TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

62ND MEETING

DAY 2

This transcript has not been edited or corrected, but appears as received from the commercial transcribing service. Accordingly the Food and Drug Administration makes no representation as to its accuracy.

Pages 1 thru 170

Bethesda, Maryland
March 26, 1999

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

62ND MEETING

Day 2

Friday, March 26, 1999

8:05 a.m.

Bethesda Ramada Inn
8400 Wisconsin Avenue
Bethesda, Maryland

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

PARTICIPANTS

Blaine E. Hollinger, M.D., Chairperson
Linda Smallwood, Ph.D., Executive Secretary

MEMBERS

John M. Boyle, Ph.D.
Corey S. Dubin
Norig Ellison, M.D.
Rima F. Khabbaz, M.D.
Marion A. Koerper, M.D.
Jeanne V. Linden, M.D.
Gail B. Macik, M.D.
Mark A. Mitchell, MD.
Kenrad E. Nelson, M.D.
David F. Stroncek, M.D.
Joel I. Verter, Ph.D.

NON-VOTING INDUSTRY REPRESENTATIVE

Donald H. Buchholz, M.D.

TEMPORARY VOTING MEMBERS

Paul R. McCurdy, M.D.

CONSULTANT

Michael G. Fitzpatrick, Ph.D.

C O N T E N T S

P R O C E E D I N G S

Introductory Remarks

DR. SMALLWOOD: Welcome to the second day of the meeting of the Blood Products Advisory Committee.

I am Linda Smallwood, the Executive Secretary. Yesterday, I read the conflict of interest statement that applies to this meeting. It also applies to today's session, as well.

If there are any declarations that anyone needs to make, committee members or participants, regarding their status with this meeting, please do so at this time.

If not, then, we will follow the agenda as printed. Dr. Blaine Hollinger, the Chairperson, will preside over this meeting.

Thank you.

DR. HOLLINGER: Thank you, Linda.

We are going to start off today first with a committee update on the Summary of the FDA/CDC-sponsored Tick-borne Diseases Workshop, and Dr. Tabor will give us that update.

Committee Update

Summary of FDA/CDC-sponsored Tick-borne Diseases Workshop

DR. TABOR: Good morning. I am Dr. Edward Tabor from the Office of Blood Research and Review.

A workshop on the potential for transfusion transmission of tick-borne agents was co-sponsored by the Centers for Disease Control and Prevention, the Food and Drug Administration, the National Heart, Lung, and Blood Institute, and the Department of Defense in Decatur, Georgia, on January 14th and 15th, 1999.

The purpose of the workshop was to review the known and potential risks to the blood supply from tick-borne agents and to determine whether additional donor questions or policies regarding at-risk donors could be put in place to prevent blood donations containing such agents.

At the present time, there are no specific donor questions recommended by the Food and Drug Administration for the purpose of identifying and excluding potential donors who are at risk for having tick-borne infections.

Nevertheless, there is one specific question used by most blood centers that ask if the prospective donor has ever had babesiosis, and the American Association of Blood Banks recommends that donors with a history of this disease be indefinitely deferred.

Also, although there is no specific question for Borrelia burgdorferi, the agent that causes Lyme disease, the AABB recommends that donors with a history of Lyme disease have completed a full course of antibiotic therapy before being allowed to donate.

In addition, several nonspecific questions asked if the donor is feeling well, has lost weight, has been under a doctor's care in the past 12 months, or has taken aspirin in the past three days. Furthermore, each donor's temperature is taken at the time of donation.

The problem of regulating to prevent potential donors with tick-borne infections from donating is compounded by the existence of several different tick-borne infections that could present a risk in the same donor population.

These include ehrlichiosis, babesiosis, Rocky Mountain spotted fever, and Lyme disease. An infected individual could be infected with more than one of these agents. Any policy ideally should apply to the prevention of all four, however, even though the infections could occur simultaneously, it is also true that the incubation periods and geographic distributions vary.

The problem of potential transmission of tick-borne agents by blood products became apparent during the Public Health Service response to the threat of possible transmission of ehrlichiosis by blood donations collected at Fort Chaffee, Arkansas, in 1997.

In June of that year, National Guardsmen who had donated blood in three blood drives that were conducted among new arrivals over a four-week period at Fort Chaffee,

were recognized to have had symptoms of a tick-borne infection upon their return to a nonendemic area.

A decision was made after consultations among the FDA, the Centers for Disease Control and Prevention, and the Department of Defense, to recall all blood and blood components collected at Fort Chaffee since the onset of that tick season in April, in other words, blood products from blood drives collected during May and June.

Physicians of recipients of the products that had already been transfused were notified of the relevant symptoms and appropriate treatment. Guardsmen attending the later training sessions that summer were advised not to donate blood for four weeks after departure from the base.

Upon later investigation, nine probable cases of Rocky Mountain spotted fever, four confirmed cases of Ehrlichia chaffiensis, and one possible case of dual infection were established among 377 donors at the base. Nevertheless, no cases of transfusion transmission were identified among 10 recipients of units from infected donors.

In the following summer at Fort Chaffee, 1998, a Public Health Service interim recommendation was made to allow new arrivals to donate blood if they had arrived less than 48 hours before and to advise Guardsmen to refrain from donating for four weeks after departure.

However, the Department of Defense decided to discontinue collections at Ft. Chaffee all together in 1998.

The difficult questions that arose in connection with this outbreak stimulated the CDC, FDA, NHLBI, and DoD to organize a workshop on the subject. The following is a summary of the data regarding the possible risk of these infectious agents for transfusions, and the conclusions of the workshop.

The discussion focused on the four tick-borne agents that appeared to present a possible threat to transfusions in the United States. The first of these agents that I will discuss is Rickettsia rickettsii. Rickettsia rickettsii, the agent of Rocky Mountain spotted fever, has only been reported to be transmitted by blood transfusion once, a case that occurred in 1977.

The transfusion consisted of whole blood that had been donated during the incubation period of a documented case of Rocky Mountain spotted fever. The donation occurred three days before the onset of symptoms in the donor. The incubation period in the recipient was six days after transfusion.

Although Rickettsia rickettsii can be transmitted by transfusion and the organism can survive in refrigerated blood, both of these factors demonstrated by this case, the brief period during which the agent is in the blood prior to

symptoms, up to three days, the full incubation period is usually less than seven days, probably explains the rarity of reported transfusion transmitted cases.

The fact that fever probably begins at the same time that the agent first becomes present in blood, as seen in experimental infections in nonhuman primates, would prevent most infected persons from being accepted as blood donors. Furthermore, persistent cases of Rocky Mountain spotted fever are rare and even when they have occurred, the persistence of the agent in the blood has not been documented although it has been found in other tissues.

In fact, it can be isolated from the blood of infected persons only from two to nine days after the onset of symptoms.

The second agent discussed was Ehrlichia species. Although Ehrlichia species could theoretically be transmitted by transfusion, this has never been documented, not even in three recipients of infected blood donated at Fort Chaffee who were followed with clinical and serological observations.

Nevertheless, transmission by transfusion is theoretically possible. Ehrlichia can be cultured from spiked blood even after storage at 4 degrees centigrade for at least 27 days, however, because 91 percent of culture positive individuals have fever, they would not be accepted

as blood donors.

In one controlled study in Connecticut, antibodies to Ehrlichia, indicating past infection, were detected in similar numbers of blood donors with and without histories of tick bites in the preceding six months, about 3 percent in each group. This indicated that asking about recent tick bites would not be a useful screening question.

The third agent discussed was Babesia species. Babesia microti has been documented to have been transmitted by red blood cells or platelets, perhaps due to residual red cells in the platelet concentrates in more than 20 cases. In addition, one case has been documented that was caused by a newly described related species known as WA-1. Most cases occurred in splenectomized patients and more than half were fatal.

The difficulty in screening donors for Babesia infections is greater due to the fact that most infections are asymptomatic and parasitemia can persist for greater than three months. In a study of the donor who transmitted the WA-1 strain, parasitemia was documented for at least seven months and probably for as long as 13 months.

In a study of spiked blood stored at 4 degrees centigrade, Babesia survived for at least 21 days. Two of the reported transfusion transmitted cases, in fact, involved red blood cells that had been stored for greater

than 21 days and one case involved a unit of frozen red blood cells.

In the months since the time of the workshop, an article appeared in the Journal of the American Medical Association documenting Babesia microti infections in three recipients of portions of a unit of red blood cells from a single donation by an infected donor. Two of the three infected recipients remained asymptomatic during their infections.

The incubation periods from the time of transfusion to a positive PCR or positive hamster inoculation assay ranged from 12 to 28 days. Three other recipients of portions of the same unit or its platelets were not infected.

The fourth agent discussed was Borrelia burgdorferi, the cause of Lyme disease. This agent could theoretically be transmitted by transfusion, but there are very few studies available. In general, no transmission by transfusion was demonstrated. In studies of small numbers of donors at high risk for infection, these were persons with detectable antibodies or who resided in an endemic area, but for whom there were no studies to document parasitemia.

Ninety-seven percent of persons with positive blood cultures for borrelia burgdorferi have symptoms, in

most cases either fever or the characteristic rash of erythema migrans. The 33 percent with fever would be rejected as blood donors. There is, however, a theoretical risk.

The organism can be found in the blood of infected patients or in acute Lyme disease, Borrelia burgdorferi can survive under experimental conditions for at least 25 days in whole blood at 4 degrees centigrade, and the agent can be transmitted to experimental animals by I.V. inoculation.

Thus, further epidemiologic studies in human transfusion recipients are needed before the transfusion risk can be ascertained.

The meeting ended with a panel discussion, and the panel discussion drew four conclusions.

The first was, of the four main tick-borne agents that present a possible risk to the blood supply, the Babesia species is the one that has by far the greatest importance based on current epidemiologic evidence, and it may pose an even greater risk than presently recognized.

The second conclusion was no improvements in donor screening questions could be suggested, because so many of the tick-borne agents cause asymptomatic infections and so many are acquired in unremarkable locations near homes.

The third conclusion was that research is needed to develop tests for screening. Currently available tests

for these agents are too expensive for use in screening and/or detect antibodies that are so prevalent that too many uninfected donors would be excluded if the tests were to be used for screening.

The fourth conclusion was that experimental methods to inactivate infectious agents in cellular components of blood may be a fruitful area for research to try to prevent transfusion transmission of tick-borne agents.

Thank you.

DR. HOLLINGER: Thank you, Dr. Tabor.

That concludes the committee update. Any questions of Dr. Tabor in regard to the workshop?

[No response.]

DR. HOLLINGER: We are going to then have our beginning open session today. The first one is on Clinical Trial Endpoints for Immune Globulin Intravenous (IGIV). I am asking the presenters to stick to around 10 to 12 minutes for each one to talk.

We will start out with Introduction and Background by Dr. Golding.

IV. Clinical Trial Endpoints for Immune Globulin Intravenous (IGIV) - Informational

Introduction and Background

DR. GOLDING: I am the Director of Plasma

Derivatives in the Division of Hematology at CBER in the Office of Blood. I am combining my two talks into one talk.

[Slide.]

I am going to be talking about immune globulins intravenous, manufacturing issues and clinical trial issues. The people that have helped me over the years to learn about these manufacturing issues are John Finlayson, John Tankersly, and Mei-ying Yu, and the people that have been involved with the clinical trial issues are Tony Lachenbruch and Peter Bianchini.

[Slide.]

Just as a background, just to remind you, we still have an IGIV shortage. I am not going to go through all the different FDA actions regarding this shortage, but I would like to mention that during this process, we have been holding a dialogue with industry to try and get new IGIV products to market.

We have been involved with them in pre-IND studies, discussing ways of using IGIV that are used in other parts of the world, and part of the dialogue has included the Immune Deficiency Foundation. This has been a very important part of the dialogue because the IDF has a panel of experts who have been very helpful in discussing these issues.

What I will be talking about today, a large part

of it was presented at the IDF workshop on March the 5th of this year.

[Slide.]

The first thing I am going to be talking about is manufacturing and to try to give you a basis why, at the FDA, we think each product should be regarded as unique and why immune globulin should not be treated as single generic biologics.

[Slide.]

In terms of plasma fractionation and the manufacture of these products, there are a large number of variations, and if we start out at donor selection, you can use either source plasma or recovered plasma, and this makes a big difference because biomarkers and higher in the source plasma donors.

If you look at the number of donors for each product, these are different, and this can impact on viral safety, on the efficacy of the immune globulins, and the number of dimers is proportional to the number of donors. I will tell you a little bit later about how we think dimers may be important.

Also, the demographics are important, so infections in a certain area may not necessarily be common in another area, and this also relates to viral safety and efficacy.

As you all know, plasma is a very complex protein solution consisting of hundreds, maybe thousands of different proteins, and we know that low concentrations of some of these proteins in the final product may have far-reaching effects. I cite two examples here of plasminogen and prekallikrein activator. It has been shown that very small changes in pH during one of the steps of fractionation can result in plasminogen ending up in higher concentrations in the product, and plasminogen can have a devastating effect on the stability and efficacy of the immune globulins.

Prekallikrein activator can be activated to a cascade of producing vasoactive substances which can have effects ranging from hypertension to shock. So, having a very small concentration of these contaminants in the product can make a difference to the safety and efficacy profiles.

[Slide.]

Now, the manufacturing methods themselves, the standard method is the Cohn-Oncley method. Most manufacturers use a five-step method, but there are different parameters at each step, the pH, the temperature, ionic strength, alcohol, and protein concentration.

If you compare flow charts from different manufacturers using the Cohn-Oncley, you will not find any

two flow charts that are identical, so there are many differences between the way manufacturers use this manufacturing process. In addition, manufacturers have added chromatographic steps, particularly ion exchange, and have added in recent years viral clearance steps, so in addition to the viral clearance that you get through the Cohn-Oncley, there are deliberate steps, such as solvent detergent, heating, nanofiltration, and others, and these steps also may impact the safety and efficacy profiles of the product.

[Slide.]

Excipients. Different manufacturers use different excipients in their products. Some use albumin. There was an example where the albumin was added after the bulk IGIV was manufactured, and then this was subjected to a chemical treatment which led to changes in the albumin, which were found to induce allergic reactions.

It has been recently appreciated by us that some of these products which have high sucrose content are associated with an increased incidence of renal failure. So, depending on the excipients, again, you can influence the safety profiles of these products.

The dimer content, this has been studied by Don Tankersly, and he has shown that the increase in dimers is proportional to the number of donors. We don't know for

sure, but these dimers may be associated with activation of complement, and they may even have a beneficial property in that they may protect against autoimmune disease.

In terms of class and subclass, we know that there are some individuals who are selective IgA deficients and also have immune deficiency for other immune globulins. If those patients receive products that have some IgA, they may develop anaphylaxis. This is rare, but a very serious side effect of these products.

Some manufacturers remove IgA by a chromatographic step, but when you remove the IgA, you end up also removing the IgG-4, which is a subclass which may play a role in some infectious diseases.

[Slide.]

So, what I have been telling you is that the manufacturing is a multi-step process. It is different from one manufacturer to the other, and, in fact, to me the most striking example is that if one manufacturer tried to change its manufacturing by just moving from one plant to another plant, they were using the exact same process as far as they could tell, but they were unable for many months at the new plant to manufacture the product in the same way as that manufacturer before.

This just gives you an idea how complex this process is, and that is very difficult to replicate.

[Slide.]

As I have indicated, variations in the process can have far-reaching effects on both safety and efficacy. So, our conclusion is that each product should be regarded as unique, and immune globulins should not be treated as a single generic biologic. In fact, there are no biologics that are considered generic.

[Slide.]

I am just going to go over the proposed trial. This was put together mainly by Tony Lachenbruch. This is an example of a trial. It takes into account what we know about the limited number of patients that are available for such a trial.

What we are talking about are patients with primary immune deficiency who, in the most part, are receiving immune globulin products, so the trial would be comparing a new product to a product that is already approved.

It would be a controlled, randomized, non-inferiority study, and we would be looking at safety, pharmacokinetics, and efficacy data.

[Slide.]

To establish safety, again, we would be using non-inferiority compared to an approved IGIV. There are two types of side effects here. There is a panel of side

effects that are referred to as common, which are mild or moderate, and there are more rare side effects, for example, the anaphylaxis to IgA.

The sample size should be sufficient to determine that common ADRs are not more frequent than those in the approved IGIV.

[Slide.]

For PK studies, the principles would be that you have to have a washout period, so these patients are already on a IGIV product. The half-life can vary from 30 to 40 days in these patients. You would need several half-lifes before you could perform the study, and these are the parameters that are important - the maximum concentration attained, the time to reach that maximum concentration, the area under the curve, the half-life, and trough levels are the lowest levels just prior to the next infusion, and this is used by practicing physicians to determine how frequently to give the product.

Again, for the assessment of the PK data, this would be a non-inferiority study, and the difference would not be greater than 0.2 compared to the control IGIV. In other words, the new product should not have a profile which is more than 20 percent than the approved product.

[Slide.]

In terms of efficacy, efficacy again would be

established on the basis of non-inferiority compared to approved IGIV. The primary endpoints would be a clinical outcome related to infections. The secondary endpoints would be IgG levels, hospitalizations, and there are many others.

[Slide.]

Sample size should be sufficient to determine whether the new immune globulin is not less effective than the approved immune globulin product.

This is the sample that Tony put together using a one-sided test assuming 80 percent power and 95 percent confidence level. If you looked at the number of infections, assuming that one infection per patient would occur in the control group, you would have no more than two infections per patient in the experimental group, and this would give a sample size of 28 patients in the control group, 28 patients in the experimental group.

On the other hand, if you looked at the proportion of patients with infections, assuming that the difference is not more than 20 percent and that the difference is from 0.25 to 0.45, in other words, the proportion of infected patients increases from 25 percent to 45 percent, the sample size would be that the control group would have 80 patients, and the experimental group would have 80 patients.

[Slide.]

In conclusion, safety and PK studies are essential. In the efficacy trial, we would ask for a primary endpoint with a clinical outcome, surrogate endpoint such as immunoglobulin trough levels, and others should be secondary endpoints, and may be validated during coming trials.

The numbers required for non-inferiority trials should be feasible based on the example that I provided to you.

Thank you for your attention.

DR. HOLLINGER: Are there any questions for Dr. Golding? Yes, Dr. Ellison.

DR. ELLISON: I have a couple. First, during the washout period, would he be receiving the non-inferiority product?

DR. GOLDING: You would have two arms, and you would randomize to a control group and the new product.

DR. ELLISON: And the new product would start immediately?

DR. GOLDING: Before you did the PK study, for both arms, you would have to have several months to wash out whatever other product they were getting before, so after three or four months, you would then start your PK test.

DR. ELLISON: The patients who are receiving this product, as well as the control group, who is going to be

paying for the product?

DR. GOLDING: Usually, the sponsor, the manufacturer pays for the product.

DR. ELLISON: It goes back to the discussion we had yesterday about patients paying for a research product in an era of cost containment.

DR. GOLDING: Well, to my knowledge, only studies that have been set up in the past, and I would think this would continue that the sponsors provide the material.

I think Dr. Lachenbruch wanted to say something.

DR. LACHENBRUCH: Peter Lachenbruch, also known as Tony.

Dr. Ellison was asking about the washout or I was thinking more of it as a wash-in period where the subjects would not go off the IGIV product. Whatever product they got, they would be assigned to, they would be on that product until there was stability, and the remaining product, the old product was out of the system.

DR. HOLLINGER: Dr. McCurdy.

DR. McCURDY: At one of the meetings, the workshops, that was involved in discussion of pool size for various different plasma protein derivatives including immunoglobulin, one of the manufacturers discussed for safety reasons moving many of the plasmapheresis operations from the coasts to the central part of America where there

is a difference in marker rates.

