, and I think we're saying they're actually not getting their costs met. Right? I mean I think we can be stronger.

DR. BRECHER: So you prefer shortfall. So have resulted in shortfalls rather than disconnects.

DR. EPSTEIN: Or it could also be under-reimbursements of the costs.

DR. BRECHER: Well, except we're using reimbursement a lot in that sentence. We're--that

would be the third time reimbursement is used in that sentence. Resulted in shortfalls. No. Have resulted in shortfalls. Is shortfalls one word? Yeah. So get rid of the space between the two words. Make shortfalls one word. Yeah. Reimbursement of IGIV products and their administration costs. Of IGIV products and their administration. Yeah. Take the "of" out. And get costs out at the end. Delete the "costs" at the end of the sentence there. Period. Mm hmm. All right. Anyone want to make a motion for this? Jerry?

DR. SANDLER: I motion that we pass the text projected on the screen, send it to the Secretary of Health.

DR. BRECHER: Okay. Let's read it into the record. I think there is--well, I know there is an extra comma after January up there. So we can--this is January 2005.

"The committee finds that:

One, since our prior recommendations of January 2005, there is a worsening crisis in the

availability of and access to IGIV products that is affecting and placing patients' lives at risk, e.g., patients with immunodeficiency;

Two, the changes in reimbursements of IGIV products under MMA since January 2005 have resulted in shortfalls in the reimbursement of IGIV products and their administration; and

Three, immediate interventions are needed to protect patients' lives and health.

We, therefore, urge the Secretary:

One, to declare a public health emergency so as to enable CMS to apply alternate mechanisms for determination of the reimbursement schedule for IGIV products; and

Two, otherwise to assist CMS in identifying effective short- and long-term solutions to the problem of unavailability of and access to IGIV products in all settings."

So all in favor of this, everyone who's happy with this--voting members, raise their hands.

We have 12 in favor. Any opposed? Any abstentions? Okay. This is unanimous. Oh.

Thirteen? Thirteen in favor. Jerry?

DR. SANDLER: I wonder if the committee would consider signing this individually to make a point. The last time we communicated this to the Secretary, with a cover letter I assume that was probably signed by Dr. Holmberg, I--or it was signed by you--I'm wondering if the committee thinks individual signing this since if I've got it right everyone will be here tomorrow. We could all sign this.

DR. BRECHER: What's the committee's pleasure? Does everyone want their name, their signature on this?

Alternatively, if everyone could forward an electronic signature, we can just insert them at the bottom of the document when we get it all together, because there will be other recommendations that we're making tomorrow and that--it won't be finished tomorrow.

DR. SANDLER: Now, the sense I'm trying to communicate is he's paying a ton of money to have us come and have us meet. We send up a

recommendation. It hasn't even been acknowledged. I don't know how the other members of the committee feel, but I feel that there must be another way of communicating that would perhaps get his attention.

DR. BIANCO: Jerry, it's--the Secretary is new in the job. Let's give him a little bit of time.

DR. SANDLER: I would if it weren't for what I heard this morning. I'd give him time--

DR. BIANCO: I think--

DR. SANDLER: Except the people who spoke today are losing IGIV level as we speak. And the first one who gets a staph pneumonia, is on, you know, is something that is on our heads.

DR. BIANCO: I was as touched as you were, and I think that we can commit him to that. We can at least throw our names in the letter. We don't have to create a bureaucratic nightmare.

DR. BRECHER: All right. We have a half an hour left. What I would just like to suggest is that we just toss around a few thoughts about what we heard about surveillance today and where we

might be heading tomorrow with a recommendation.
So I'm open to comments and suggestions.

DR. ROSEFF: I have a question. Does anyone know the status of MERS TM and if it's effectively doing what it's set out to do and how many participants there are. I haven't--not that aware of it.

DR. SANDLER: Sounds like a question for you, Jay.

