

BLOOD PRODUCTS ADVISORY COMMITTEE
CENTER FOR BIOLOGICS AND EVALUATION

Meeting Of:

BLOOD PRODUCTS ADVISORY COMMITTEE

(DAY TWO)

June 20, 1997

Quality Suites Motel
Shady Grove, 3 Research Court
Rockville, Maryland 20850

Proceedings By:

CASET Associates, Ltd.
10201 Lee Highway, Suite 160
Fairfax, Virginia 22030
703-352-0091

TABLE OF CONTENTS

	<u>Page</u>
Committee Updates	1
Derivative Warning Labels - Dr. Lewis	2
HTLV-I/II Memorandum - Dr. Cowan	9
Uniform Blood Labeling - CAPT. Gustafson	20
Open Committee Discussion	
II. Inadvertent Contamination of Plasma Pools for Fractionation	
A. Introduction - Dr. Tabor	33
B. Current Procedures - Ms. Godziemski	44
C. Risk Assessment - Dr. Poffenberger	48
D. Viral Inactivation of Plasma Derivatives - Dr. Lynch	65
E. Epidemiology of Transmission of Viruses by Plasma Derivatives - Dr. Tabor	85
Open Public Hearing	96
Mr. Hartin, Alpha Therapeutics Corporation	96
Dr. Morgenthaler, Swiss Red Cross	112
Dr. Hostoffer, Immunodeficiency Foundation	117
Dr. Ewenstein, National Hemophilia Foundation	125
Mr. Burke, Consumer	128
Mr. Bell, IPPIA	131
Open Committee Discussion	
G. Committee Discussion and Recommendations	136

P R O C E E D I N G S

(8:30 a.m.)

DR. SMALLWOOD: Good morning and welcome to the second day of the fifty-fifth meeting of the Blood Products Advisory Committee. I am Linda Smallwood, the Executive Secretary.

Yesterday I read the conflict of interest statement. I will not read it again today, however, the contents of that statement apply to today's deliberations where appropriate.

I would like to announce that the Chairman of the Blood Products Advisory Committee, Dr. Scott Swisher is absent for this meeting. Dr. Blaine Hollinger will be the acting chairman for today.

We will proceed with the agenda as identified. I just wanted everyone to know that the procedure with respect to committee updates, that the FDA personnel will be providing the committee with a status report of the items as identified. These particular issues are not for discussion. The committee will not be asked to make any type of recommendation; it is just for their information only.

At this time I will introduce to you the acting chair of the committee for today, Dr. Blaine Hollinger.

Agenda Item: Committee Updates

DR. HOLLINGER: Thank you.

We have a very full agenda today, and I think a very important agenda. We'll start out today with committee updates. The first one is by Dr. Richard Lewis, who will speak on the derive warning labels.

Agenda Item: Derivative Warning Labels - Richard Lewis, Ph.D.

DR. LEWIS: Thank you, Dr. Hollinger.

CBER has been having ongoing discussions throughout 1996, with the American Blood Resources Association, ABRA. These discussions resulted in CBER's request to include specific warning statements in product labeling of plasma derivative products. Further, CBER requested monthly reporting of the infectious disease transmission by manufacturers to CBER.

These labeling changes were to be submitted by February 6. That's because presently all labeling changes for biological products are submitted to CBER for approval prior to their incorporation.

Our requests were issued in a letter of December 20, 1996, and although the specific wording suggested has not been entirely endorsed by industry, CBER has received labeling changes from most manufacturers. In fact, 16

manufacturers received the request, and 11 have responded. Of those responding, they did not all accept the exact wording that was suggested, however, in general the differences between what CBER suggested and what has been submitted were minor, and we have drafted additional comments to those manufacturers.

Our first suggestion requested a warning statement be placed on the product container and on the package. It is shown in the overhead here. We asked that it say, "The patient and physician should discuss the risks and benefits of this product."