That undoubtedly influenced the composition of the IgG preparations made by that manufacturer. Was there any requirement for redoing clinical trials with that change in the donor base?

DR. GOLDING: I am not absolutely sure that I know if that really took place. Maybe somebody else knows that that took place. I think that was an idea. I am not sure that that really took place. We do know that there are products out there that come from donors that are mainly in the Midwest, and other products are mainly from donors on either the East Coast or the West Coast.

There is a difference in viral markers, but because of the viral clearance that is in place for all the manufacturers, we don't think at this time that that makes an impact on safety. Of course, there is always the theoretical possibility that there are some viruses out there that we haven't yet discovered that are more common in people in areas where the general biomarkers are high. I don't think we have an answer to that at this time.

DR. McCURDY: I wasn't thinking so much of safety because I agree with you that the inactivation steps and screening steps, and so forth, are likely to be very useful, but I suspect that the immunoglobulin composition, the antibodies present in people in different parts of the

United States may differ for that reason.

I think also there were problems that were both predicted and occurred when hepatitis C antibody screening took place, and perhaps some of the other antibody screening. What I am saying or what I am trying to say is that the donor composition for these immunoglobulin preparations and perhaps for others is extremely complex, and to require every change, every movement of a donor site or every change is the donor population to undergo additional clinical trials would be absurd, and the pool size, which I think is now upwards of 50, 60,000 at least would seem to take care of a large portion of the variation in antibody composition.

DR. HOLLINGER: Dr. Epstein.

DR. EPSTEIN: The answer to your question, Paul, is that yes, there was a manufacturer that shifted its donor base by going to donor centers in the Midwest for the lower marker rates. We did not demand revalidation of the product.

Of course, the concept is that the marker positives are removed from the pool, and that is true wherever you donate.

DR. HOLLINGER: Does the FDA require for any product like this, for IVIG, if it is going to be used for a specific thing, certain concentrations in that product,

let's say, even hepatitis B, hepatitis C, or for some other use, does it require certain amounts of antibodies into a particular product?

DR. GOLDING: Yes, there are regulations which require that they have antibodies to measles, diphtheria, polio, and the newer anti-hepatitis B surface antigen, but that is the limit of it. In other words, there are obviously many infections out there that are important for this patient group, that we don't ask testing for that, and I think it would be an improvement if that was implicated.

One of the discussions that was going on between us and the IDF is to try and include additional testing for specific antigens and to validate that testing during the coming clinical trials, so that that will also be in place.

A lot of the manufacturers are also looking at anti-hepatitis A antibody, but that is much more important in terms of IG intermuscular than the IGIV preparation.

DR. HOLLINGER: Also, I probably should know this, but can you explain to me the non-inferiority trial? That is a new term for me. What does it mean or what is a non-inferiority trial?

DR. GOLDING: I will let the experts handle that.

DR. HOLLINGER: Joel, or anybody else here?

DR. LACHENBRUCH: The idea of a non-inferiority trial is to show that a particular product is about the same

as the competitive product or standard licensed product, and you just don't want it to be too much worse than the other one.

So, what you would say is the number of infections per year on a standard product might be one or two, say it's two, and you would say that we will consider the new product acceptable if we can demonstrate that its number of infections per year is not worse than three. So, you are saying we will take a little bit worse, but not a lot worse.

In fact, in order to show that typically, you would have to have an observed rate substantially less than one different from the other, so you might see if one showed up as two, the other would have to be maybe two and a half.

DR. HOLLINGER: Thank you very much.

Yes, Joel.

DR. VERTER: Tony, is this similar to what the literature calls equivalence trials?

DR. LACHENBRUCH: Typically, equivalence trials have a lower bound also, so that is more commonly used in generic drug approvals. They want to show that typically in area under the curve is, say, within 80 percent to 125 percent of a standard. Does that sort of help you? It is sort of a one-sided equivalent.

DR. VERTER: Fine.

DR. HOLLINGER: Any other questions? If not, we

will move on to the other presentations. These are presentations from the Immune Deficiency Foundation. The first presenter will be Mr. Thomas Moran.

Presentations by Immune Deficiency Foundation

[Slide.]

MR. MORAN: My role this morning is to restate for this committee the obvious, so the service I can perform is to do it quickly and then move on to people that have more substance to offer.

[Slide.]

The Immune Deficiency Foundation, in short, is a patient organization serving people with primary immunodeficiency diseases, and our role basically is to help people in their day-to-day living.

[Slide.]

This is six of the over 50 diseases which fall into the category of primary immunodeficiency diseases. Essentially, what they have in common are that people have intrinsic defects in their immune system and can't mount an effective immune response to common challenges.

Prior to the IGIV treatment, the prognosis for our patients was frankly grim.

[Slide.]

There are about 20,000 primary immunodeficient patients in the United States on IGIV therapy. We consume

approximately 6 million grams of IGIV annually.

[Slide.]

With respect to the effectiveness of this therapy, in a study that was done, a survey of nearly 3,000 patients in 1996, the patients reported excellent, very good, or good health, nearly 70 percent of our patients reported that status. In other words, IGIV perceived by patients as an extraordinarily effective therapy and leads to a near normal or healthy lifestyle.

[Slide.]

Supporting this contention, again remember that we have a population that either have no or very weakened immune response, and in that same survey in 1996, 74 percent of our patients reported not a single hospital night in the prior year, which is a phenomenal success story.

[Slide.]

In mid-December of 1997, the Immune Deficiency Foundation, as well as industry and others, became aware of a national shortage of IGIV. In the two-month period between December 15th and February 15th, over 2,000 patients individually contacted the Immune Deficiency Foundation expressing the fact that they could not obtain IGIV therapy. After February 15th, we simply stopped counting.

[Slide.]

In April and August of 1998, we conducted two

surveys of physicians to get some data behind the effects of the shortage.

[Slide.]

First of all, between 90 and 94 percent of physicians told us that they had trouble obtaining IGIV.

[Slide.]

And then in response to a question of how they dealt with the shortage, they indicated that infusions were being postponed, they were needing to switch patients to different IGIV brands, they switched patients to less preferred IGIV brands, increased the interval between infusions, reduced dosages, and in some cases, couldn't get product whatsoever.

[Slide.]

When asked whether this had a health effect on their patients, in April and August, between 45 and 50 percent of physicians reported that these strategies for coping with the shortage had a negative effect on the health of their patients.

[Slide.]

We then did a survey in April of 1998 also of patients to get their take on the shortage.

[Slide.]

Of 60 patients reporting adverse health effects in that study, 31 reported more infections and malaise, 9

reported adverse reactions to new brand, 6 reported cases of pneumonia, bronchitis, and lung infections, 7 stress and anxiety, and 7, the adverse health effects were not specified.

[Slide.]

In summary, 80 percent of our patients, similar to our physician data, reported problems obtaining IGIV, and of those patients who had reported problems getting IGIV, 56 percent reported those adverse health effects that I just outlined.

[Slide.]

IGIV is used both off-label and on-label. I want to point out that I think that IDF in its experience, we would like to discuss medical necessity rather than on-label and off-label usage. There are some off-label uses for whom the IGIV therapy is extremely medically necessary, so the distinction on-label and off-label, although helpful, is not the only signpost with respect to the medical efficacy of the therapy.

[Slide.]

Let's quantify the shortage for a moment. In 1996, the six U.S. IGIV brands released to the U.S. market, there were about 17 million grams, 17,000 kilograms of IGIV released to the U.S. marketplace. In 1998, that number was down to 15.2 million, or a drop of nearly 2 million grams.

1997 was somewhere in the middle, but the point I would like to make here is that the shortage occurred in 1997. We can assume that there is somewhere in the neighborhood of 16 million grams release in the U.S. market in 1997. So, a drop of 1 million grams from 17 million to 16 million cause, in effect, a catastrophic shortage.

What that tells is that in 1996, when 17 million grams were released, we basically had a situation where supply equaled demand, and, in fact, we know the demand for IGIV therapy, because of off-label usage, has been increasing it is estimated about 8 to 10 percent a year, so just the take away from this slide is that if we look at 1996, release of 17 million grams in the U.S. market, we have a situation where supply equaled demand in 1996. We are now 2 million grams below that level in 1998.

[Slide.]

Taking that a little bit further, if we assume that supply equaled demand in 1996, the demand increases annually at the rate of about 9 percent, which I think is a conservative estimate, that tells us that in 1998, the estimate for demand for IGIV would have been 20.2 million grams.

[Slide.]

What that says is that we have a 5 million gram shortfall during 1998 in the U.S. marketplace. I should

point out also that as of Wednesday of this week, two days ago, the International Plasma Producers Industry Association came out with a report on the IGIV supply on the U.S. marketplace, and what we have is a nine-day supply in inventory and in emergency supply programs in the U.S., and it is not hard to imagine scenarios where a nine-day supply could turn into a zero day supply, one manufacturer with a recall or withdrawal or strike, in the trucking, Federal Express strike, any other number of scenarios, so we are down to a razor-thin margin of IGIV in the U.S. market.

Let me just simply finish by saying that IGIV therapy is the difference between health, between life and death really, for primary immunodeficient patients. We are 5 million grams short in the U.S. marketplace, and that situation is getting worse. We have a nine-day margin of supply in the U.S.

There is a substantial interest both with respect to U.S. companies to bring new products to market, products that would, for example, increase the yield of IGIV with the same units of plasma. There are a minimum of eight companies outside the United States who are interested in bringing products to market. You can well imagine the opportunity from the marketing or selling standpoint of getting product to the U.S. market.

The IDF has been working closely with FDA and with

these companies in order to try to come up with some strategies to make the kinds of trials and licensing requirements manageable, both from the standpoint of patient safety, but also from the standpoint of getting these products to market as rapidly as possible.

You are going to hear in a moment from Dr. Jerry Winkelstein and Dr. Richard Stiehm. The IDF sponsored a workshop about three weeks ago to see whether or not the IDF could assist in developing trial designs that would both preserve the health and safety of folks taking these products, but also get these products to license as quickly as possible.

With that, I would like to ask Jerry Winkelstein to come up to the stage.

DR. WINKELSTEIN: My name is Jerry Winkelstein. One of the hats that I wear at least is that I am the Chairman of the Medical Advisory Committee for the Immune Deficiency Foundation and run some of their medical programs.

[Slide.]

What I would like to discuss in the next six slides are the factors which may influence the ability of any group to perform clinical trials, looking at IVIG in patients with primary immunodeficiency diseases, and these will be factors that I think will, in fact, influence the

performance of these trials and their ability to be performed well.

[Slide.]

Two years ago, the Immune Deficiency Foundation received a contract from the National Institutes of Health to assemble and maintain registries of eight of the primary immune deficiency diseases to be used as a national resource, to gather information about these diseases and provide a resource to individuals who were going to do clinical or basic science research on this group of patients.

As a first step, we wrote to over 17,000 physicians who are members of specialty or subspecialty groups whom we thought might have some connection with patients with primary immune deficiency diseases, and had them fill out a simple, one-page questionnaire asking them how many patients they "cared for" with these eight different diseases.

What I have done on this slide is show you that these three disorders in which IV gamma globulin is used were estimated by their physicians to occur as many as 5,000 patients in the United States for common variable immune deficiency, the majority of whom are adults, 400 hyper-IgM syndrome, and about 900 patients with the prototypic immune deficiency disease X-linked agammaglobulinemia.

[Slide.]

This sounds like a generous estimate and that there should be plenty of patients, but the reality is when we then sent them a form to fill out to validate the diagnosis in the clinical situation that occurred in their patients, a simple, four-page form that can almost be filled out by memory, and looked back at those physicians who had registered those patients, we looked back at what they had estimated they had versus how many patients they actually did have, and that is summarized on this slide.

For instance, the first hundred physicians to enter patients in the common variable immune deficiency disease registry initially estimated they had 435 patients, but have actually registered only 263.

With X-linked or other forms of the hyper IgM syndrome, 23 physicians estimated that they had 402 patients, which was highly unrealistic because, in fact, only 81 patients have been registered by those same 23 physicians, or about 20 percent of what they estimated that they had, that they really have.

So, physicians, I would suggest, especially in this field, tend to overestimate the number of patients that they have.

[Slide.]

If you look at the distribution of physicians who

said that they had patients with common variable immune deficiency disease, a relatively small number of physicians out of the total, about 40, had the majority of the patients.

The largest number of patients, as well as the largest number of physicians, were in physician groups that carried between 1 and 4 of these patients, which, of course, would influence their ability to participate in large clinical trials.

So, there is a maldistribution, if you will, or a skewed distribution of patients.

[Slide.]

Another factor influencing the ability to do these clinical trials is where the patients are receiving intravenous gamma globulin. This is not from the NIH study, but rather from the IDF patient survey, and the patients sure should know where they are getting their gamma globulin.

Less than half are receiving gamma globulin either in a hospital setting or more commonly in a hospital clinic. The majority, 60 percent, are receiving their therapy either in a home setting, 40 percent, or in their private physician's office, 1 to 2 patients per physician. So, the majority of patients are not receiving IV gamma globulin that I would feel is conducive to a geographic or clinical

situation that would allow clinical studies to be done easily.

[Slide.]

Finally, the question of who would pay for this always comes up, so I also looked at the IDF patient survey for this, and as you would imagine, the great grand majority of patients have third-party payers paying, they are not self-payers, and the ability of them to convince or their physicians to convince any third-party payer to pay for this kind of activity could certainly be limited.

[Slide.]

In summary, there are at least four factors that I think must be taken into account that would influence the ability of clinical trials to be done in patients with primary immune deficiency disease.

One is the total number of patients, in reality, the total number of patients is limited. The distribution of patients, the majority of patients are seen in centers or by physicians who seen one or two of these patients, and not too many more. The majority of patients receive their IV gamma globulin in an out-of-hospital clinic setting, usually, at home, and therefore would be inconvenienced if they were asked to participate in this kind of study.

Last, but certainly not least, a consideration of who would pay for this is not insignificant for most of the

patients.

I would be glad to answer questions if anyone has any, if not, I could turn the podium over the Dr. Stiehm.

Dick.

DR. STIEHM: Thank you. I am Richard Stiehm, Professor Pediatrics at UCLA, and I have been involved in multiple IVIG trials including the first one that licensed IVIG.

[Slide.]

Our problem is that we were asked to design an IVIG efficacy study for multiple products, limited number of patients, concurrent controls, i.e., the patient would be on his own gamma globulin and limited time based on the fact that there is this shortage, and we have to respond to it.

So, the Immune Deficiency Foundation sponsored a workshop that was summarized by Dr. Golding a few weeks ago, and since that time, we have had approximately 10 or 12 conference calls with members of the committee, with the IDF staff, expert panel, the FDA, and industry, and we hope we have come up with at least a start to a solution.

[Slide.]

The proposed study that we suggest may satisfy both our patients and the FDA, would include patients on primary antibody deficiency requiring IVIG. This basically includes X-linked agammaglobulinemia patient, common

variable immunodeficiency, over age 3 on IVIG for at least three months.

We think that this should be a double-blind study, comparison with the present IVIG, which is the licensed IVIG product, the duration would be 12 months. We suggest 30 in each arm.

We suggest that the primary endpoint might be the days of fever, and I will explain that in a bit, with a secondary endpoint is the number of serious infections. In addition, we plan to do IgG and IgG subclass levels, an antibody titer which would include certain antibodies that are not currently required, and pharmacokinetics, as Dr. Golding mentioned.

[Slide.]

The possible efficacy markers that we considered included the number of serious infections, less serious infections like bronchitis, sinusitis, and otitis. The problem with these are they are very hard to document what is bronchitis. The day so hospitalization is good, days of antibiotics isn't so good because of different prescribing habits.

Work or school absence is also difficult because some people keep their kids home all the time, and other people go in with a raging fever, or the number of days of fever.

[Slide.]

From this survey of the Immune Deficiency Foundation, it might suggest that serious infections still were pretty common even though patients on IVIG had markedly less hospitalizations than previously. This has to be discounted a little bit because these include all patients with immune deficiency including some with T-cell or cellular immunodeficiencies, so that the frequency of hospitalization is much more common in those particular patients.

[Slide.]

Using serious infections would be a great endpoint because you can document it, and some possible definition of a serious infection include pneumonia by x-ray--no one will argue with that--sepsis or meningitis by culture, a visceral abscess, liver abscess or osteomyelitis by imaging, or a temperature of 102 requiring hospitalization. These are all quite objective.

The disadvantage, the patients on IVIG at adequate doses rarely will reach one of these side effects, and based on a meta-analysis or a review of the literature, I estimate that this is not going to occur more than 5 to 6 percent in the patients per year.

[Slide.]

After much soul searching, this is a possible

alternative, using the days of fever. This has the advantage it is a common event, and we estimate about three to four febrile days per year, say, a temperature over 100. It is objective, you can do it with an ear thermometer. It is an accepted correlate of infection. You heard in the first presentation you don't accept blood donors if they have a fever.

Serious infections will count more than minor infections because you are going to have more days of fever. In addition, you can quantitate the degree of fever because, in general, it correlates with the severity of infection.

[Slide.]

I based the number of days of fever on these two studies. Bernatowska did a very nice study, a crossover study in 1987, of 12 children receiving either high dose IVIG or low dose IVIG, 100 mg/kg versus 400 mg/kg, and she identified that there is about 10 days of fever per patient per year on high dose IVIG, and low dose incidence was about double that.

Another study done by Charlotte Cunningham Rundles looked at adult patients and patients receiving adequate or high dose IVIG, had about 13 days of sickness per year, and on low dose an increase was about 4-fold.

So, based on a guesstimate that about one-third of these patients were sick, might have a fever, I came up and

I think it is reasonable, about three or four fever days per year.

[Slide.]

So that these are these estimates. The high dose patients, the dose that would be used would be three to four days per patient per year, low dose would be six to eight patients per year, and, of course, if you don't get IVIG, it is going to be about 6-fold that number of days of infection.

[Slide.]

These would be a suggested efficacy endpoint of this particular trial. The number of days of fever, and we would include the total episodes, as well as the percent of patients, and the secondary endpoint would certainly be serious infections, but we don't think we are going to meet many of these endpoints.

So if we have a trial using 30 patients, we are going to have 90 to 120 days of fever or one or two serious infections in this group, and if the patients were not getting this product, although none of them will, this would be about 600 days of fever, six to 12 serious infections a year.

[Slide.]

The other assays that I will mention briefly that we would suggest should be done as possible surrogates is

IgG levels. Currently, most of these products that have been licensed have used an IgG level of a delta of 400 mg percent as indicating a therapeutic efficacy. Indeed, we would also like to do the distribution of the IgG subclasses, at least IgG1, 2, and 3.

We also think the trough antibody levels are very important because this will identify if these patients are being protected against less serious infections like chicken pox or like tetanus or diphtheria.

We think that, however, all these patients should be studied for diphtheria intubate, measles, and polio, and hepatitis B, the four currently recommended antibody titers, and then since the main infections that these patients get is pneumococcal infections, four antibodies to four of the pneumococcal polysaccharide should be required.

[Slide.]

We would do pharmacokinetic studies after a six-month period of the wash-in period, as someone mentioned, and repeat these as necessary. We don't think that every patient needs a pharmacokinetic study. I think a subgroup of these, and if the pharmacokinetics look okay on six patients, they are probably going to be okay for all 30, and we would suggest as additional studies, although not as primary points, a much more extended antibody titers done at entry after six and 12 months, and these titers would be

compared to obviously the antibody content of the intravenous gamma globulins, as well as that level achieved in other patients doing well on standard IVIG.

This is a proposed solution, and it is a way to continue the dialogue.

Thank you.

DR. HOLLINGER: Thank you, Richard.

Are there some questions for Dr. Stiehm or any of the other people who presented this morning? Yes, Dr. Linden.