DR. EPSTEIN: Well, I think it's more a question right now for the blood organizations. We did a pilot study at FDA, and I think this goes back two or three years to see if we could simply directly import MERS TM into the FDA reporting system under AERS/MedWatch. But the conclusion was that we could not. There were many issues, some of which were database and compatibility, but some of which cycled around the difference between a mandatory and a voluntary report, and how much of the information in MERS TM would--you know, could be disclosed in the FDA system and so forth.

So I think, you know, I'm not in a

position to comment on current use other than to say that we remain interested in ways to import it into our system, but that we're not currently using it in our system.

DR. BRECHER: Karen.

MS. LIPTON: Yeah. I actually was talking a little bit about this with Matt, and I served on an advisory committee to AHRQ that was under a contract to try to rationalize all the reporting systems. And there was quite a lot of work done among these organizations, just in terms of what data we're trying to--you know, we were trying to collect. I think one of the things you have to decide up front is what's the use of the data, because in many ways you can't use the same vehicle for everything. But there is quite a bit of progress made on that, and one of the models was MERS TM, and what I would like to see if we're going to make a recommendation is that we somehow get a hold of that information and some of the work that they had done, because there was quite an in-depth analysis of this and with a lot of people

from a lot of different organizations talking about it and I think they have some good data. It would be nice to have us have access to that information before we make any specific recommendation.

When you really get into the detail of trying to construct or make recommendations about reporting, it is a lot trickier than you'd think, and I don't think we want to misstep or send the wrong message, because I think we should be careful what we're going to ask for.

DR. BRECHER: Merlyn?

DR. SAYERS: We've been involved with MERS TM for a number of years, and our enthusiasm is certainly nowhere near as boisterous as it was before, largely because we're not getting any software support. Software support.

DR. BRECHER: Software support. Yeah.

DR. SAYERS: So that renders the whole system relatively inefficient.

DR. BRECHER: Jeanne?

DR. LINDEN: Yeah. I'd also just like to point out the difference between a system that you

might use internally in your institution to look at your particular factors versus a national aggregate data effort, because you're really looking for two different things, and I don't think you can take the former and say we're just going to adopt it via the latter. I mean you can take pieces of it, but I mean MERS TM really falls in the first category, and I think we're looking for the second category, more like some of the other things we heard about today.

DR. BRECHER: Well, we certainly have a fragmented system of surveillance. It's--we'll hear some more about that tomorrow. Matt?

DR. KUEHNERT: Yeah. I think, you know, rather than--I think before we get to specifics, maybe we need to just all be agreed that such a comprehensive system is needed and what those uses would be, because I mean it's pretty clear the details are going to be very difficult. So the first question is, you know, what is the need for such a system? What's the purpose? What's the objectives? And then we can get to, you know, how

to build it. But it just seems like starting from that point would be the way to begin the discussion.

DR. BRECHER: Well, I guess the other related question is those countries that have a uniform system, are they doing better than we are with our fragmented system? Jay?

DR. EPSTEIN: Well, on that very point, I think we need to remember that hemo vigilant systems such as exist in certain other countries measure the known and we kind of have two different issues going on simultaneously, one of which is trending things, tracking and trending the things we know, and the other is detecting and responding to things that are new. And we shouldn't get confused about them being the same, because they're really not.

DR. BRECHER: Good point. Excellent point. Jeanne?

DR. LINDEN: Yeah. One other--I agree completely with Jay's point that yeah, we're talking about detecting new things, you know, not

just what we know, but also Karen and I were just discussing there's a difference between surveillance of adverse events like infections, there's nothing we can do about that--they're there--versus error reporting systems. And certainly there are some, you know, hemo vigilant systems that do both, but, you know, again not to harp on MERS TM, but I mean that was really oriented towards errors that in the system that we can change versus how can we identify these infectious diseases. But I agree with Jay. The reporting systems only detect things that we know about, not things that are new.

DR. BRECHER: Now, this committee has visited the whole question of errors in the past, although it's been some time. And then there is new technology that's coming to market, such as the radio frequency devices. So maybe that's something that we could rehit in a future meeting.