DR. LINDEN: This is for Mr. Moran. I would like to preface it by saying I am not disputing at all, that clearly you have documented that there have been problems with shortages.

My concern is about the data and the way they are presented. My question is really what are the response rate was on these surveys, because my recollection is the last time we saw these data, the response rate was fairly low, so that this is not representative because you are going to see a significant non-responder bias I would expect, that is, you would expect that the people who would bother to respond to a survey like this would be most likely to be the ones who had a problem, and those who did not have a problem might not bother to respond.

So, unless you had an excellent response rate, I

would not think these would be representative.

MR. MORAN: I am going to ask the author of the survey to respond to that.

DR. BOYLE: It depends upon which survey you are talking about. As we indicated before, that patient survey about what health problems are you having is not representative. We got basically 100 or so back because we put it out in a very quick period. We wanted it simply to validate what we were seeing from the physician surveys.

The physician surveys, the 25-plus patients, the response rate was about--actually, the completion rate was about 70 percent, which is astonishing for a physician survey particularly given the short time frame.

So, those are the two things we were talking about. The physician survey, high response rate, very definitely projectable. You can assume that that relatively small group of non-responders may have had lower rates, and if you want to, you can discount a bit, but basically, you have got a higher rate than you would normally get in a federally-sponsored physician survey. The patient survey should only be used to answer the question that was posed to us, which is what kinds of problems are the patients having.

DR. HOLLINGER: Dr. Verter.

DR. VERTER: Along the same lines, I wonder if you could clarify something for me. The figures that you

presented suggested that between 1996 and 1997, there was a decreased supply, and allowing for maybe even a 10 percent increased need, I would calculate that the shortfall was somewhere between 14 and 17 percent in the amount of grams needed to supply the people needing it.

Yet, the survey suggests that 90 percent had difficulty. Now, is that an issue of distribution? I mean that is an overwhelmingly different difference.

MR. MORAN: No, and it was a shock to us. I mean this is another piece of data which is we had 2,100 phone calls in a two-month period of time, 2,100 individual patients in a two-month period of time.

The analysis that we have come up with was that during most of 1997, in fact, supply had exceeded demand, that the pipeline was being emptied, and that at some point in time, essentially, the cupboards were bare, and so that that shortfall we had been--during 1997, when there was approximately 16 million grams released, the 14 percent shortfall that you mentioned, we were eating into the inventory during the entire year, so that at some point in time, December 15th, or somewhere in that ball park, basically, not only were the cupboards bare in the hospital pharmacies, but also in the pipeline, so we have been eating interview available inventory.

So, it had that effect almost immediately,

dramatically. We sort of felt it was almost like a tidal wave. It took three to four months for the market to adjust, and so there were serious spot shortages throughout the country.

For example, we had testimony of six months ago, Texas Children's Hospital testified that they went somewhere from an allocation of 2,500 grams a month of IGIV for their normal use down to less than 200, and that occurred over a brief, 30-day period.

So, I think at the point that the pipelines and the cupboards were bare was the point at which it had that effect.

DR. VERTER: A question for the Chair or the FDA. Are we supposed to try to critique the design of the trial? What is our function here? I mean it has been very informative. I could probably take an hour critiquing the design and making suggestions. I doubt that that is what you want. What is the goal for the committee?

DR. GOLDING: It is just really mainly informative to indicate to the committee what kind of actions are being taken and what is in process. I think the trials that you have had presented to you are samples.

What really needs to happen now is that a sponsor needs to submit to the FDA a trial that will be along the guidelines that have been discussed, and then the FDA can

deal with that in that situation. I don't think we are asking the committee to say whether this trial design that we have suggested or that the IDF suggested are appropriate trial designs.

We just I think would appreciate some feedback that, in general, we are on the right track and that these kinds of trials in this kind of circumstance are reasonable and are within what a proper clinical trial would require.

MR. MORAN: I think it is fair to say--let me just quickly comment--that last summer and fall, there was an enormous amount of interest, both domestic and foreign companies, in terms of getting new IGIV products licensed in the U.S. market.

I think it is fair to say that in discussions with FDA over the kind of trial that was described by Dr. Golding and Dr. Lachenbruch, that there were some practical problems that were identified during those discussions between FDA and most of these companies.

So, what IDF has done is sort of brought forward a slim-downed version, so to speak, that still addresses clinical endpoints. What we are trying to do is bridge a gap between a more stringent style of study and the realities with respect to the ability for companies to perform these studies within reasonable cost and time parameters.

So, this is just to put it in context what we are trying to put forward a solution that deals with the reality of the patient population, where they are seen, and those kinds of things, as a means maybe of restimulating the interest by many companies to get IGIV into the U.S. marketplace, which seemed to have waned a little bit over the last four or five months.

DR. LACHENBRUCH: Joel, I think we would be delighted to talk with you on this. As you can imagine, it has been three weeks since that conference, and as was mentioned, there has been a lot of phone calls back and forth, and we had about a two-hour conference call last Friday on this, and I will be more than happy to talk with you, and I am sure IDF and whoever they are working with would be quite happy to work with you at the break.

DR. HOLLINGER: I think the issue is really brought before you here to talk about the clinical trial endpoints, informational, I think we could discuss it here, too, at the same time, if you want to, Joel.

Before we do that, though I want to finish up with the open public hearing, and don't go away because we will be coming back to you all. There is one person to talk, and then we will come back to the other.

In the open public hearing, one person has asked to speak, Judy Ranallo from IDF, and if there are others, I

will entertain that, and then we come back to the comment.

Open Public Hearing

MS. RANALLO: Good morning. My name is Judy Ranallo. I am President of the Ohio Chapter of the Immune Deficiency Foundation. As you are aware, the chronic shortage of IGIV has been going on since the fall of 1997, a situation that as a mother of an immune deficient patient has gone on far too long. For my son, Sam, IGIV is the difference between life and death; this is also the case for many thousands of patients and their families for whom IGIV is life sustaining.

I am here today to address this Advisory Committee because the current shortage should not be allowed to continue. Solutions must be found. Therefore, the licensure of new IGIV products is of great personal concern to me.

My son, Sam, was born in February of 1983. Sam was premature, diagnosed as developmentally delayed, and placed on a series of medications to treat low blood sugar and a seizure disorder. He did not respond well to the medications prescribed and at the age of four began having a series of serious infections.

In a two-year period, Sam had three surgeries, tubes were placed in this ears, his tonsils and adenoids were removed, and he had upper GI problems. As a result, he

suffered hearing loss and was not allowed to return to school due to his severe health complications.

He was then diagnosed with asthma and epilepsy. He has skin infections which would not heal, and his sinus passages were destroyed due to infection. Sam averaged 12 to 15 serious infections per year, many that require hospitalizations. His health was not improving and he continued to deteriorate, making our life a nightmare.

Finally, at the age of seven, Sam was diagnosed as a primary immune deficient patient and placed on IGIV. Sam has continued to receive IGIV for the past nine years, every three weeks. In the summer of 1998, we had his 100th infusion party, which we celebrated with family and friends.

Since beginning IGIV therapy, Sam has not had any serious infections and the rate of infection has dropped from 12 to 15 a year to two to three minor infections per year. Sam is here today and will tell you a little bit about himself and his wonderful accomplishments.

As a mother, I know that Sam is at risk of developing an infection that could serious debilitate him or kill him if he doesn't receive his gamma every three weeks. It is this fear that brings me here today on behalf of my family and the thousands of people whose lives depend on regular IGIV infusions. We often do not know if our infusion will take place as scheduled until 24 hours in

advance. Imagine knowing that IGIV means a normal healthy life for Sam and knowing that it may not be available for him tomorrow.

Solving the current IGIV shortage and increasing the supply in the U.S. marketplace is the responsibility of manufacturers, government, and patient organizations. In congressional hearings held in May of 1998, the FDA stated that new products entering the marketplace could increase supply.

To date, no new IGIV preparations have been licensed, and only one significant licensing trial is underway. I hold you responsible for finding ways to expedite licensure and increase supply to ensure that the thousands of patients for whom this product is life sustaining are able to receive their treatment. For my son and many others this is a situation where failure is not an option.

Thank you. I would be happy to answer any questions that you may have.

MR. SAM RANALLO: Good morning. My name is Sam Ranallo. I want to thank you for giving me this opportunity to speak to you today.

I am a 16-year-old freshman in high school. I work part time during the week and during the school year. I recently got my temporary driver's license which is making

my mom a little nervous. I am also starting to date, which is also making her very nervous.

This past fall, I was the starting goalie for my soccer team, my school team, and I recently completed my wrestling season with a 21 and 2 record while wrestling for a team that was ranked 18th in the nation. I am a Merit Roll Student and admired by my teachers and my fellow students. I am also immune deficient. IVIG therapy is a part of my life and it has been for the past nine years. My life is normal because, and only because, of IVIG.

I am very dependent on my 21-day, 25-gram infusion schedule to keep in top shape. Like my mom mentioned, my life before IVIG was a wreck with the chronic illnesses and constant surgeries. By leading such a normal life now, I can't imagine but do know what my life would be like without it.

I managed to wrestle the entire wrestling season without a single infection. Without my infusions I was infected 12 months out of the year. My goal in life is to become a middle school guidance counselor. I need IVIG therapy to accomplish this and every other goal I have set for me in my life.

I desire to grow up and guide the future generations of children in the U.S. In order for PID patients like myself to lead normal lives, it is imperative

that the concerns surrounding the shortage of IVIG be addressed.

Thank you.

DR. HOLLINGER: Thank you, Sam, for coming here and sharing that with us.

Are there any other comments from the public in this portion of the public hearing? Yes, please. State your name and organization.

MR. GOLDSMITH: Yes, my name is Jonathan Goldsmith from Centeon. I would like to thank the BPAC for its careful consideration today of the trial designs that have been put forth, and I would also like to bring to their attention that there are also alternative routes of administration that might fall under these same kind of research criteria, such as subcutaneous administration of IGIV, that might also help eliminate this shortage.

Thank you.

DR. HOLLINGER: Thank you.

Are there any others?

DR. WINKELSTEIN: Mr. Chairman, would it be okay if I added one additional comment? I don't want people to be left with the wrong impression. The trial that has been designed between the FDA and the IDF's "expert panel," at least I personally do not want it to be perceived as a substandard trial that has been designed to compromise or

deal with the shortage.

If there were no shortage, this trial, I believe, would be medically still an appropriate trial. I do not believe in any way that there has been a compromise in terms of the proper trial design. I wanted to be sure that everyone understood that point.

DR. HOLLINGER: I am going to close the public hearing, and I am going to open it up to the committee for comments and discussion. We have some time for this.

I am going to start with Mr. Dubin.

Committee Discussion

MR. DUBIN: Can we also ask questions of the group?

DR. HOLLINGER: Yes, sure.

MR. DUBIN: Tom, I think clearly one of the things that has presented IDF with the problem is kind of the explosion of off-label use of this product in recent years, and certainly one can look at the manufacturer's sales pitch as part of that problem, and doctors working to find different treatments with AIDS patients, peripheral neuropathies, things of this nature.

Any ideas who we are going to solve this problem in terms of how much product is going into off-label use versus how much is going to on-label use?

DR. HOLLINGER: I think that is a good question,

Corey, but I did notice also you mentioned that there were 6 million grams used in primary immune deficiency, and there is 20 million or 18 million that is manufactured. That means more than twice the amount is used for off-label use. Is that correct or incorrect?

MR. MORAN: I think the estimate is about over 50 percent use off-label. I have two points. One is off-label doesn't necessarily mean not medically necessary, and you are all more familiar than I am with the idea of drugs get licensed for certain indications, and then they are used for other indications, and they are as effective.

IDF, our role in this is not to sort of create a hierarchy of misery or to create a competition among and between patient groups, and so we kind of are perhaps even less aggressive on that point than you would imagine.

I do think that what has happened behaviorally speaking, is that throughout the United States, in hospital pharmacies, to some extent in home care companies, and other sites, rationing protocols have been developed all over the U.S., which has benefited our patient population, perhaps Kawasaki syndrome is another use, and Guillain-Barre syndrome, which is an off-label use for which it is a highly effective and necessary treatment.

So, what has happened is kind of collectively and independently, institutions throughout the United States

have developed these kinds of rational protocols. I do think that enormous restraint is needed in several areas. For one thing, the more experimental uses or I would say uses for which there is not substantial proof of benefit, CDC several weeks ago published an MMWR, which reviewed several of the FDA on-label and off-label use in an NIH consensus conference on this subject, and all the University Hospital Consortium study on this point, and I would refer your committee members to that document for review on that.

But I think that it is unfortunate that the way the situation needs to be handled now is by sort of draconian kinds of rational protocols, and I think to some extent it is creating spot shortages throughout the U.S.

It clearly is affecting our patient population. Those are not seen at major university hospital centers are more adversely affected it seems than those that are, and I think we need to get the shortage behind us because, frankly, this is a therapy that has a lot of positive use.

DR. HOLLINGER: Dr. Macik.

DR. MACIK: I just wanted to see if we could get some idea, because it seems like we are saying on-label is treatment primary, and off-label is everything else. There are clearly other things that are on-label, and what is the percentage of total product that is used?

We have three categories. We have the primary.

We have the other on-label like in ITP, which I have had lots of problems getting product to treat in the last years, and then the things like Guillain-Barre, which are kind of new treatments in a way, but have had great success, so, or as you said, medically indicated.

The other thing that becomes important, though, is that your product has special needs, that treatment of some of these other disorders don't. For example, you need certain titers, various antibodies in your product to fight off chicken pox and to fight off the various pneumococcal, whereas, the way this product is used in other diseases, you don't need those antibodies present.

So, if you design trials or require that new manufacturers coming on-board must meet these minimal to get their product on or limited to the treatment of a very small group, although very necessary group of people, you are going to really slow down getting product available for everybody.

MR. MORAN: I am going to comment and then I am going to ask Dr. Stiehm and Dr. Winkelstein to follow on, but basically, one of the objectives of the trial that IDF outlined is to validate, if you will, surrogate markers.

One of the issue confronting our population and the companies that want to get to license is the business of introducing the concept of infections as primary endpoints

in the study, and this has a lot of effect vis-a-vis the number of patients involved in the study, the complexity, and the time involved.

So, our starting position as a group was to say there are good surrogates that are available that would make these studies more expeditious, and they include IgG levels, as well an antibody titers, and so forth.

We incorporated the FDA thinking vis-a-vis the infections as primary endpoints. We have added elements to the trial that would not be a requirement for licensure, for example, the antibody, but as long as the blood is being collected anyway, you know, begin to do some studies on, for example, antibody titers that would down the road validate these markers as surrogate endpoints as opposed to primary endpoints, so we are not recommending, unless Dr. Stiehm or Dr. Winkelstein have a different point of view, in which case we are, just so you know who is in charge here.

We are adding those elements to the trial, not as a criteria for licensure, but rather to validate surrogate endpoints, so that several years down the road, it may even get to more expeditious trials, but I would like Dr. Stiehm to comment.

DR. STIEHM: I think you categorization of three types should be increased to four types. There is primary immunodeficiency, other on-label. Then, there is uses which

are proven, like Guillain-Barre, and then there is all these others that people use, and, for example, there is four illnesses that I think use about 20 to 30 percent of the IVIG products - asthma, recurrent abortion, chronic fatigue syndrome, and infantile autism.

Now, there is no information that these illnesses are benefited by IVIG, however, a number of doctors use them a lot, and they have to use very large doses or they do use very large doses, so that the university hospitals have effectively dealt with their gamma globulin shortage by making a prioritization where on-label use gives a priority, and you simply cannot get IVIG if you want to treat infantile autism, which I think is useless anyway.

DR. WINKELSTEIN: . In terms of the content of antibody restricting its use of availability for other groups, I think that is probably not a practical concern because most of the pools contain sufficient antibody, so that the donors that are used, if you will, for the product that might be used in immune deficient patients would not necessarily have to be different than the donors used for other indications in which antibody is not properly the surrogate for clinical efficacy.

The danger, however, is that it is conceivable to carry the antibody screening past the point of being appropriate, that is to say, to take a ridiculous example,

if you said that antibody positivity for a viral infection like hepatitis C was an appropriate criteria for exclusion, one would not want to go to saying that antibody titers for the pneumococcus, by analogy, would be an inappropriate donor pool.

I know that sounds like a silly statement because it is so obvious, but nevertheless, for some people, they have made this transition to equating antibody titers, which is really what we are really what we are looking for, with surrogacy, if you will, for active infection, which is not what we are looking for.

DR. HOLLINGER: It is my understanding that IVIG does not contain anti-HCV antibodies, is that correct? Since 1994 or 1995.

Dr. McCurdy.

DR. McCURDY: A statement was made that one of the responses to the shortage was to shift the patient to a less desirable brand. Do we know that the basis of less desirability is?

DR. WINKELSTEIN: In terms of efficacy, I don't think that is the proper use of the term, but what does happen, though, is that patients tend to wind up on a brand that they tolerate in terms of their comfort level both during and for the two or three days after the infusion, these are the mild to moderate side reactions. They are not

anaphylactic reactions or even anaphylactoid reactions, they are not infectious presumably in origin.

But what does happen is there is a natural selection that most of us go through. If brand A gives the patients a day of fever after the infusion and some myalgias, we will switch to brand B. That then gives us a patient population who becomes comfortable finally on one or another of the licensed preparations.

When there is a shortage, we used what we could get, so that there was, in fact, a great deal of patient discomfort in switching from the brand that they had self-selected over a period of time to the brand that became available, so I think that is the explanation.

DR. STIEHM: There is no evidence that I know of that switching brands decreases the susceptibility to infection, however, there are literature studies to show that certain brands are more reactive than others.

DR. McCURDY: In this inventory that was taken, and we have a nine-day supply as of two days ago, I guess, where is that supply? Where is it physically located?

DR. HOLLINGER: We have representatives of the companies here that may want to comment, but essentially, I think it is on the loading dock or in inventory. You know, you add the pallets that are ready to ship, and that is where it is. I suspect that that is where most of that

inventory is.

DR. McCURDY: Several weeks ago I became aware that some transfusion service directors and some major hospitals appeared not to be particularly concerned about an IgG, intravenous IgG shortage, and that raises the question in my mind as to whether it is irregularly distributed around the country.

In one of my former lives, I was responsible for a major blood center, and when blood became short, such as in the early part of January, the demand for blood went up by 30 to 50 percent, largely because apparently of over-ordering and attempts to stockpile.

I am just wondering whether there are some places that are more effective in stockpiling or getting what they need than others, which may distort the picture a bit.

MR. MORAN: That certainly is a theoretical possibility. I think the other thing is that the marketplace has been accustomed to the shortage, and so that there is perhaps less--first of all, there are rationing protocols in place in many of the settings where IGIV is dispensed, number one; and number two, I think that patients, treating physicians, and pharmacists are accustomed to being on the brink, so to speak, and perhaps less panic reaction when the inventory gets low.

DR. KOERPER: I think it also depends on where the

physicians are practicing that you are surveying. At our large university hospital, we have had relatively little problem getting IVIG although it may not be the preferred brand that each patient would rather get.

I used to be able to talk to pediatricians in towns six hours away, way up in Northern California, through treating a child with ITP with IV gamma globulin. Now, those pediatricians way up in Northern California, their small hospitals cannot get the IVIG, so all those children now must come down to San Francisco in order to get this treatment.

So, if you asked me, I would say, no, I am not really having any trouble getting IVIG, it may not be the preferred brand, but I can get it. If you ask the pediatrician up in Eureka, he can't get the IVIG, so it depends a little bit on the sample.

DR. WINKELSTEIN: The answer to that question also is that 60 percent of my patients do not come to Hopkins for their IV gamma globulin. They are in home health care companies on the Eastern Shore, the Del Marva Peninsula, Western Pennsylvania, et cetera. The shortage that I have had to deal with for those patients has been through home health care companies and small community hospitals, whereas, Hopkins obviously has probably been given some preferred treatment by the suppliers.

DR. HOLLINGER: State your name.

MR. JACKMAN: I am Dennis Jackman, Vice President for North America for IPPIA, International Plasma Products Industry Association.

Somebody was asking a question about where the product is that is out there, and it is in the distribution pipeline. Companies have made a number of efforts over the past years to try to get that distribution as close as possible to the provider and to the end user, to the patient, so there are a lot of efforts in that regard, so it is basically in the distribution pipeline going out as rapidly as possible.

In terms of spot shortages, the gentleman referred to maybe spot shortages. Our data show a consistent shortage, and we provide monthly data to FDA, to some of the patient groups, and to a number of other people that show that our U.S. distribution versus inventory is at a low level, it is well under one month's supply. It has consistently been that way. So, it is a good indicator of the balance of demand and supply, and it has been about a few weeks of balance there, so we have a consistent shortage, and we recognize that, and are making a lot of efforts to try to address it.

DR. HOLLINGER: Thank you.

Dr. Epstein.

DR. EPSTEIN: The shortage question obviously has great public health importance, but I just wonder if we couldn't have a little bit more discussion about the clinical trial design, which is really our topic for this morning.

These are related, of course, because approving new products is one of the strategies for dealing with the shortage. I just wanted to focus on two particular points and solicit comments from the committee.

One point is that the size of trials has to be driven by two things. One is safety, and the other is efficacy. I think that what has really been put in front of us is the difficulty of doing a large trial. It has been explained what that is so. That is a perceived obstacle, of course, to completing trials, and the novel idea that has been proposed is the use of number of febrile days as the primary clinical endpoint.

I think that what has been shown here is that if the agency were to accept that, that much smaller trials could be done. Indeed, the size of the trial at that point might be dictated by the denominators needed for safety rather than the denominators needed for efficacy, which is sort of astonishing.

But I think it would be helpful to the FDA if we could get some feedback from the committee what members

things about febrile days. We don't have to come to closure today, but I think that your comments would be useful.

DR. HOLLINGER: That is what we will do for the time that we have remaining. I would like to start with Richard for just a second. You mentioned fever as an efficacy endpoint, and you presented two groups which looked at fever, and which they talked about a 10 per patient per year, and one was 13 per patient per year, and then in the next slide, when you put fever as an efficacy endpoint for the same high dose if IVIG, you dropped to three to four days per patient per year, which is different than the two studies which use fever as an efficacy endpoint.

Then, the other question is on the same line, for people that use NSAIDs, or other things like this, how does it alter using fever as an efficacy endpoint over a period of time when they are taking things which will lower the fever to perhaps normal in some patients? Could you deal with those, Richard?

DR. STIEHM: We think that fever would be useful. In terms of how we estimated that, one of these studies showed actually the days of fever, the other was the days of illness. I made estimates that about a third of those patients had a febrile day.

Days of fever has the advantage in my thinking of not only being a frequent event, three or four years per

year, but also that it would quantitate how severe these infections were. For example, if you had bronchitis for three days with a fever, each day that would count as three episodes.

We did exclude or we would exclude the fever that is associated with the product. So, we suggested that days of fever for two days after IVIG would not count, and if you are counting the days of febrile episodes, we probably would require at least a week between one febrile episode and the next to count it as a separate occasion

As far as I know, there has not been any studies using days of fever except for this one study, and I think I reviewed the literature pretty well, but I think that based on my thinking, this would be a reasonable outcome.

DR. HOLLINGER: And the issue about most individuals would take something for their fever, which might drop it to normal, how is that going to affect that kind of endpoint?

DR. STIEHM: I think it is going to normalize out between the control group, the patients on regular IVIG, and those that are on the new product, so I think that there is going to be a built-in control by having concomitant controls.

We think that the patients should be treated with their own IVIG product because that is the one they are

comfortable with, and it will be very difficult to enroll patients if you ask them to switch to either a new IVIG that they have never had before, as well as experimental one.

DR. WINKELSTEIN: I might say that I think the reality is that at least for most of the patients, if you would use days of fever rather than hours or numbers of medications that they take, the antipyretics will not influence your outcome because the majority of patients take antipyretics in response to fever rather than prophylactically, so I think days of fever will not be largely influenced by antipyretics.

DR. HOLLINGER: Dr. Nelson.

DR. NELSON: It seems to me that given the shortage and the situation, that a trial in a small number of patients like has been proposed with these biologic endpoints is quite reasonable, but I wonder. One of the issues that always comes up is after a product is licensed, there really should be continued evaluation of its efficacy, and that isn't required of all products, but in this particular product, I would think that there would be possibly an opportunity to do that.

In other words, a product might be licensed based upon no significant difference in the days of fever, but in the year or two after licensure, if there was a mechanism to continue to collect data on that new product, there might be

something attached to the license or so that if it was found to really be an inferior product later, that it could be re-reviewed.

I don't know if that is feasible from the FDA standpoint, but from the characteristics of these patients and the patients that might be involved in such a study, I would think that it would, given those that are under the care of specialists that have fair numbers of patients, there might be continued evaluation over a longer period.

DR. GOLDING: There have been some preliminary discussions between myself and Tom Moran of the IDF, that would address some of these issues. The sort of verbal agreement that we have come to is that the IDF would establish a post-marketing surveillance mechanism both to look at efficacy and to look at adverse events.

That would provide the FDA with an additional sense of assurance about these studies. In the past, Phase IV studies have had a very dismal record, but what we are talking about here is that the IDF, who will represent the consumers, will be following up these patients and providing us with that data, so I think there is a reasonable chance that those data would be made available, and that would answer those questions. It would be very helpful to us.

Regarding the fever endpoint, I would just like to make a very quick comment, and that is, that any endpoint

that you use has to be validated, in other words, some of the thinking of it could be very simple-minded, but you have to know that a patient can measure, use whatever instruments used in measuring temperature in a proper way, and you have to test this.

You have to be sure that they can do this in a reliable way, and you have to have a whole lot of additional factors in place like when are they going to measure their temperature, what temperatures are we talking about that are significant, how is it going to be recorded, many different factors, and there should be some plan for training and validating that these patients can do this in a reliable way, because if this is what the whole trial is going to hinge upon, you need to be sure that this test is really a valid test.

DR. LACHENBRUCH: I have one comment that wanted to make regarding the use of their own or the IGIV that the patient has been on. I think this is a very hazardous course to go on, because the patient's own IGIV will be the one that they are not reacting to, and so there is a very real possibility of substantial unblinding of the study as it goes on, and this could affect either efficacy or adverse event reporting.

DR. HOLLINGER: Yes, Dr. Stroncek.

DR. STRONCEK: I think the endpoint of fever is

fine, and it should work out well as long as it is measured appropriately. The issue on control, I don't quite understand how this would be controlled. Would you study the patients on their own products for a year or two? Would their products be blinded, and would they cross over after a year, so this would be a two-year study, one part of it they get their own product blinded, and then the next year they would get the test product? And, of course, that would be randomized?

DR. STIEHM: I think that they should be randomly assigned to either a standard IVIG or the tested IVIG. I think it is feasible to use a standard IVIG that is already licensed, I don't think that is an insurmountable problem.

I think patients would prefer to stay on their own, but I understand Tony's reservations about the fact that they could be unblinded, but I would propose either a year of the new product or a year of the old product.

DR. HOLLINGER: I suppose two years would take too long, but it would be nice if you had a crossover study where they got their own product plus the test one.

DR. STIEHM: That really makes a two-year. The problem with crossover is that the days of infection change from season to season, and the patients that get the product during the winter may have more infection.

DR. HOLLINGER: Dr. Verter had initially brought

up some questions or some thoughts about this. Could you give us your comments, please.

DR. VERTER: I have a feeling that some of what I am going to say was probably discussed between the FDA and IDF, but I don't know, so I will say it anyhow.

First, let me comment on what Dr. Epstein said. I agree with him, but I would change it slightly. There are at least two things that will drive the trial's safety and efficacy, but in particular, and in very particular in this case, I think resource is another issue, that whereas in cardiovascular disease you may have 500,000 MIs to shoot at if you are going to do an MI trial here, it looks like the maximum number that you can have is a cohort is 20,000, and, of course, you will never get 20,000 to do this thing, and they may not all be relevant for what you want to study. So, that is a very big issue.

The other aspect of resources is, of course, as has been mentioned before, who is going to fund the study. I think here, if it has not already been discussed, maybe there is an opportunity here for industry and NIH, perhaps philanthropic organizations, and the IDF to come together to do what I would consider somewhat of a better study.

I think for a number of reasons that have been stated by the FDA and perhaps one or two of the committee members, days of fever is a very difficult and clearly a

surrogate outcome. However, it may be the only outcome that is practically feasible in this setting. I am not willing to concede that yet, however, but I haven't been privy to all the discussions.

In my mind, and this a little pie-in-the-sky type stuff, I think what you do is decide--let me back up just one second. It is a unique opportunity to do a trial that won't come around again probably, and the idea of trying to do post-marketing surveillance will never be as good with respect to efficacy or safety as when you can do it in a trial, because you have a head-to-head comparison.

I mean if that is all that you can do, that is all you can do, but let's start with the gold standard, and I would advise everyone who is interested in doing this to sit down and say okay, what would be the gold standard study, what is that we are really trying to look at, and is it at all feasible to come with that study, fund that study, get the patients and the community to cooperate in doing that study, and go forward with it.

Now, if that is not possible, then, you can step down, but I wouldn't start at the bottom and not worry about the top. To me, you know, 30 patients in a group or even I think Tony had 70 or 80 in a group, you are likely to miss some serious problems, some serious side effects, and perhaps even an increased rate of infection.

We all know that fever doesn't correlate 1 to 1 with serious infections that are treated either out of hospital or in hospital with antibiotics, so it is truly a surrogate, and the clinical trial literature is littered with surrogates that didn't pan out when the better trials are done.

So, it is kind of a cautionary word, but I realize the limitations.

DR. HOLLINGER: Dr. Boyle.

DR. BOYLE: Let me clarify one of the things that Joel is raising in terms of resources, because it is going to give you a perspective on what we are talking about.

As we indicated earlier, there is a shortage, and the shortage will grow because of the growing number of persons who are using IVIG even among the immune deficient patients.

As was indicated earlier, there may be eight or 10 companies that are willing to bring new products in if they can get licensed. Each one of those products requires a trial. If, in fact, you enroll all available immune deficient patients in the gold standard trial, you would successfully bring one new product into the market, and the rest would be left on the outside.

So, one of the things in terms of thinking through sample designs, looking at the fact that they will have to

be repeated trials over the next few years to address the issue of the shortage in the marketplace.

In terms of the trials themselves, we know from the data available, the data that has been presented in the literature, that the difference between IVIG and no IVIG can be demonstrated with a sample size of 10 or 15 per arm, the difference is that extreme.

Some of the other things that were presented as concerns, for instance, the issue of the ability to detect increased renal failure is so rare that no single trial is ever going to be able to identify that.

You will only be able to identify those types or things with post-marketing surveillance. Consequently, what we are basically saying is that even a small sample size will demonstrate whether we have got effective IVIG or ice water. No sample size that is feasible can detect the rare events. That is going to have to be done with post-marketing surveillance.

What we are trying to find is an intermediate sample size where repeated trials are practical for different products, so that hopefully, we can address the issue of the shortage because to end with a metaphor, we are talking about not just IVIG, or immune deficient patients, we are talking about other medical necessities, and given the situation, we are all starting to look like the Donner

party, you know, eyeing each other as meat for the winner, and we would just as soon find our way out and back to civilization.

DR. LACHENBRUCH: In response to Joel, the sample sizes of 28 and 80, the 28 was based on the number of infections per patient, being able to pick up a rise from 1 to 2 per year, basically a change, whereas, without it I think we were talking about 18 to 20 per year. Dr. Stiehm and others can tell me I am full of baloney. The 80 patients per arm was based on detecting a difference of 0.25 to 0.45 in the proportion of patients who had no infections.

So, the fever days was something that has literally been developed quite, quite recently, so I would just point out that a lot of these things are precisely what you are worried about.

MR. MORAN: I would also like to say there have been conversations between IDF and National Institutes of Health and industry on the points that you raised. The distinction I would make is that if one imagines several, multiple trials going on simultaneously, there are opportunities to do some science that needs to be done to develop a gold standard that everyone would salute.

In fact, NIH has expressed interest, as has industry, as have our investigators. The distinction is the difference between requirements for licensure in a specific

trial and data that can be gathered and collected during in the course of doing a trial that does not have an effect on licensure per se, but gets to the goal that you just point out, and there is a lot of interest in doing that in these studies.

DR. VERTER: One follow up to Dr. Lachenbruch. I figured that out, and I worked it out while you were sitting there. But what I was referring to, I didn't refer to it quite well, was the delta in your calculation is very large, and I am a little concerned about that.

DR. HOLLINGER: Richard, just one question on the fever. At what level are you looking at?

DR. STIEHM: I would suppose 100 degrees, and I agree that fever by itself is a surrogate, but on the other hand, fever with some sort of other manifestation of infection, such as cough. The problem with immune deficiency patients, many of them are chronically ill, they have chronic sinusitis that is almost incurable, and so that it is very difficult to document trivial infections.

So, my suggestion, as you heard, was to say days of fever, and, of course, that would assume that you would rule out other causes of fever, for example, if they had taken a drug and got a drug reaction, so you could eliminate those.

DR. HOLLINGER: Maybe 100 degrees is a little too

low, I mean for these patients. Maybe you would want to look at something a little higher than that.

DR. STIEHM: Well, that needs to be negotiated.

MR. DUBIN: Just to step back for a second and come at it from maybe a larger overview, I think obviously one difference we see is in these patients the need is more critical. In hemophilia, we can let a bleed go, we can proportion resources a little differently, we can prioritize factor for use in head bleeds, things of that nature.

I think in parts of this community, that is not real, and yet at the same time, we are looking at a marketplace that has been unable to deliver. Fifty percent, almost 50 percent are off-line, at least two of the major manufacturers are off-line, and the marketplace has been unable to supply enough product.

At the same time, we as consumers demand enough product to get the job done, but then we as consumers want to beat the FDA over the head when something goes wrong. I am trying to step back on this one and take an overview, because I think something we have learned at the table is this is consistently a cost-benefit analysis, and I don't necessarily mean just an economic or an economic cost-benefit, but when you start talking about fast-tracking or moving quicker, people are going to get hurt.

The new diabetes drug is an example. I think we

don't always step back and look at this and think about it, and I am not arguing against doing it at all, but I think this analysis is out of the picture. We raised in a meeting with the Commissioner recently the question of post-marketing surveillance of AIDS drugs because we are getting daily reports, our phones, from people in hemophilia with AIDS who are seeing some pretty significant and dangerous side effects to some parts of the cocktail.

But I think in some way we are saying to FDA fast-track it, then, we are wanting to kill them when it doesn't go right. Somehow I think we have to begin to balance this, and I think somewhere in this equation, while we have the specific discussions of designing trials and figuring out how to do it, we also have to have some overview picture, discussion that we don't always seem to have about what the tradeoffs are and how we are going to address the larger questions that we seem to keep running up to, the marketplace being on one hand, being unable to deliver the needs of clients and patients in a number of communities, and I wanted to make sure we put that on the table.

This has been a learning experience for those of us in hemophilia that have come to this table. We have really had to look at this larger picture more and more, and understand it more.

DR. HOLLINGER: Any other comments from the

committee? Questions? Responses? Dr. Mitchell.

DR. MITCHELL: I like the idea of having fever as an endpoint, but then the question is how do you define fever. The temperature, as you know, varies on the time of the day that you take it, that you measure your temperature. It is likely to be lower in the mornings than it is in the evenings.

I just think that that needs to be taken into account. There needs to be some kind of standardization of what fever is, and 100 seems kind of low to me also. Those are just my comments.

DR. HOLLINGER: Dr. Macik.

DR. MACIK: The concern I have, I think that I don't have any trouble with fever, don't deal with pediatric patients, but I do deal with an awful lot of patients that we use an awful lot of immunoglobulin, and it seems like what is happening is we are focusing on getting a trial going for a small subset of people, so that we can get products licensed, which is good because they need it.

But how do we know that, because we focused in, you know, we know that once a product is available, it goes wherever it is going to go. Do we know that there is some protection that just because this group provided the study that allowed a product to come on market, that this group will have a product when it is all done, that it won't all

just be siphoned off to all the other indications.

It is nice because this group is small, it has an easy-to-look-at endpoint relatively, fever, infection, so from a company's standpoint or the FDA's standpoint here is a nice group you can go in and do a reasonably fast study, you know that they die without the product, and you know that most products probably are going to be the same, you know, it is easy to look at.

But when all this is said and done, and you bring more product on, are they going to have product after all? Is there any way that you can assure supply? We are focusing in on supply here, but it is equally deadly for the severe ITP patient that doesn't have their IVIG.

These are populations also, and this is a much larger use population than the immune patient. I hate to see something be too slow getting in new products, and also to come in on one indication, and perhaps have a patient turned away because the pharmacy--it doesn't surprise me, a blood banker may not know there is an IVIG shortage because most of the products are handled through pharmacy now--but that they would say, well, we are going to send this to the indicated use, and not give it to the non-indicated use.

This is part of the bigger picture that I think Corey was bringing up. I think it is great to design trials, but we also have to look at where we are going, what

are we going to accomplish when the trial is over, are the group that sacrificed to get this trial done going to benefit when the trial is all finished.

MR. MORAN: I would just like to make one quick comment, and that is that the trial that is being proposed or the sample protocol really, is to my knowledge--and FDA is in the room--it is far more rigorous than any of the trials for the currently six licensed brands.

So, we are not wanting to create the impression--and I think Jerry reiterated it, but I will just repeat this again--that this is kind of substandard trial. The one that was proposed this morning by the IDF is far more rigorous than any of the trials that licensed the current six brands in the U.S market. Your other points I agree with completely.

DR. MACIK: I didn't mean to--I don't think the trial is a problem. I think it is a fine trial. I don't have any problems saying it is a substandard trial. I am just saying that what I fear is that your population of patients are going to be used as the guinea pigs over and over again, as the entryway for companies to get into the market, and then your patients, when it is all said and done, may not benefit because the market goes to the other indications.

DR. WINKELSTEIN: You raise a very important

point, and we don't articulate this as often as we should. We talk about off-label, on-label, efficacious versus non-efficacious, and we should also include in the equation whether there are substitute or alternative therapies short term, long term.

For these patients, there literally is no substitute or alternative therapy, whereas, for some of the other indications, not all, but some of the other indications, one can use an alternative therapy on occasion because alternative therapies existed before the development of IVIG.

How to control distribution is something that I find very awkward to talk about because I am not sure that I would know how to do it even if I had the control over the distribution, and as Tom Moran said, the Foundation is not especially interested in trying to prioritize use in that way because we certainly want to compete for a limited resource.

Having said that, I think that practicing physicians have to remember that there is no alternative to the use of this medication in these patients.

DR. MACIK: But it is not necessarily the practicing physician that makes the rationing choice. That is a problem. I guess my question is, is that we expending a lot of energy about trying to get something quickly in to

this group, but why aren't we developing protocols for the ITP as an entryway for companies to get IVIG on the market, because this is a huge group that there is many more patients available, and if part of the purpose of this is to get product in the market, then, let's look at other ways in addition to your trial that we can get product into the product.

DR. HOLLINGER: I am going to end the discussion at this point. We are at the break for this session. So, we will begin again at 10:30. It is now 10:05.

[Recess.]

DR. SMALLWOOD: We are reconvening and we are starting with our final topic for today.