DR. BRACEY: I think one of the issues in terms of reporting errors at the level of the hospital is that the hospital listens to a

different voice. It really doesn't listen that much to the FDA with the exception of those elements that are mandatory. The hospital listens to JCAHO. If you are going to get hospitals to participate, you have to get to the executive level of the hospital organization, not at the blood bank level, because what happens is at the blood bank level views errors and accidents as potential litigation issues and what they're always told is to not discuss those, to not give out information. So there's a tremendous amount of underreporting because it's not required, and generally people in hospitals are told not to discuss that sort of information.

DR. BRECHER: Although I guess what we heard today is that FDA is rethinking that.

DR. BRACEY: I have another question on another subject and that is some time ago, I understood that there was the notion or the development of a concept of a strategic blood reserve, which could potentially be useful potentially in certain catastrophic situations. Is

there such an entity that's been furthered.

DR. BRECHER: Karen, it's all yours.

MS. LIPTON: Well, the answer is we developed it and thought about it. I think that at this point, I think the issue is a funding issue and I think we have taken it as far as we can. I think that every organization has its potential or knows how far it can push to cover issues in an emergency. I think AVC has a very nice system they've developed. I think Red Cross does, too. I think that there are limits to that, but I don't think that the blood community intends to go further at this point because it just doesn't appear to be high on the radar screen in terms of the things that are going to be done in the public sector, and that's fine. But I didn't want people to think we were pursuing it any further at this point.

DR. BRECHER: Jay.

DR. EPSTEIN: Well, Karen, correct me if I'm wrong, but the committee recommended trying to move toward the seven-day inventory as a

fundamental strategy of preparedness for potential disasters and to avoid shortages.

And is that now or is that not now an adopted strategy or at least goal of the blood organizations?

MS. LIPTON: I think the problem, Jay, is that in all of these initiatives we said what we would need is some effective funding at the HHS level for donor motivation, mobilization, and that hasn't been forthcoming. So we have again private initiatives with the Ad Council, and we're working on some things, but if we're really talking about getting to a seven-day inventory, I would say it's a goal.

DR. BIANCO: It's a fantasy. I--there are resources that we have applied so far.

DR. BRECHER: We prefer virtual reality.

DR. BIANCO: Yeah. But we'll get there if we put the resources, and people have made a tremendous effort, and actually the supply in recent times has been better than we all expected.

But I want to go back to the reporting.

I'd like us not to talk about reporting as an isolated event. I think we have to talk about reporting, analysis, policy making, best practices. It's all together. If we just report a lot of data, it falls into some computer somewhere, and we never know what is happening. I think Mark asked a very important question. We put a tremendous effort on bacterial contamination in the last year, year and half, and a lot of dollars. Did it work? And so--

DR. BRECHER: Other comments or questions?

Paul.

DR. HAAS: Probably just the obvious and that is all the more we talk about all this data, I betcha' all of those of you who would be collecting and using the data are always asking where the resources to do this, and now we're inside of a particular eight-government agency that doesn't necessarily have that money, but we have to figure out some way to make the case that if we're really serious about blood safety and availability, more resources need to be directed in this way.

DR. BRECHER: Well, that sounds like a recommendation for tomorrow, at least it's shaping up as a recommendation.

Other comments or questions? Jerry, did you want to say anything? Hmm? Are you guys ready to call it quits for the day? Jerry.

DR. HOLMBERG: I just want to encourage you to go back and read the e-mail that I sent you before the meeting, and the idea of the bio vigilance, and, you know, just what Jerry was mentioning earlier about most other countries are looking at what is known and I think that what we're looking at is what is known but what also is unknown and how do we make sure that we look at that, and the question that I had sent to you is a bio vigilance program of added value to the U.S. blood--U.S. health care system and reducing the risk of emerging infectious diseases. And so I would encourage you to think about that tonight as you try to go to sleep.

DR. BRECHER: All right. With that, I'll say today's meeting is adjourned, and I will see

you all bright and early tomorrow at 6:00 a.m.

8:00 a.m.

[Whereupon, at 5:12 p.m., the Advisory
Committee recessed, to reconvene at 8:00 a.m. the
following day.]

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