Dr. Hollinger.

DR. HOLLINGER: Thank you.

The final topic for this meeting is a topic we have visited before, and it was presented to us I guess it was last time, and I think there were some issues regarding an algorithm and putting it together again. This will be on the Inadvertent Contamination of Plasma Pools for Fractionation (HIV, HBV, HCV), and Review of Algorithm. Dr. Tabor is going to be our only speaker today. You have three hours, Ed.

V. Inadvertent Contamination of Plasma Pools for Fractionation (HIV, HBV, HCV): Review of Algorithm

DR. TABOR: I always like people to get to their planes on time.

[Slide.]

We have discussed inadvertent contamination at BPAC three times before. In June of 1997, we discussed those cases of inadvertent contamination in which a donor who prior to donation tested negative for all the tests that we require or recommend is discovered to, in fact, have had a positive test after the plasma has been pooled.

At the June 1997 meeting of BPAC, the staff of CBER presented data showing that the processes of manufacture of plasma derivatives that includes steps to remove and inactivate the viruses that were under discussion, that is, HBV, HCV, and HIV, in fact, are more than adequate to handle any amount of contamination, any amount of virus that could be present due to an inadvertent contamination, also documented that there had been no transmission of any of these three viruses since 1987 except for the so-called Gamma Gard incident in 1993 to 1994, and no transmissions at all since 1994.

Then, in September of 1997, we dealt with another type of inadvertent contamination, the situation in which a donor who has answered in the negative to all of the donor questions that are designed to eliminate donors who might be infected with one of these viruses and whose plasma had

tested negative for all the tests that we recommend or require for these three viruses, is discovered to, in fact, to have answered the questionnaire incorrectly or is otherwise discovered to be a member of a risk group after this plasma has been pooled.

Again, we discussed all aspects of removal and inactivation related to this type of inadvertent contamination. That was in September 1997.

Then, in December 1998, we brought to BPAC a proposed algorithm for the first type of inadvertent contamination, that is, the type in which a test is discovered to have been positive, and the discovery is made after pooling.

In the discussion at BPAC in December 1998, the committee made some recommendations for changes that would improve the algorithm, and also in the discussion, some members of the committee suggested that we modify the algorithm to address the other type of inadvertent contamination, the type in which a risk factor is discovered after pooling.

Members of the committee suggested that, in fact, the situation was not all that different, and in addition, you have negative test results, and so today I am going to be showing you some proposed algorithms for both of these types of inadvertent contamination.

Now, as I said, we are talking only about inadvertent contamination by hepatitis B virus, hepatitis C virus, and human immunodeficiency virus 1 and 2, and we throughout the past two years have limited our discussion to these three viruses in order to be able to handle what is really a very, very complex topic.

The reason we chose these three viruses is these are viruses for which we have tests available, and they are also viruses for which viral inactivation and removal procedures are present in the manufacturing processes for plasma derivatives.

As I have said, we have divided it at present into two categories, those involving test issues where a test is discovered to be positive, and those involving risk factors or donor issues, and for these three viruses, risk factor issues or donor issues are really window period issues because we are talking about individuals who are negative for very sensitive tests to detect hepatitis B virus, hepatitis C virus, and human immunodefiency virus.

So, if they have answered one of the donor questions incorrectly, there is obviously in that situation a small chance that they could be infected, but if the tests are all negative, it means if they are infected, they are in the window period.

[Slide.]

The June 1997 BPAC, the follow recommendations were made by the committee. The first recommendation was when notified of inadvertent contamination of a fractionation pool, with units reactive for HBV, HCV, or HIV, FDA should immediate and uniformly quarantine or recall all products as a first step, and then determine regulatory action based on an assessment of product risk, for instance, the impact of virus removal or inactivation.

So, basically, what BPAC was recommending was that we act on a case-by-case basis, and that we take into account the degree to which the removal and inactivation steps would impact on any virus that could be present.

[Slide.]

The second recommendation in June 1997 was in such circumstances, FDA should not modify its actions on the basis of product shortages.

[Slide.]

The third recommendation in June 1997 was that in such circumstances, FDA should not make any distinction between in-process and final products.

[Slide.]

In September 1997, again just to remind you, when we were discussing the situation in which it is discovered after pooling that one of the donors answered a donor question incorrectly, BPAC recommended that in cases of

inadvertent contamination of a pool, consisting of units negative for HIV, HBV, or HCV markers, containing unit from a donor with a subsequently discovered risk factor, FDA should determine regulatory action based on an assessment of product risk.

[Slide.]

They further recommended that an assessment of product risk should consider the maximum level of contamination that could occur, and the capability for virus removal and inactivation in the manufacturing processes for the derivative.

[Slide.]

Also, in September 1997, BPAC recommended that quarantine of distributed product cannot be dispensed with even if there has been a record of GMP compliance by the company.

And what they meant there--I guess I should say what you meant there--was that just because the company has always had a good GMP record does not mean we can assume that the GMP record for this particular lot was also good, that we have to look at GMPs.

You also recommended that a negative nucleic acid test on the donor pool or subsequent test negative donations by the donor could in some circumstances obviate the need to destroy the product.

[Slide.]

I am going to show you some proposed algorithms, and for these algorithms, we defined a positive test as a repeatedly reactive screen accompanied by either a positive supplemental or a situation in which the supplemental was not done.

That would apply to tests for the following serologic markers: HBsAg, Anti-HCV, Anti-HIV 1 and 2, or HIV p24 antigen. We also are defining as positive, but treated in a slightly different way, as you will see on the algorithm, investigational tests, and at the present time we are really talking about primarily NAT tests that are positive on pool or minipool, or any of the serologic tests applied to a pool or minipool.

[Slide.]

This is the first algorithm, and this algorithm applies to whole blood, and to some extent--I realize some of you in the back cannot see this--I assume that all of the committee members received a copy of this with your packet. Unfortunately, those of you in the back will either have to move up or just listen. We are not permitted to distribute this at this stage of its development.

A positive test is discovered, and there are two footnotes there. The first footnote, Footnote A, states that, "Anytime a confirmed positive test result is belatedly

found on an individual unit, the unit must be destroyed if it has not yet been pooled." That makes sense obviously.

Footnote B is, "if the positive is a result from testing a pool, the result should be repeated to verify that it is correct."

Well, if this unit has not yet been transfused, it should be destroyed and if it has already been shipped, the consignee should be notified to destroy it. If it is the result of a positive, using a licensed test, the donor should be deferred, prior collections should be quarantined, and if it involves HCV or HIV, a lookback should take place.

There is a footnote there, which is Footnote H, and for the purposes of these algorithms, I am using the word "lookback" to indicate both lookback and recipient notification.

If the unit has already been tranfused, the recipient should be notified, the donor should be deferred obviously if it involves a licensed test, prior collections should be quarantined, lookback should occur if it involved HCV or HIV, and if recovered plasma has been shipped, the consignee should be notified and you should then follow the second algorithm, which is the algorithm for plasma.

In a minute I am going to show you portions of this to make it easier to follow, but I am showing you this way.

Is it possible to focus that slightly?

DR. HOLLINGER: I don't think it matters, Ed.

[Laughter.]

DR. TABOR: At some level, we would all be happy not to do algorithms, but the blood and plasma community want them. I think we have got a workable algorithm here, and those of you who have copies can follow the printed copies.

[Slide.]

This is the algorithm for a positive test discovered on plasma. I am going to divide it up into three parts for discussion, the first part being the top portion, and then I am going to show you the lower left 60 percent, and then the lower right 60 percent.

Well, when a positive test is discovered on a pool or a unit of plasma, again, the same footnotes A and B that were on the previous algorithm, the most important being A, that if the units has not yet been pooled, it should be destroyed. That is also shown over here.

If it has not yet been pooled, it should be destroyed. If it is a licensed test, the donor should be deferred, prior collections quarantined, and lookback for HCV and HIV.

If the unit has been pooled or processed, the pool or the products should be quarantined, and if it has been

shipped, the consignee should be notified to quarantine the products.

We are now looking at the lower lefthand portion of the algorithm. If a sample of the original unit is available, and a supplemental test has not been done, we are suggesting that it is possible to perform a belated supplemental test on the original unit.

Obviously, if the supplemental test has been done and it is either positive or indeterminate, then, the donor should be presumed to be infected for the purposes of this algorithm, but if it has not been done, and a sample of the original unit exists, a supplemental test can be done now. If it is negative, it is assumed that the screening test was false positive, and the pool or product can be released.

If the supplemental test is positive or indeterminate, one must assume that for the purposes of this process that the donor was infected. If it was a licensed test, the donor should be deferred, prior collections quarantined, and lookback should be done in the cases of HCV and HIV.

At this point, a comprehensive GMP evaluation should be done. Footnote D is there to define what we mean by a comprehensive GMP evaluation. A comprehensive GMP evaluation should be done by the fractionator to verify that virus removal and inactivation occurred. GMP inspection by

FDA would be done as needed. Fractionators will send reports to FDA listing all GMP evaluations that were conducted because of inadvertent contamination.

If the GMPs were shown to have been followed and virus inactivation and removal steps have been reliably done, then, the pool or product can be released. This is based on the data that I presented in the June 1997 BPAC and updated in December 1998, showing that the virus removal and inactivation steps that are currently in place for all products licensed in the United States are adequate to inactivate or remove more than the amount of virus that could be present due to inadvertent contamination by any of these three viruses.

If the GMPs are not adequate, in general, the pool or product should be destroyed and a recall issued. There is a footnote, footnote F. . There are some cases in which reprocessing of the pool or product is permitted in situations approved by FDA, so in those situations, reprocessing would be permitted.

[Slide.]

I am now moving to the lower righthand portion. This portion deals with a positive on an investigational test or other situations in which the original samples was not available for retesting.

If the positive was on an investigational test,

and footnote C there states that disposition of the unit and the status of the donor should take place or should be evaluated as defined in each IND.

So, what you have to do with the positive unit and what you have to do with the donor would have been determined in discussions with FDA at the time that the IND was approved.

If there is a positive on an investigational test or an indeterminate result, it should be in situations where an indeterminate can exist, the donor should be presumed to be infected and then you enter the GMP portion of the algorithm again, you should quarantine prior collections and lookbacks occur in cases where HCV or HIV are involved.

If a supplemental test had already been done, obviously, you would consider the donor infected. If a supplemental test had not been done on the original sample, and no sample of the original was available, we are suggesting that it is possible to test a later sample for all appropriate tests for the virus in question.

I guess an example of this would be, for instance, suppose you had a repeat reactive for anti-HCV, but no supplemental test was done, and no original sample was available, but the material from the donor was already in a pool or final product, if you were able to locate the donor, bring the donor in, and do all available tests, all tests

that were scientifically thought to be reasonable to determine that this donor had never had that virus in question, that we would agree to look at that as a possible way to lead to further consideration of that pool.

If all of these tests on the later sample were negative, and the virus in question was HCV or HIV, you would assume that the original test was a false positive, and the pool or product should be released.

However, if all the tests on the later sample were negative, and the virus in question was HBV, we feel that you would still have to enter the GMP evaluation cycle, and the reason for that is given in footnote E, which states that, "Regardless of the results of HBV testing of a later sample, the remote possibility of a 'silent HBV infection' makes it necessary to verify that GMPs were followed."

Those of you who are familiar with the literature are aware that at least in certain cases, there have been reports of the detection of HBV DNA in individuals who did not have hepatitis B surface antigen. Most of those reports have been in liver cancer patients, but there are some other reports that suggest that in order to be certain that any remote possibility of HBV being present was properly dealt with, that you should enter the GMP evaluation cycle to make sure that any virus that could have been present was properly inactivated or removed.

So, again, in situations where you have a positive investigational test, a positive supplemental test, or if no supplemental test is present, but no later samples available for testing, or were later sampled, was being tested and all results were negative, but the virus in question was HBV, you would then do a comprehensive GMP evaluation of the same type I described before, that is, comprehensive GMP evaluation by the fractionator to verify the virus removal and inactivation steps, and in some cases where felt necessary, FDA would do a GMP inspection, and the reports would be sent to FDA by the fractionators for GMP evaluations done for this purpose.

If the GMPs are adequate, the pool or product can be released; if not adequate, they should be destroyed except where reprocessing is permitted, and a recall should be issued.

Now, I am going to go ahead to the next algorithms and we can come back to these for discussion.

[Slide.]

The algorithms for risk factors or risk factor type inadvertent contamination are a little simpler. This is the algorithm for dealing with the discovery of a positive risk factor on a unit of whole blood which could involve recovered plasma, and when a risk factor is discovered, if the unit has not yet been transfused, the

unit should be destroyed or any consignee should be notified to destroy it. The donor should be deferred, and there is a footnote there, footnote G.

"The donor must be deferred. In addition, if the donor can be located, all licensed tests for markers of HCV and HIV should be done on a newly obtained serum sample. If any tests for HCV or HIV are positive or indeterminate, lookback should be conducted, and all prior collections for this donor should be quarantined."

If the unit has already been transfused, the recipient should be notified, the donor deferred, and in circumstances that I just described, under footnote G, there are some situations where lookback should be done, quarantine of prior collections should take place, and any consignees of recovered plasma should be notified.

[Slide.]

Then the algorithm for dealing with plasma should be addressed. For source plasma units or recovered plasma units in which it is discovered that a risk factor is present that was not picked up during an initial questioning of the donor, as I said, if it has not yet been pooled, the unit should be destroyed, and other appropriate steps taken.

But if the unit has been pooled or processed, the pool or product should be quarantined, and if the final products have been shipped, the consignee should be notified

to quarantine the products.

The donor should be deferred, and if he can be brought back for obtaining a later sample, further testing should be done and if the tests are positive for HCV or HIV, lookback should take place. Quarantine of prior collections should occur, a comprehensive GMP evaluation should be done by the fractionator with inspections by FDA as needed. If the GMPs are adequate, the pool or product can be released. If the GMPs are not adequate, the pool or product should be destroyed and a recall issued.

[Slide.]

Now, we are in a very rapidly moving field here, as you heard yesterday. The situation is changing more rapidly than at any previous time in the history of regulation of blood products, and we now have nucleic acid testing of minipools being done under IND. I think at some point in the future we are going to have nucleic acid testing of individual units when the technology is available and affordable.

When nucleic acid testing of minipools becomes licensed, and when nucleic acid testing of individual units is possible and licensed, we are going to have to reevaluate these paradigms. We are going to have to have modifications made to the algorithms.

I think that the use of nucleic acid testing of

minipools that is going on today and will increase during the course of 1999 is going to greatly reduce the incidence of cases of inadvertent contamination, and we will modify these algorithms as needed in the future.

[Slide.]

I have the questions for the committee here, but basically, we are asking the committee in two questions whether these algorithms are appropriate. So, rather than my reading the questions at the moment, let me just go back to the algorithms and beginning with the algorithm for the situations where there is a positive test discovered after pooling, and ask the committee if there is any discussion you would like to offer and any suggestions you would like to make for further modification of the proposed algorithm.

DR. HOLLINGER: Ed, before we could do that, we have one person in the open public hearing who wants to speak, and then we can go through that, and then I think we can come back. Is that all right with you?

DR. TABOR: That is fine.

DR. HOLLINGER: There is one person who asked to speak from the IPPIA, Jason Bablak.

Open Public Hearing

MR. BABLAK: Good morning. My name is Jason Bablak. I am Director of Regulatory Affairs for the International Plasma Products Industry Association.

Our members produce approximately 80 percent of the plasma derivatives for the U.S. market and approximately 60 percent worldwide.

I would like to briefly address the subject of inadvertent contamination and respond to at least the second half of the FDA proposed algorithm.

The subject of inadvertent contamination has been discussed by this committee several times. Today, I would like to limit my comments to the second part of Dr. Tabor's discussion.

I would like to talk today about instances when a fractionation pool contains a unit from a donor with a subsequently discovered risk factor that would have disqualified him had it been known at the time of donation.

A couple of things I would like to point out about these. First of all, it is important to keep in mind that all these units have passed all the serological screening tests in full compliance with FDA regulations, and these tests include hepatitis B surface antigen, antibodies to HIV-1 and 2, the HIV p24 antigen test, and antibodies to hepatitis C.

I would like to also say that our members are implementing nucleic acid testing for these viruses under the FDA's IND procedure, and also that it is important to point out that each manufacturer has robust procedures in

place that are designed to ensure that documentation for all released lots has been thoroughly reviewed to assure quality control and adherence to good manufacturing processes.

As part of the safety process in plasma manufacturing, all donors are asked a series of questions and must pass a brief physical exam prior to donating in an effort to assure the collection of high quality plasma and to screen for any potential risk factors.

Donor screening is the first of many safety layers throughout the manufacturing process and works to limit potential viral contamination by eliminating donors who theoretically could be in the early stages of infection as a result of certain risk factors.

Our industry has further enhanced this safety layer by introducing the qualified donor standard which ensures that every donor has tested negative at least two times before his plasma is used for further manufacturing.

Occasionally, these risk factors are not discovered until after a donor has already donated. The discovery of these risk factors after a donation, also known as post-donation information, can happen in many ways. These can include instances where the donor answers a screening question differently or otherwise identifies a risk factor during a later donation that would have excluded him from making the previous donation had that information

been known at the time.

Once this information becomes available, the firm will perform a lookback to identify units affected by this information. FDA regulations require that firms perform a lookback of up to 12 months depending on that particular situation, and that is used to identify all units with that particular post-donation information report.

For source plasma donors who are permitted to donate up to two times per week, this can equate to a large number of units that need to be traced even though all these units have already tested negative.

All the units and inventory are captured and removed from further processing before they are pooled. The introduction of our voluntary 60-day hold allows us to capture many more units than we did before this was instituted.

Additionally, the commitment of our industry to perform nucleic acid testing further reduces the potential of infectious but undetectable window period units from entering the manufacturing process.

The processing of plasma derivatives includes steps that remove or inactivate certain viruses that may be serologically undetectable. These virus inactivation procedures are so robust that the epidemiological data shows no plasma derivative produced by a U.S. manufacturer,

licensed manufacturer, has transmitted HIV, hepatitis B, or hepatitis C since the introduction of the current procedures in use by our members.

Our members also follow strict procedures for release of finished products including a comprehensive quality review of the entire record for each lot. A typical batch release will involve the review of thousands of data points collected throughout the manufacturing process.

The final product review encompasses all process parameters, in process and final specifications, testing and compliance with validation and FDA licensing requirements including all the data related to the viral inactivation processes that I just described.

After that, all products are subject to release by CBER, as well. Only products that meet all final requirements are distributed by a company.

Dr. Tabor just presented an algorithm describing actions that he believes need to be taken when instances of post-donation information are discovered including quarantining lots affected by a post-donation information report pending another GMP investigation.

In an effort to understand how this recommendation would affect the supply of these products, our members collected data on the frequency of post-donation information reports and the number of units, manufacturing pools, and

final products that would be affected by this policy.

The total number of post-donation information units is small relative to the total number of units processed by our members. It is somewhere around 2700ths of a percent of the total units collected and processed.

As everyone knows, it is necessary to pool plasma units in order to manufacture plasma derivatives. Our data shows that through this process, one post-donation information unit could easily be linked to many manufacturing pools, leading to nearly 100 percent of final lots being affected at some point during the life of that particular product.

Under the plan for quarantining these lots, virtually all the plasma derivatives manufactured by our members will be placed on quarantine and unavailable for patient use pending the result of the GMP inspection.

As I stated earlier, each company reviews the batch records for each lot as part of a comprehensive quality assurance program. Firms also monitor quality through its lifetime by stability testing program and by investigating product technical complaints and reported adverse clinical experience. The FDA also releases each lot before it is distributed to patients.

These release procedures employed by our members, when combined with the viral clearance procedures included

in the manufacturing process, provide concrete assurance of product safety as the epidemiological data presented in the past has shown.

The additional measures discussed here will not add to the safety of these products. They will, however, have a significant impact on the availability of these products for patients.

Thank you and I would be happy to answer any questions the committee may have.

DR. TABOR: Blaine, could I add something? The information supplied by IPPIA is very interesting and I think will come into your discussion, but I want to emphasize one semantic point.

We are not introducing really any new procedures here. Inadvertent contamination is an ongoing problem that we have had to deal with throughout several decades at FDA, and what we are trying to do is have some kind of organized way of dealing with it that is acceptable to the Advisory Committee and to the public.

So, what we have got here is a proposed algorithm, but it is a proposed algorithm. We are not really proposing new procedures as such. The algorithm is really there for discussion.

DR. HOLLINGER: Mr. Bablak, does your organization feel that there is something different than what Dr. Tabor

has just said, because I think that is correct, what he has proposed is just trying to look at an algorithm to do this.

Do you see anything different?

MR. BABLAK: I think one of the major differences that we are concerned about, and maybe it hasn't been discussed completely, is the issue of putting the products or the pools on quarantine until such additional actions are taken.

If you are talking about products that are released, putting them on quarantine, I think, one, equates to a recall, and secondly, if you are putting them on quarantine before they are released pending some additional inspection of either GMP or viral clearance procedures, then, there will be an additional delay in releasing these products.

DR. HOLLINGER: Just a question and then Dr. Epstein wants to say a note here. You don't put products on quarantine, then, if you get post-donation information anyway?

MR. BABLAK: I think what happens right now is that each is done on a case-by-case basis, and certainly products that have been released are not recalled at this time.

DR. HOLLINGER: I think he is talking about quarantine, not recall right now.

MR. BABLAK: There is no mechanism for quarantining already released products.

DR. HOLLINGER: Okay. Understood.

DR. EPSTEIN: I think that the algorithm that is being proposed does suggest an extension of current policy because it is lumping all risk factors. I think that what Dr. Tabor said is correct, that there have been occasions where we have taken these kinds of actions based on risk factors.

It is just that the algorithm lumps them all. So, for example, we had a situation in which there was post-donation information that a donor who was screened negative had donated red cells, platelets, and plasma, and his red cells and platelets transmitted HIV.

At that point, we had risk information about the plasma even though it was a marker-negative donation, we knew for a fact that that was a window period donation. So, although it was not marker-positive and would fall in the risk factor category, we felt that we should be taking all of the stringent steps that are outlined in the algorithm.

On the other hand, I think what is disturbing IPPIA and as stated by Mr. Bablak, is that if we lump all risk factors into that category, then, you have a different scenario because of the probability that the donor is in the window may, in fact, be very low based on some of the risk

factor information compared to other risk factor information.

So, I think that the answer is that everybody is right. What Mr. Bablak is saying is, well, aren't we applying case-by-case decisionmaking, and that is true, and what Ed is saying is aren't we applying this algorithm to risk factor, and sometimes that is also true.

So, I think that the trick here is that we need to have a little bit of clarity about when is a risk factor a trigger for this, is it always a trigger for retrieving all prior components and notifying the donor and quarantining the products, and doing recalls, et cetera. That may be overkill even though it is sometimes exactly what we want.

DR. HOLLINGER: I suppose it would be similar to the fact if somebody called up and said three days later or four days later that he had eaten at a restaurant where now everybody has got hepatitis A, and he ate the same thing everybody else did. That is a little different than if he said I had hepatitis, I forgot to tell you, but I had hepatitis back in 1965 or 1970 possibly. I mean those would be a comparable type thing where you would have to look at it individually.

DR. TABOR: I would suggest that for the discussion that we take up the algorithms dealing with positive tests first because you have seen those, and it

ought to be possible to dispense with those more rapidly than the ones for risk factors which you have not seen before and which are really being presented for the kind of discussion that Mr. Bablak is bringing us.

DR. HOLLINGER: We can close the public hearing. Is there anyone else in the audience who wishes to speak during the time that is open for public hearing? If so, please identify yourself. If not, we are going to close the public hearing and then we will get started with the discussion.

DR. MITCHELL: I have a question for Mr. Bablak.

DR. HOLLINGER: We can go back and ask the questions. I just want to make sure that there is not someone else here from another organization who wants to speak.

If not, then, I am going to close the public hearing portion of this, and we can still ask questions of everyone as we have done in the past.

Committee Discussion

DR. HOLLINGER: I guess the question is, Ed, you would like to at least go over the algorithms first and deal with those initially, and then come back and open it up?

DR. TABOR: I think anything is okay, but I do think if we divide them into the ones you have seen before and the ones you haven't seen before, maybe we can be more

likely to cross one of them off our list.

DR. HOLLINGER: Burning questions here with a couple of committee members, or actually there is three, three burning questions here among this group.

Go ahead, John.

DR. BOYLE: I just wanted to clarify we are only talking about risk factors for HBV, HCV, and HIV, we are not talking about, for instance, a risk factor for CJD that comes up later?

DR. TABOR: That is correct. The topic is just too broad and complex to deal with that. If you approve these algorithms as written, unfortunately, that will mean that we will probably come back to you with the other category next time.

DR. HOLLINGER: So, again, the risk factor you have dealt with here is just hepatitis and HIV risk factors.

DR. TABOR: Just hepatitis B and C and HIV.

DR. HOLLINGER: Post-donational risk factors information.

DR. TABOR: That is correct, and hepatitis A would be in the other category.

DR. HOLLINGER: Dr. Nelson.

DR. NELSON: What do you regard as a supplemental test for hepatitis C? Is it RIBA and PCR or the cutoff, signal to cutoff?

DR. TABOR: What was intended was a licensed supplemental test, not talking about cutoffs which are really only supplemental for the purposes of the HCV lookback. We are talking about a licensed supplemental test.

DR. NELSON: The last time I tried to check on the RIBA-II, it was over $200. It is useless.

DR. TABOR: The RIBA-II kit, the price charged by a manufacturer for the RIBA-II kit to people who do not get a government or university discount, I think is something like $4,000 for a kit that tests 28 samples and has a couple of controls.

DR. NELSON: I took it out of the grant at that point.

DR. TABOR: Nevertheless, these kits are being used by blood banks and plasma collectors. I mean they are already being used, and they should be used when you have a repeat positive screening test in order for the donor to know whether they are infected or not.

DR. HOLLINGER: Dr. Stroncek.

DR. STRONCEK: On your algorithm, you have some of these arms where you won't do an inspection to look at CGMPs, but will the FDA know somehow when a manufacturer has released product based on this algorithm through the error and accident report?

The second question is how broad is the intent to use this? I am not sure if this happens anymore, but in the old days the issues were an FDA inspector would come out and look at records and say for various reasons, well, the blood center had a run for infectious disease testing that they didn't think was valid, so basically, then, those test results are considered positive and you have to recall the plasma.

Could you use this algorithm to bring those donors back? To me, that is a different situation.

DR. TABOR: First of all, let me answer and then maybe ask Dr. Epstein to comment, as well.

In the discussion at BPAC in December, we touched on the GMP issue a little bit, and in our discussions in FDA, we came to the realization that to have actual GMP inspections by FDA in each and every case would just be completely impossible. We are in a situation with markedly reduced resources in FDA.

We have had a couple of years running now with 25 to 33 percent budget cuts. We do not have the inspectors to do that, and it would prevent all the other inspections, and everything would come to a total standstill.

So, as a result, we added in the footnote that we expected the fractionator or whoever was involved to look at their own records to make sure that there were no GMP

violations in steps that would affect virus removal or inactivation.

They would report to us, and they would have a very short time frame on the reporting as they do for error and accident reporting, and it would be up to us whether we required an inspection.

DR. HOLLINGER: This is a real travesty. As Ed has said, you know, I mean we are asking the FDA to do more and more things, and giving them less and less money. I mean this is really ridiculous, and we sit here at these meetings all the time talking about the importance of these things, like GMP, and stuff like this, and then cut the budget for the FDA without cutting budgets for other organizations. It's crazy.

Mark, did you have something?

DR. MITCHELL: Yes, I had a couple of things. One is to follow up on that. How often now do you do an inspection for GMP, and are they regular or are they irregular?

DR. TABOR: I would like to get someone else to answer that. I don't know if anyone from Compliance in the audience, probably not. Can I ask Dr. Epstein to answer?

DR. EPSTEIN: The requirement under statute is every two years, biannually, however the compliance program that we have in place does adjust the frequency according to

the compliance history of the firm. I am just talking about routine periodic inspecting. There are also for-cause inspections that are done as needed.

Also, in the last several years, we have been doing more frequent inspecting of the fractionators because of the recognition that there was an industrywide problem with GMP compliance. So, the general answer is that certainly prospectively, it would be no less than every other year, however, the reality is that they have been a lot more frequent in the last couple of years, and that will go on until the GMP problems are resolved.

DR. HOLLINGER: Dr. Khabbaz.

DR. KHABBAZ: I have a couple of questions relating to the risk factor algorithm.

DR. TABOR: It would be nicer to discuss the positive test algorithms first, if that is possible.

DR. HOLLINGER: Dr. Bianco?

DR. BIANCO: I had a question that is a contribution, it is not part of a public statement, or an attempt to make a contribution.

I think that a concern that all of us have is on how you translate an algorithm to a compliance action. What I was going to suggest is that as the discussion goes on, we turn the charts that Dr. Tabor has created upside down.

Essentially, the most important step in all that

is not to go through indeterminate or positive test results, or this and that, it is the statement that he made that if you achieve compliance, it's okay, that the product is okay in most of those situations.

So, that probably should be the first step, and then if it is documented to the satisfaction of the agency, and obviously under the eyes of the public, everything else becomes much smaller, and all the running around with quarantines and product recalls, and all that becomes much more reduced.

This is probably that is where the resources should be if there is a need for the agency to make those inspections, but I am sure that the fractionators and the other organizations that provide, for instance, the recovered plasma in the blood centers have the responsibility to have their own staff and their own quality programs to do those CGMPs to the satisfaction of the agency.

DR. HOLLINGER: I would tend to agree with you if one could have the personnel at the FDA to do the GMP testing, and as Ed has mentioned in one of his slides, the fact that someone has been in compliance before doesn't necessarily mean that they are complying at the present time, so if you could start something initially and eliminate it even before you get to which I would say more

labor intensive efforts, then, I think it would be a better approach.

DR. BIANCO: The fractionators certainly could contribute to that effort.

DR. HOLLINGER: Dr. Koerper.

DR. KOERPER: I just wanted a clarification on the HBV part of it where--

DR. TABOR: Do you want me to put on the slide?

DR. KOERPER: Yes, please.

DR. TABOR: On this part?

DR. KOERPER: Right, over there where it says "HBV. Evaluate GMPs." So, this is a situation where a positive HB surface antigen test--

DR. TABOR: Essentially, yes. Confirmatory tests had not been run.

DR. KOERPER: But what you are saying is, following that line, all tests are negative. So, subsequently you retest.

DR. TABOR: Let's say you had someone--and we do see these kinds of reports where presumably to save money at a blood bank, and there is a positive HbsAg, but a confirmatory test was not run, and there is no remaining samples, what we are saying is you can get a later sample that is negative for every hepatitis B marker, it is negative for surface antigen, anticore, anti-Hbs, nucleic

acid testing is negative, it is really unlikely that that person ever had hepatitis B, however, because it is hepatitis B, and there are now some reports of silent infections with hepatitis B, we feel that we still need to look at GMPs in the case of hepatitis B, whereas, with hepatitis C virus, if you had a repeat reactive anti-HCV by EIA, but a RIBA test was not run, you could take a later sample from the same individual and if they were nucleic acid test negative and anti-HCV negative, you could assume that they had never had hepatitis C virus and that you had a false positive.

DR. KOERPER: But I haven't had a chance to ask my question. My question is, could someone who not only was missing all markers for hepatitis B infection, also the nucleic acid test was negative? That was my question. If the NAT test is also negative, can you still call that a silent carrier? Where is the virus?

DR. HOLLINGER: I would agree with what you are saying. I think, Ed, to me if somebody had a positive test, but you couldn't confirm it, and you came down and got a later specimen, and they were not anti-HBC-positive--

DR. TABOR: Or anti-HBs-positive.

DR. HOLLINGER: Or anti-HBs-positive, well, anti-Hbs, I really wouldn't mind, but if they weren't anti-HBC positive, I don't know of any patient in that--I have not

seen any data that would suggest that that patient is at risk for being infected with hepatitis B at the time. Then, you would say you are talking about somebody--and I know about the silent infections that you are talking about. There is a lot of controversy about that issue. As Dr. Koerper said, if you did HBV DNA, I mean you would have to establish it. I don't know of any transmission in that group.

DR. TABOR: What you are saying is--and I think it is probably a good point--you have someone who was HBsAg positive before on the donation without a confirmatory test being done, you bring them back in, and they are negative for HBsAg, they are negative for anticore and anti-HBs, showing that they have never seen the virus before, and in addition, their nucleic acid test negative, you should be able to release the unit or the product.

DR. KOERPER: Why wouldn't that go over with the HCV and HIV as a false positive?

DR. TABOR: It should.

DR. HOLLINGER: On this first one, the positive test, plasma, are there any questions about the algorithm on that particular algorithm? Dr. Fitzgerald.

DR. FITZPATRICK: I just had a question on the GMP evaluation. Dr. Epstein just said there is a widespread GMP problem in the industry, but because of lack of resources,

FDA has to rely on the industry to do their own evaluation. It seems to be a big conflict.

DR. EPSTEIN: That isn't what I meant. We have been intensively inspecting the plasma fractionators and have been taking compliance actions, as appropriate, and have been reinspecting in follow-up to warning and injunctions, and have been rather intensive in our oversight.

What I think has been said and correctly by Ed is that we do not have the resources to do a for-cause inspection each and every time there is going to be a report of a positive result or a risk factor. However, we have done those without hesitation anytime we have felt that there was a threshold of seriousness, for example, HIV positivity reported in a fractionation pool. So, I think there is some gap of understanding here. What we are talking about is that we don't have the resources to inspect every single case of a report, however, we do have the resources, and have applied the resourced, to address the overall GMP status in the industry.

DR. HOLLINGER: Dr. Buchholz.

DR. BUCHHOLZ: I wonder if we could have an idea of the number of events which occur in a given time period, say, a year, in terms of a unit being found to be positive or a donor found to be associated with a risk factor. Is

this 1,000 times a year, is it 10 times a year?

DR. TABOR: It is a small number of times a year, I can't give you an exact number. I think we may have discussed that in December, but I don't remember the details with regard to positive tests. The information with regard to risk factors, I know Mr. Bablak has. Maybe he has the answer with regard to positive tests also.

MR. BABLAK: Actually, I don't have it for positive tests. Certainly that is something we can figure out. I think it is significantly lower. But for the risk factors, and it is important I think here to point out that the data that we collected, and the way it is being talked about right now includes all risk factors for the hepatitis viruses or HIV, which include anything from getting a tattoo, getting your ear pierced or any other part of your body pierced to more possibly concerning types of risk factors.

But for us the data was there were about--and I don't have the reports, but I have the units that were involved in this, and for our four member companies, it was about 19,000 units over a calendar year.

DR. TABOR: First of all, I want to thank Mr. Bablak for bringing that data because that is the sort of information that is very useful in a discussion like this especially when we get to the risk factor algorithms, but

there is no question that the number of situations where a positive test is discovered is far lower than that.

MR. BABLAK: I would imagine it is magnitudes of 10 lower.

DR. TABOR: Certainly, they should be reported to FDA, and we certainly see a very small number each year, but nevertheless, it is something that we have to deal with repeatedly.

Dr. Epstein, would you agree with that?

DR. EPSTEIN: Yes. Also, the numbers have gone down. There was a period in time when we were finding on inspection various compliance problems that led us to conclude that marker reactive unit had been pooled, and these were things, for example, that we would call testing into compliance where there was a reactive screen, but additional testing, and the center decided the unit was okay based on multiple negative tests after the initial screen, and we would have regarded that as marker positive donation.

But I think that the bottom line is that true events are infrequent, that it is a handful in a year's time, certainly less than a dozen, perhaps less than six, and it has also been less frequent in recent years.

DR. STRONCEK: Jay, would this algorithm be appropriate for these--my understanding is everything has got to be in compliance, so if you had someone "testing into

compliance," you couldn't use this algorithm then or you are avoiding this question, and not really sure yet?

DR. EPSTEIN: Well, I think the subtlety always comes in trying to figure out what you are dealing with. I think the bottom line is that if we think that a marker positive unit was pooled, we would apply the algorithm.

Now, when does that come in play, you know, we deal with myriad variations of testing errors and accidents, you know, wrong volume pipetted, problem with a reagent, scheme not followed, no supplemental test, I mean there are myriad variations on this.

DR. STRONCEK: Now, you said that. This isn't just window period contamination, this could be a unit then that got through that--

DR. TABOR: The issue of window period contamination is the risk factor, the risk factor algorithm. Here, we are talking about positive tests.

DR. STRONCEK: If it is a positive test on a unit, and then you are recalling a unit that was collected six weeks ago, and maybe this would apply, but this algorithm is for--

DR. TABOR: No, this is not for a recall of a prior collection necessarily. I guess I hadn't thought about that.

DR. EPSTEIN: I would say that a lookback unit

would be a risk factor unit, because that is not a unit that had a positive test.

DR. STRONCEK: I am confused then. If you get a real positive unit through, then, there has been a violation of CGMP, so if there has been a violation of GMP, then, are you saying that there would be no other violation of GMP?

DR. TABOR: What we are talking about is a kind of event that does occur, and it isn't always because people are doing something wrong. There are, as you know, a certain percentage of human errors in every large number of laboratory evaluations. There are also situations that Dr. Epstein was referring to where I guess those are GMP violations, but it may have been one test run where there was a violation.

DR. EPSTEIN: I think that what you are pointing out is that pooling of a positive unit shouldn't happen according to the schemes we have in place, and you are correct, but the GMP error or deviation may have happened at a very different level of the system than the fractionator, so, you know, you might have had an error at the level of the collector, and yes, there was a GMP breach, and yes, we want to find it and correct it, nonetheless, the fractionator is now in the situation of having processed or fully manufactured a positive unit.

So, I think it is not such a helpful distinction

to ask whether we should separate GMP deviations as a set from positive units as a set. Yes, if a positive unit gets in, generally, there was a GMP breach somewhere, but still you have the situation to deal with.

Now, sometimes what happens is new discovery. For example, we had a situation in which a European control authority introduced a novel test on the plasma pool and made a discovery of antibody positivity. The fractionator was testing both their units and their pools for HIV antibody, however, it turned out that there was disparate sensitivity of the assays, and we never did find the contaminating unit, but we were able to confirm that there was antibody in the fractionation pool just by looking at a different assay.

So, you know, you can get into situations where it is seemingly no one's fault, but still it happened, and then there will be situations in which it implies that there was a breach somewhere, but you can't always find the breach. You know, the sample mixup, for example, would be another example where the correct unit got released, but it got released as negative because it was some other segment that got tested. That kind of error can be very hard to trace.

DR. TABOR: And so the GMPs that we are talking about verifying are the GMPs at the manufacturing level.

I wonder whether we could address the issue. I

realize that Mr. Bablak was talking about risk factor issues in inadvertent contamination, but he raised the question of whether quarantining materials was going to create too much of a shortage of materials if products or pool were quarantined for a period of time long enough for the fractionator to evaluate whether GMPs had been followed in the removal and inactivation steps.

I think that is something we ought to address. Blaine, do you want to get a discussion going on that?

DR. HOLLINGER: Yes. Dr. Khabbaz.

DR. KHABBAZ: Actually, one of my questions related to that, and I think what he addressed is the infrequency of post-donation risk factors, but I don't understand why would these units affect what you said was all pools, does it have to do with the way the units are pooled, I mean is one collected unit--how many pools does it go into?

MR. BABLAK: Probably the easiest way would be to go through a hypothetical example of how a typical manufacturer could pool a particular product through the manufacturing.

For example, say, you had a manufacturer who started out initial pooling with between 3,000 and 5,000 liters to start the initial manufacturing pool, and assume then that you do perhaps three of those runs a week. So,

then you would end up with three different starting pools of anywhere from 3,000 to 5,000 liters.

If you then figure out that you probably make--once those pools are initially fractionated, they are processed in intermediates, and then sometimes during the processing, those intermediates are grouped together, so that if you have three starting pools, then, you may end up with one pool of intermediates from those three starting pools, so any one of those original pools that would have had one of these units would affect all three, then, of those initial starting pools.

If you figured out that if you are doing perhaps anywhere from 150 to 175 initial pools each year, then, you would only need 50 to 100 of these units, not reports, but units to affect your entire manufacturing process.

A second part to that then is because you are not dealing with just a report, one donor could have many units involved in that, so if you have one report, it could be as many as 50, maybe even 100, probably on the outside, but you could have many, many individual plasma units from that one particular report.

DR. KHABBAZ: A suggestion had been made, I think, in the past, as we discuss pools, about pooling units from the same donor, I mean grouping them together, and would that not alleviate that problem?

MR. BABLAK: With the way that source plasma donors donate, they donate over a typical period of maybe one to two times a week, so there is no way you could get one person's plasma in one particular pool, because it is an ongoing process, so as the units come in from inventory, they are held for the 60 days, then they are initiated in the pooling process. It is an ongoing process, so you can't just have one person's or several people's plasma, because it is collected over a time period.

DR. NELSON: Maybe you could outline or I am not clear on what is involved in a GMP evaluation, does that mean shutting down the plant for a month, or does that mean just reviewing records for a few hours, or when you say the action that has to be taken is an evaluation of the GMP by the manufacturer or by FDA depending on the situation, what does that imply, what does that mean?

DR. TABOR: Let me begin the answer and then I will have to get some help on the second part of it possibly from people who have been through a GMP inspection.

What we intended was for the manufacturer to go back and check their own records to ascertain that all records were complete and that all of the appropriate steps that were important for virus removal and inactivation had been followed, and to submit that to FDA.

Now, I assume that in an emergency situation

working around the clock they could do that pretty fast. If it required an actual inspection by FDA, which might be the case, for instance, if there were a manufacturer that had had multiple GMP violations in the past, and we wanted the assurance of an FDA inspection, that would obviously take much longer and actually can take quite a while.

Is there anyone else who would like to comment on that?

DR. THOMAS: There were actually three components to the assurance that we have that a viral inactivation step is effective time and time again. One is the laboratory measurements of how many logs of reduction the step can achieve for a particular virus, and that has been discussed here before.

The second component is the validation of that step as it applies to the manufacturing process. That is a detailed and very comprehensive study that speaks to the application of the process in a manufacturing plant. The third component is a set of very detailed manufacturing records that is kept for each and every lot that records that the critical controls and process parameters were observed during the manufacturing.

In the context of an investigation, therefore, assuming that the effectiveness was demonstrated in the first instance, and the method was validated correctly in

the second, what would be needed was a record review of the manufacturer of the implicated lots to ensure that they followed written procedures.

DR. TABOR: Assuring that the right temperatures and pH's were reached, and so forth.

DR. THOMAS: Exactly.

DR. HOLLINGER: How much time does that take generally?

DR. THOMAS: That would depend on the step itself, but I would imagine that the examination of the records themselves would probably take an hour or so, and then a review of that review by the quality organization would add some additional time, but we are not talking about weeks and weeks.

DR. WEINSTEIN: Mark Weinstein, FDA.

I just want to add a comment to that. Sometimes, in fact, the company does not have the plasma tree well worked out for a particular unit, in other words, they have to trace where the unit went, what products were affected by it in order for the batch records to be reviewed, and we have had occurrences where this has taken weeks for a particular manufacturer to find out what the plasma tree is and where the units went, so there can be a significant delay.

DR. HOLLINGER: Mr. Bablak.

MR. BABLAK: Just addressing certainly on the risk factor side, I don't want to say that this is for the positive test side, but all of the lots that are released have already gone through a significant comprehensive review of all of these procedures, so then to go back and do it again for particular lots creates some redundancy, and then certainly if you are talking about all lots, then it is almost like you are releasing it and then you are saying, well, wait, are we sure that the data we released is actually the right data.

So, you are getting into how many times do you need to look at this before you are sure that the data is actually what it says it is.

DR. HOLLINGER: Are you saying, then, every lot that is released, actually, the temperature, time, all these things that we talked about, has actually been looked at by the FDA or by the company?

MR. BABLAK: It's by the company. The company does a comprehensive batch review for every lot that is released, so this data is already being looked at. It is not that it is there and only looked at under certain circumstances. It is looked at for each individual lot that is released, it is part of the lot release protocol.

DR. HOLLINGER: Have there been times when the company has said that the GMP looks all right, and somebody

else comes in and say it hasn't looked okay?

MR. BABLAK: I can't speak to that. That would be an individual company--

DR. EPSTEIN: You know, you have just put your finger on the issue, Blaine. When we look at the batch record and there are no deviations, you can be done in an hour. When you look at the batch record and the batch record is incomplete, or there are documented deviations, the deviations might have been investigated, on the other hand, they might not have been adequately investigated or they were adequately investigated and then the right steps weren't taken, or the deviation was recognized, but nobody put together that the bounds of the excursion were outside the validated range of the process, nobody considered the implications, et cetera, so that is where it all gets complicated.

So, let me make this simple. Let's say that the viral inactivation step requires a certain temperature and there was an excursion when that batch was manufactured, and it was at the wrong temperature or it was at the correct temperature but not for a sufficient time.

Well, at that point you have a scientific question to resolve, is that a safe batch or isn't that a safe batch, and this is where it all gets complicated. So, what Mr. Bablak states is correct, that the systems that are designed

and are in place do require checking the batch record as part of batch release, but the trouble is that when you get into the details of were there any deviations in that manufacturing record, what you find out is that deviations are not uncommon, this can't be helped, it is human activity, but, you know, you need to know that they were all adequately addressed and all the time, and all we are saying is that if there was a threat to that product lot, we want to be very, very sure that all potential problems were addressed and buttoned down, and that is what this is all about.

DR. TABOR: I think that is particularly true. We can come to the risk factor type contaminations later, which are obviously more complicated, also because in the window period, for at least one of the viruses you may be dealing with somewhat higher titers of the virus, but for positive test inadvertent contaminations, if all the inactivation steps had been done correctly, I think we all feel confident that the material will not transmit infection.

On the other hand, I don't think any of us would want to see material manufactured with incomplete inactivation steps infused if it contained what turned out to be a test positive unit. In terms of the time it takes for a company to ascertain that, I think if they go to the records, and they find that there has been a deviation,

well, they could stop there and just decide that they were going to throw out the products from that pool.

DR. HOLLINGER: Other responses from the committee? Discussion? Yes, John.

DR. BOYLE: We are just dealing with the first question now, the one related to the positive test, correct?

DR. HOLLINGER: I don't know if we are dealing with any question, we haven't even had the questions, but basically, we could put the questions up.

I am going to ask if the committee would want to do this. We are supposed to take a break here and come back, but personally, I would rather move on through here. I think we can get this done in a reasonable period of time, and then we will be finished, if that is all right.

Why don't we have the questions.

DR. TABOR: I will read it for you. The first question states, "For inadvertent contaminations of plasma in which the contaminating unit was found to have a positive test for HBV, HCV, or HIV that was not recognized at the time of donation, does the committee agree that the algorithm provides suitable responses for FDA to take?

I guess I would modify that just to say the algorithm with the changes suggested by the committee today. I think after you spoke about the issue of HBV and silent HBV, I think we can take that box out if we specify in a

higher level box that NAT testing is one of the tests that has to be done. And then also the comment made by Dr. Hollinger about supplemental tests.

DR. HOLLINGER: Ed, this question is not tied in with the second question, so we can deal with this one first?

DR. TABOR: We can deal with this one.

DR. HOLLINGER: Are there any specific comments on this particular question? Yes, David.

DR. STRONCEK: You will use judgment to make sure on the number of units? Almost always, I am sure these are one unit contaminating 10,000, but if there were some event where there were more than one unit, you would use your judgment, I assume.

DR. TABOR: I think if there were more than one unit in the pool, and we knew about it, the alarms would go off, but I think the answer to that is yes.

DR. HOLLINGER: The question has been read. With the comments and revisions that Dr. Tabor has described before, so I won't re-read it, I will ask the committee to vote on the question.

All those in favor or vote yes on the question, let's raise your hand.

[Show of hands.]

DR. HOLLINGER: All those opposed or voting no?

[No response.]

DR. HOLLINGER: All those abstaining?

[No response.]

DR. HOLLINGER: Dr. Smallwood.

DR. SMALLWOOD: Results of voting. There were 14 yes votes, there were no "no" votes, no abstention votes. The industry representative indicated that he agreed with the yes votes.

DR. KHABBAZ: I have a question on the algorithm, the risk factor. I was kind of wondering, based on what we heard from FDA in terms of the frequency and the limitation or difficulty of FDA conducting GMP review of these, whether there may be room for NAT testing of pools when we are talking about risk factors.

You are talking about testing donor if you can find him, but if not, would NAT testing of the pool, and if it is negative, alleviate--

DR. TABOR: Can I reword your question to make sure I understand it? You are saying could this algorithm be modified to use NAT testing of the pool to help determine whether there is any reason for concern?

DR. KHABBAZ: Right. In the box where you say "Defer donor, quarantine, 5 collection."

DR. TABOR: Are you proposing that this could be used to eliminate the possibility of having to look at GMPs?

DR. KHABBAZ: I am wondering whether it has room as an option in there, yes.

DR. TABOR: Maybe that is something that the committee should discuss.

DR. HOLLINGER: Do you think it should be done? I mean where would you put it in, at what point? We are talking about the two sections on risk factor, aren't we, two algorithms on risk factor here?

DR. TABOR: Right. I mean we can focus on the one about plasma. If you are suggesting using that as a way to get off this track, you could put NAT testing here, if you have a negative NAT test, would that stop you proceeding further? Or if you put it here, after deferring the donor?

You are going to defer the donor because the donor had a history of hepatitis or whatever. You have to defer the donor. You have to go look for the prior collection. But then if you can get the donor back or on that sample, it is test the individual sample from that donor.

DR. HOLLINGER: If the donor was negative, I presume obviously the donor was negative for all these markers, just didn't mention that they had this risk factor, but all the markers have been tested, so they are serologically negative, is that correct, Ed, at this point?

DR. TABOR: Let's say you have a donor who calls up and says, by the way, I have had X, Y, or Z sexual

practice, and I forgot to tell you, that puts a donor at risk for these three or at least two of the three infections.

You defer the donor because they are now a deferrable donor, you quarantine the prior collections, and you bring that--you either have the original sample or you bring him in for another sample, and you run all the tests on them, the same way you did on the lower righthand part of the other algorithm, and everything is negative including NAT, you are saying basically then that you do not have an infectious donor because you have a single unit NAT test and no antibodies or any kind.

DR. HOLLINGER: If you are limiting this to the risk factors only for hepatitis and HIV--and we are not talking about babesiosis and other risk factors or something else that they might call about, hepatitis A or other things, and I think these are individual things you would deal with, for me it would be all right, then, if they were tested with NAT, because they could have been in the window period at the time.

It depends on the circumstances obviously of what they are calling you about, but in essence, yes, I think you would want to do that.

DR. KHABBAZ: If you have the information, but you can't get the donor back to be tested, whether--and I raise

this as a question for discussion--whether you could NAT test the pool, and if the pool is negative, and I raise that because of the discussion of FDA conducting GMP regulations and the frequency of these risk factors, et cetera, could you then stop?

DR. HOLLINGER: One of the problems, I think maybe as you heard here, is that sometimes these pools are very large, like 3,000 or 5,000, and that really moves it perhaps out of the potential for detecting somebody in the window period in some of these tests, so you would almost have to go back to the donor. At least I would feel more comfortable if the donor could be test ed.

DR. KHABBAZ: So, if it is not there in the pool, you can't detect it, if it is there, but not to a level that you can detect by NAT, you would still be concerned?

DR. HOLLINGER: If it were negative.

MR. DUBIN: But let's be clear, we are talking about pools that are about 60,000. We are not talking about 5,000 or 6,000, we are talking about 60,000.

DR. HOLLINGER: Mr. Bablak.

MR. BABLAK: The 60,000 limit is based on exposures in the final product. Any of the manufacturing pools are significantly smaller than that. So, if you are talking about an initial manufacturing pool or where you would be doing your testing, the volume there is somewhere

between 3,000 and 5,000 liters.

DR. TABOR: If we did add this to the algorithm, it would provide a very strong incentive for fractionators to have a retention sample of each individual donor, because if they knew they could avoid having to look at GMPs by doing NAT and other testing on a single donor sample, they would keep a donor sample, you know, half an mL or an mL.

MR. BABLAK: A couple other things I would like to address around this whole discussion on NAT testing is, first of all, I think if you are going to talk about retesting the donor, some time period needs to be discussed because, for instance, with source plasma donors, the next one may actually have already been tested if this person is coming in on a regular basis. So, in that case, is that sufficient to show that that person is not carrying any viruses?

The second thing is the manufacturers are all implementing PCR testing for the three viruses, and so under the INDs that they are all doing, they are not testing individual units, but doing a matrix of minipools, and would that be sufficient then to show that there is no contamination of that particular unit with a non-reactive response from the particular minipool.

DR. TABOR: I would like to reword what you said because I think it is an important point. What is going on

now is minipool testing, and if a donor had come back in the next week and that sample would have been subjected to all licensed tests on the individual donor sample, but the NAT testing would have been done on a minipool, so it is not the same thing as testing NAT on an individual unit.

I don't want to at this point offer an opinion on the relative merits, but I think that distinction has to be made. It is not the same thing.

DR. HOLLINGER: Dr. McCurdy.

DR. McCURDY: I think there are experimental data that either have been published or are about to be published that would suggest that HIV RNA negative individual units may be non-infectious. So, I think that an individual donor unit that is tested for HIV using NAT procedures would probably be all right. I am not so sure about a pool although for HIV, that is probably reasonable.

The studies for HCV and for HBV I think have yet to be done to demonstrate that NAT is a very good predictor of infectivity, that is, NAT negativity is a good predictor of non-infectivity, I think is probably a better way to put it.

So, I think for individual donor testing on a retained sample, I think NAT testing for HIV would probably be sufficient. I think I could accept that. For the others, I think we need more data.

DR. HOLLINGER: Mr. Dubin.

MR. DUBIN: (a), I want to agree with Dr. McCurdy because I think there are still some questions to be answered; (b), I want to remind the committee that 50 percent almost of the manufacturers are under consent decree for GMP violations, so I am not very comfortable when I start hearing about putting in a step that drops the GMP evaluation because of that, and I think that is important.

I want to keep putting that on the table because we seem to miss that in our discussions regularly. It is not an FDA problem, it's a manufacturer's problem. The FDA has done its job by going to consent decree, but I don't want to set this discussion up as if we have got a clean GMP record out there and enough test results to justify this kind of step because I think, as Dr. McCurdy said, on hepatitis C, the data is not in, and on PCR testing HIV in terms of individual donor, the probability is higher, but in terms of a pool test, not clear.

DR. EPSTEIN: I think the problem that we are butting up against right now is that what all of this is really about is belt and suspenders, and let me explain why.

It is a statistical certainty that window period units enter fractionation pools. Now, the frequency at which that occurs goes down the better our screening procedures are, both donor deferral and donor testing, and

we have seen, you know, yesterday in great deal just how low that is going to go with even just minipool testing of the donor.

But still the bottom line is it is a statistical certainty that window period units will continue to enter fractionation pools. Now, when you really reflect on this, what does it mean?

It means no products are safe if there isn't GMP adequacy, whether you know about a risk factor or marker in the donor or you don't. So, first of all, you have that paradox that the myth that the product is safe when you don't have a history of a risk factor or having pooled depositive tests is correct, is not a right way to think about the problem.

So, then, what happens? Well, some of the time you learn that through some presumed error, a positive unit or a risk factor unit was pooled. The difference in that scenario is that you know it happened, but probably the number of times that it happens and that you don't know far exceeds the number where it happened and you do know.

Then, the question is, all right, so are the products any different because you happen to know that you pooled a high risk unit. The reality is the products aren't any different when you happen to know that you pooled a high risk unit. It is just that the expectation is that in the

cases where you know, you have an obligation to be very thorough and make sure nothing went wrong.

But the reality is that the products that were made from units where there may have been a high risk unit, and you didn't know, are subject to the very same concern.

So, what we are really talking about is when, in the case of additional information is it appropriate to take additional steps, and I guess the history of the subject has been that it is important to do that because in the cases that have been investigated because of some precipitating event, we have discovered that the validation or the process validation or the handling of manufacturing deviations wasn't always optimal, and then we have made safety decisions about the products.

But the reality is that those same conditions affected pools and product lots when we didn't know there was a precipitating event and that is the dilemma here. I can very well see the argument that nothing additional needs to be done when you have a unit where you learned about particular risk because what is at issue is whether GMP is adequate generally.

Conversely, I can see the argument that, well, when you know, you have a higher duty, and so you should do something more, but at that point it becomes quite unclear what is more that is necessary, because the things that you

are thinking of that are more that are necessary really ought to be the things that are being done anyway all the time.

That is the dilemma and that is the circularity, and I think that is the point that we have finally come up against. So, to make the matter simple, if NAT testing ought to be done on every donation, being as a minipool, and on every fractionation pool as a final quality test on the pool, then, theoretically, it shouldn't matter whether you have a known incident or you don't have a known incident, because you have a negative pool.

So, you know, my dilemma is I can see this going either way, and that is why it is in front of you.

DR. HOLLINGER: Thanks for that task, and thanks for bringing us back to reality a little bit. I think that is a very important point, that these products are safe if everything else is going on, and for myself, I can see one thing, of going down through an algorithm and if information comes back, the simplest thing would be to test the sample, test it completely including that on another sample from the donor, and then if that is positive, then, you have to go and do everything else that goes on down through the algorithm. If it is negative, then, you don't have to go through the GMP and everything else. I would feel comfortable with that personally.

DR. BUCHHOLZ: I would like to echo concurrent with that thought. I can appreciate the idea of wanting to quarantine, but I do think the point that was made from the audience relative to the impact of that on the manufacturer's process, I don't know as I have heard anyone who in fact can reliably estimate in what way that would impact the manufacturing process, and I think that is, on a practical level, a very real concern.

Dealing with what Dr. Epstein said, that positive units have undoubtedly gone into pools in the window period, I think if you look in the recent era, there is an enviable safety record even though that must have been happening time and time again.

So, I would suggest the idea that you have proposed in terms of NAT testing of the donor implicated either in an existing sample or a procured sample might be a very nice way to address the concerns of all parties.

DR. HOLLINGER: John.

DR. BOYLE: As I understand it, one of the differences that we are talking about here is that all risk factors would be equal, that is, any risk factor would trigger either the NAT testing or the quarantine, and so on.

My question is what is the distribution of callbacks on risk factors? I mean are 75 percent of them tattoos, you know, are 75 percent of them IV drug use? Can

anybody tell us?

DR. TABOR: I think Mr. Bablak is the only one who might have that data, but I doubt if he does at present.

MR. BABLAK: No, we didn't collect that specifically. Given the information that we had about this particular meeting, it was going to be all risk factors, so we didn't go through the tremendous effort of trying to break down what the different post-donation information reports would be.

One thing I would also like to bring up when we are talking about NAT testing, if you are talking about testing samples rather than the minipools, you are talking about needing to store many millions of individual samples over the life of a particular product, because for post-donation information, you may not get that until six months down the road when you certainly no longer have anything left of that particular unit.

So, if you are going to need to store millions and millions of samples over a particular time, you need to catalog that, have storage for that. There is a lot of extra process. I think with all the manufacturers going to minipool testing, certainly, if that will be good enough to release a product initially, that should also be good enough to release a product or a pool based on any kind of additional information that you might have on that

particular unit.

DR. HOLLINGER: Dr. McCurdy.

DR. McCURDY: I think one probably should distinguish between viruses when one talks about minipool testing because I believe yesterday there was some discussion, and certainly in other fora there has been discussion, that minipool testing for hepatitis B virus is much less likely to add much safety because the viral load levels in individual units are relatively small. For HIV and HCV, the minipool testing may be better.

I think even with that, it depends on how you define minipools. Some of the minipools that comprise more than 500 or 1,000 specimens are likely not to be as sensitive even for HCV and HIV.

DR. TABOR: If I could just sort of try to draw some of these things into perspective, I think in the discussion so far, three questions have been brought up, and I think you are going to have a hard time answering two of them.

One of them is whether quarantine can be tolerated in this algorithm because of supply issues and the impact on supply.

Number two, whether NAT testing can be inserted as another branch or step in this algorithm, and, number there, whether that NAT testing has to be broken down by virus and

whether it can be done on minipools rather than on individual samples.

I think you are going to have trouble answering a couple of those.

DR. HOLLINGER: Dr. Koerper.

DR. KOERPER: Once again, I want to be sure we are clear on our parameters here. This is a donation that has passed all the testing before it got pooled.

DR. TABOR: Correct.

DR. KOERPER: and what I am hearing is that minipool NAT testing is being done already.

DR. TABOR: That is correct, for HCV and at least soon for HIV, not for HBV immediately in any case.

DR. KOERPER: So, to my thinking it still boils down to was the GMP followed or not, because what is the likelihood if the minipool is negative for NAT, that then when you then locate the individual donor, that donor is going to be positive on the NAT testing?

DR. HOLLINGER: Ed, these are small minipools like 100 or 20? I mean the ones that you are talking about that are currently being done for The European regulatory?

DR. TABOR: I think it would be best if the manufacturers gave that information.

DR. HOLLINGER: So, there could be 2- or 3- or 4,000?

DR. TABOR: No, no. Since it is under IND, it would actually be better if the manufacturers stated it.

MR. BABLAK: The minipool testing, each manufacturer has their own procedure where they go anywhere from around 100 to a little over 1,000 units, but what is important to remember here it is really not the number of units, but it is the sensitivity of that particular test. So, it has less to do with whether there is 1,000 or 100 and how many units you are actually detecting.

DR. HOLLINGER: Well, there are very few tests that will detect 5--I mean if they are using a 5,000 cutoff--there are very few tests that are going to detect five copies per mL at 100 percent efficiency, maybe 50 percent or something, but not 100 percent.

Dr. Boyle.

DR. BOYLE: I am just remembering something from yesterday when we were talking about the screening test, and the different areas can add their different questions to the screening test.

Does that mean that if Baltimore added an additional measure of risk factor for HCV, something that they thought was sufficient for testing, that that would be something that would trigger a lookback or whatever industrywide if it popped up? I mean at some level I guess the question is if you are not dealing with three or four or

six or whatever are nationally recognized, because we have got a decentralized screening mechanism, are we setting up a situation where almost anything could trigger this?

DR. TABOR: That is a good point. I think as you know, the screening questions, as was mentioned yesterday, although they are FDA-approved, they are not set up by FDA. We certainly did not intend this to apply to new questions put in place by one particular center. Perhaps we need a footnote to clarify that.

DR. HOLLINGER: Dr. Nelson.

DR. NELSON: Given the historical problems with the European IVIG and hep C, I am not opposed to looking at manufacturing processes from time from time given what Jay said, that this is the reason that the product is safe, not because we are testing donors or asking questions or anything else.

It is even debatable how important the questions are with regard to the safety of this pooled product, but I think somewhere there needs to be some compromise between quarantining the product, at least for any long period of time and looking at the manufacturing processes, which I think should be done pretty regularly and having an outside agency like FDA being involved I don't think is a bad thing. In fact, I think that that may help ensure the safety of the product.

Given that, I am not sure what the NAT testing will contribute in the pool. It might help a little bit, but I am not sure.

DR. HOLLINGER: There are really a lot of issues, aren't there, Ken, I mean with all of these, not only that, but as was mentioned, you know, how far back to you go. Theoretically, you just say, you know, if the person calls up, he gives a unit of blood, then, he calls up in two or three days before he gives the next unit, and he says, you know, by the way, and, you know, you could say well, we will just go back and look at that unit again, you know, it has been tested, or get another sample. I mean that is one way of doing it, but some of this is window dressing, and I am not sure which way you would go on it, but that is one approach to move forward with this.

David.

DR. STRONCEK: This algorithm doesn't ask the manufacturers to quarantine anything they wouldn't already quarantine, that is my understanding. If these issues came up without this algorithm, they would have to quarantine the products and destroy them, right?

So, this algorithm isn't any more onerous than the current practices.

DR. HOLLINGER: Ed, could you answer that? For example, if the risk factor is discovered, what is not in

place now? I mean do they have to do anything right now? Could you take each one of those and show me what is currently done or required?

DR. TABOR: I think that happens now is that they notify FDA and it is dealt with on a case-by-case basis. I would assume that they do not quarantine anything now in this situation.

Is there anyone else who would like to comment on that? Am I wrong? Dr. Lynch.

DR. LYNCH: Well, it has been my experience that a significant risk factor would give one a concern about actual infectivity going into the manufacturing pool. If that event was discovered while the product was still within the control of the manufacturer, they would hold that product until they completed the investigation to evaluate whether or not that posed an undue risk to the product.

With respect to products that are out in distribution, if there is a significant concern over the safety of that product, then, the manufacturer and perhaps FDA would take appropriate action to address that risk.

But as Dr. Tabor said, it is a case-by-case basis very much these days.

MR. DUBIN: Any chance we can vote on the original question?

DR. HOLLINGER: We haven't seen the second

question, if you could put it up. Why don't you go ahead and read the question, if you would, please.

DR. TABOR: For inadvertent contamination of plasma in which the contaminating unit was found to have come from a donor who despite having answered in the negative all questions about risk factors for infectious diseases and despite having had negative assays for HBV, HCV, and HIV and the time of the donation, was later found to have answered the donor questionnaire incorrectly or otherwise to be at risk, does the committee agree that the algorithm provides suitable responses for FDA to take?

DR. HOLLINGER: That would be one aspect of it, but, yes, John.

DR. BOYLE: The hard thing in terms of voting on this is that what I don't understand is whether this would put us in a position of sort of perpetual revolution, that there is enough of these that it would be a constant process on the industry as opposed to there aren't that many, but it is good trigger to force them to look back.

If we could have some sense of the frequency with which this would occur, it would be easier to vote on.

DR. HOLLINGER: Dr. Verter.

DR. VERTER: Besides echoing what John said, I would just like to reiterate, you know, the often made statement around here is show me the data, and it is very

often that we are put in this position of trying to make a recommendation which, on the surface, appears to merit the consideration of our main concern, the safety of the blood supply.

But if this were to occur once a year, I think it would be a lot different than 10 or 100. I would also like to indicate one of my other concerns, which is another "show me the data" issue, and someone else mentioned it I believe.

All risk factors are being lumped together, and clearly, I think we would agree that if it is based on someone getting a tattoo, it is a lot different than someone saying, oh, and by the way, I am probably at increased risk of HIV because I did this.

DR. HOLLINGER: Mark.

DR. MITCHELL: I agree that risk factors are different and that this whole issue is very, very complex, and I think that it really needs to be looked at on an individual basis because there are many things that have to be taken into account that you can't really do in this kind of a proposal.

DR. HOLLINGER: Gail.

DR. MACIK: I would say the same thing. What is wrong with the individual look at each risk factor as what is happening now opposed to automatically? I think if you tried to use quarantine as often as you do on this risk

factor protocol, you really are going to start getting into some problems. It is not easy to quarantine, and it has already been stated that if it is out of manufacturer's hand, yes, they might notify the person they sent it to, but there is no way that person they sent it to has procedures in place to quarantine it.

So, it is saying to notify them so they can quarantine it is one thing, but is that really something that can happen? So, I think we need a real idea of how often it happens. There needs to be some level that the first thing that happens is to say, okay, what is the level of the this risk, and then go back if that risk is very high, then, you might want to implement this, but it is going to be a level where there is going to have to be interaction and discussion on a case-by-case basis.

DR. HOLLINGER: Paul.

DR. McCURDY: Am I confused or doesn't this regularize pretty much what is now happening?

I mean this reduces to an algorithm things that are now going on, does it not?

DR. TABOR: Not entirely. I would like to ask the assistance of my colleagues. I think as Dr. Lynch said, and as I said before, the risk factor issues, inadvertent contamination, are really being handled on a case-by-case basis at present.

Would you agree with that?

DR. HOLLINGER: What is the problem with continuing to act on a case--I mean there are so many variables that are here, variables of what really the risk factor is. We don't even know that, but what it is and what it might mean and how it might impact on things, and I presume that you have the right to quarantine a product if you think if you think that there is a risk here anyway, the FDA does.

I agree, I think there is really a great many variables here. Yes, Dr. Buchholz.

DR. BUCHHOLZ: I am a little confused when we talk about quarantining a product. Let us assume a donor comes in, admits to some risk behavior, and that is a regular donor that has, in fact, donated 2 unit of plasma every week for many weeks.

When that person is looked at in terms of the impact on all the products that may have gone into many pools, many products--let me just think a minute, and I will come back.

DR. HOLLINGER: Ed, these are excellent algorithms, and I think it does take a lot of effort to go through algorithms, but the fact is that you can't be good doctors and just take care of patients on an algorithm.

You can do 90 percent of the patients on an

algorithm, but there are about 5 or 10 percent of time you have got to be a doctor, and you have got to make decisions based upon individual points and individual complications and problems that come up.

DR. BUCHHOLZ: The issue relates to the quarantine. I think as a manufacturer, you have product holds or quarantines or whatever you want to call them for product that is under your immediate control in your environment in a plasma center, in a manufacturing center.

I am unclear, though, in terms of the effect of quarantine as it goes outside of the manufacturer's control, and at least in my environment, in Fenwal, which is blood collection equipment, not coag concentrates, product that falls in that category that requires some action, if it is entirely within our company, we deal with it on a hold or a quarantine basis.

If it is product that is out in the field, and we have to deal with it, that becomes a recall situation, and perhaps--I am not sure how it works with plasma co-ag factors, but the quarantine aspect of this to me, as it is described, has the potential to imply product recall, and is that, in fact, what is meant?

DR. TABOR: I understand your comment, and it is really very similar to what Mr. Bablak was saying. I think the word "recall" sometimes means something different to

industry than it does to FDA, but you are making the same point Mr. Bablak did, that if you are quarantining something that has already been shipped, you are effectively going to have to issue a recall is what you are saying in order to do that successfully.

I don't know the answer to that question.

DR. BUCHHOLZ: Because the concern is, as the point of was made earlier, for many of these donors who are repetitive donors, and where do you draw the line. Somebody says, oh, by the way, I did this. At what point in time do you say, well, it is just the last two donations since you did this, or is that person potentially suspect of riskier than normal behavior, how far back do you go because you have the potential--and I think it is pertinent in terms of some of the staff we talked about earlier this morning in terms of product availability.

You have the potential to tie up tremendous amounts of product in situations that, you know, someone had a tattoo. Well, that is a risk behavior, I suppose, but it is a little different than if someone admitted to IV drug use.

DR. HOLLINGER: Just one other thing. It is sort of like it, that testing right now in which you are telling the recipients you are not getting any less safe blood than you were getting in the first place, and this is a similar

issue here.

These donors have been tested for all these tests, and they have been found to be negative, and the product we know from what Dr. Tabor has shown us, from everything else, at least has been very safe, and except for a problem with GMP, which is another issue, you know, maybe there is not a problem to sit and deal with at that point in terms of quarantine.

Mark.

DR. MITCHELL: I still want to emphasize the importance of the risk factors. The blood that is most at risk right now for transmitting disease is whole blood, and people with sickle cell, for example, who get multiple units are most at risk. Perhaps we should be looking at ways to make whole blood safer, and again looking at the risk factors on an individual basis.

DR. HOLLINGER: Well, I just don't know what to do here. I am not sure we are going to get much--well, we are probably going to have to vote on this, and we will see.

Dr. Lynch.

DR. LYNCH: Just a fast comment on the quarantine issue. It may be simpler than we realize. If you ask yourself what is to be accomplished by a quarantine, which is to prevent the use of product during the course of an investigation that will determine whether or not the product

is safe, then, what becomes important is how quickly you can resolve that question, and if that can be done, as I have suggested, in a matter of hours, then, the need for a quarantine in that situation may not exist.

However, there are two situations where that question might not be answered so quickly. Dr. Weinstein alluded to one where you can't trace the unit to the products quickly. That is a matter of recordkeeping, and that may vary from a company-to-company basis, but until you have made that trace, you don't know what products to quarantine, so that question is a bit moot.

The second instance is when you don't have a clear manufacturing record, where there may be questions that need to be resolved, and there it may well be appropriate to quarantine the product and hold it until you resolve those outstanding issues, but I would expect that those would be the vast minority of situations where one does an investigation and comes up with additional questions.

DR. HOLLINGER: Joel.

DR. VERTER: I would just like to ask Dr. Tabor a question. Could you tell us what the consequences would be for both a yes and a no vote on this question?

DR. TABOR: Well, I think the consequences of a yes vote would be that we would start to address these types of inadvertent contaminations the way the algorithm

recommends. My guess is that in the majority of cases, as Dr. Lynch says, that this would mean a delay of a matter of hours or a day for most instances of risk factor and inadvertent contaminations.

Nevertheless, before I leave the issue of the yes vote, I think there are some things on this algorithm that I don't hear a unanimous opinion about from the committee, and those are really the questions I mentioned before.

The result of a no vote means that we go back to the drawing board. I guess if you really mean no, and if you mean, quote "no," we want you to do it on a case-by-case basis, then, I guess I would recommend that you state that in your vote or that you do a subsequent vote on that issue, because if you recommend doing it on a case-by-case basis, that is a lot easier for us than having to try to smooth out this algorithm to be acceptable to the committee.

On the other hand, if you want us to work on this algorithm, we certainly will do so.

DR. HOLLINGER: I guess the other issue is one could table it, and that would be another issue which would suggest that you wanted to work on it rather than on a "no" vote which would mean that you don't want to work on it.

DR. STRONCEK: The last question. What about new variant CJ disease?

DR. TABOR: I have had some dealing with the

concept of inadvertent contamination for many, many, many years, long before starting to deal with it for the purposes of BPAC. When I started to deal with it for BPAC in late '96 or early '97, I realized it was a broad topic it had to be divided.

We have only dealt with these three viruses, and I explained the reasons earlier, but that is only so far. I think it is very possible that we would try to address, not only new variant CJD, but other agents that are not addressed by these two aspects of inadvertent contamination we discussed.

There are the non-envelope viruses. There are other unknown contaminants that haven't been discovered yet, how should we deal with situations like that. It may be impossible to deal with that with one rule or one recommendation or one algorithm, but it is very likely that you will hear about that in the future.

DR. STRONCEK: That wasn't clear to me. So, you are saying that this question we would be voting on only involves risk factors for HBV, HCV, and HIV.

DR. TABOR: Correct.

DR. HOLLINGER: Joel.

DR. VERTER: Having listened to Dr. Tabor's answer, I appreciate it. I am not quite sure how it helped me though.

Let me tell you what I want to do, what I am going to do. I want to vote yes, but I am going to vote no, and the reason I am going to vote no is--I would almost prefer that we not vote and that we ask the FDA to work with industry to get back and answer some of the questions that were posed and bring it back. That is what I prefer doing.

DR. HOLLINGER: John.

DR. BOYLE: In explaining in advance where my vote would go, as written--let me do it differently--if the word significant risk factor was added, and then we worked toward a definition of which of these things are significant risk factors, I could vote in favor of this.

The problem is as written, the idea that--and I don't know this to be true--but the idea that we would tie up a lot of product because people suddenly decided that the tattoo that they had last week or the pierced ears they had, you know, three weeks ago, you know, that, I can't vote for, and if you add the word "significant" and then work towards a definition of significant, then, as a sensitive person, as well as somebody concerned about the blood supply, that, I can live with.

DR. HOLLINGER: Dr. McCurdy

DR. McCURDY: If I remember correctly, we gave the FDA in some of our previous votes, including the one today, the option of assessing the degree of risk as they went down

the algorithm. Perhaps in the risk factor discovered, if you added "and assessed," and permit some leeway to the agency in determining exactly how they should proceed, that might make it easier for many of the group.

DR. HOLLINGER: Yes.

MR. DUBIN: I would agree with John and suggest we add the word "significant" which cuts out some of the problems.

DR. HOLLINGER: Yes, Norig.

DR. ELLISON: I guess I am going to abstain because I wish we would bring it back. I think parliamentary procedure permits us to table, so I am going to move that we table this.

DR. HOLLINGER: Is there a second to that?

DR. BUCHHOLZ: Second.

DR. HOLLINGER: All in favor of having this issue tabled I presume for the idea of bringing it back with more specifics, much of which will have just been mentioned here at the end about questions, and wording, and so on.

All those in favor of having this motion tabled, raise your hand.

[Show of hands.]

DR. HOLLINGER: All those Opposed?

[Show of hands.]

DR. HOLLINGER: Abstaining?

[No response.]

DR. SMALLWOOD: The results of voting for tabling action on Question No. 2, there were 10 yes votes, 4 no votes, no abstentions. The industry rep agreed with the yes vote.

DR. HOLLINGER: Ed, I know how hard--I will probably be off the committee before you get this resolved, but I think the issues are, as we see it, is what do you do about the length of time, I mean is there going to be a time limit on this when somebody gives some donor information, what do you do about the worry about "significant risk," the issues about NAT testing, the issues about recall that were brought up once the final product is sent out versus just quarantined in-house, if that is, issues about whether it can be done on a case-by-case basis I think are all probably critical.

That is sort of what I hear from all this discussion today.

DR. TABOR: Thank you very much for your comment and input. It is a very difficult question.

DR. HOLLINGER: Mr. Bablak.

MR. BABLAK: I just wanted to say briefly that certainly we would be happy to work with the FDA to answer many of the questions that were brought up today. I think going forward in the future, so that we could have a better

discussion at this table at the time the questions are brought, we would certainly appreciate getting the types of information that were displayed today beforehand, so that we can address them the first time rather than having to come around a second or third time.

As you know, this particular algorithm was not released to the public, and I think that kind of hindered the discussion because we can only take guesses at where it was going even though we did get some information. I think if we would have had a little bit more, we could have provided a lot of the information today and maybe answered the question.

Certainly, I think under the FDA Modernization Act, it is envisioned that more public input will be given to these types of decisions, and we would certainly like to help with that.

DR. HOLLINGER: We would like you to be proactive, then, about this, and then getting the information to them.

I want to thank the committee, by the way. I think this has been a very good meeting, as it usually always is, and the next meeting is June 17 and 18 of this year, and we will see you all then.

Thanks very much and for all the participants.

[Whereupon, at 12:50 p.m., the hearing was adjourned.]

CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

Alice Toigo

ALICE TOIGO