Regarding this particular statement, six manufacturers responded completely and adequately. One has commented that, "they will add to all products whose labels are not limited in size;" and our only comment on that was that this might be acceptable after clarification of what products and which bottle sizes they were referring to.

One manufacturer left out reference to the physician, and worded the statement so that it was directed at the physician and it reads something like, "the risks and benefits of this product should be discussed with the patient."

Two additional manufacturers left out any example

of this statement on their container label. Generally, we see examples of the container labeled "prior to accepting that," and this is merely an administrative question that we had.

Now our second request, we asked that the warning section of the label list viral and activation methods that are used to state that the possibility that other agents may be in the product, and that all infections thought by a physician to have been transmitted by the product should be reported by the manufacturer.

This is the wording that we suggested in our letter: "The product is made from human plasma. Products made from human plasma may contain infectious agents such as viruses that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating or removing certain viruses." We asked that manufacturers include those viral reduction measures that they used in the particular product.

Further, we requested, "Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may

be present in such products. All infections thought by a physician possibly to have been transmitted by this product should be reported the physician or other health care provider to the manufacturer," and we ask that the manufacturer name and telephone number be listed. "The physician should discuss the risks and benefits of this product with the patient."

Understandably, the acceptance of this particular request has been the most problematic for manufacturers. Nevertheless, the majority of responses from industry have been answered with limited suggested changes from CBER. For instance, the sentence that begin, "Despite these measures," in one instance was substituted with the statement, "Despite these measures, such products may still potentially contain human pathogenic agents, including those not yet known or identified," and we have accepted that wording.

Another acceptable substitute includes the words, "Despite these measures, it is still theoretically possible that known or unknown infectious agents may be present."

One unacceptable comment that was, "Immune globulin products administered by the intramuscular route have not been associated with documented cases of viral transmission," and we asked that that not be included in the

statement.

A number of submitters did not include telephone number or manufacturers' name in their statement.

The final request was in the information for the patient section in labeling for plasma derived coagulation products, and we requested that that include comment that, "Parva virus B19 and hepatitis A are difficult to remove or inactivate," and a description of some of the symptoms of these particular viruses should be included. Patients would be encouraged to consult their physician if these symptoms appeared.

"Some viruses such as Parva virus B19 or hepatitis A are particularly difficult to remove or inactive at this time. Parva virus B19 most seriously affects pregnant women or immune compromised individuals." Then that was to be followed by a description of the symptoms.

Of those submissions that we received five included no description of the symptoms of Parva virus or hepatitis A. One included the comment, "The majority of Parva virus B19 and hepatitis A infections are acquired by environmental or natural sources," and we thought that this additional comment should be removed.

Of those manufacturers we heard from, two

manufacturers accepted our wording entirely; were incorporated into the labeling, and we responded to them with our approval.

To the other extreme, there were two manufacturers who submitted modified warning statement; in one case, a modified warning statement to be used for all of their plasma derived products. In the other case, there were different statements for different classes of products that were submitted.

Our evaluations of these modifications have been completed, and responses have been drafted. We expect to send those back to the manufacturers very soon. These have taken a little bit longer, because they were more difficult reviews.

Further, our December letter requested monthly reporting of infectious disease transmission associated or possibly associated with any licensed biological product. We asked that this reporting begin January 1, and we asked that it follow the calendar month, and that it be reported on the 15th of the following month. So the first report would have gone from January 1 to January 31, and the submission would have been on the 15th of February.

We have received monthly infectious disease

reports from all manufacturers that received our request, although admittedly some of the manufacturers got a slow start. Four manufacturers submitted nothing for the first few months; another four submitted only partial reports. The April reports, which were due on May 15th, were all submitted within a few days of the particular due date. This represents regular reports for 65 affected products.

So in summary, most of the manufacturers accepted our suggested wording, and are incorporating it into their labeling. Some have made minimum changes that CBER has either accepted or suggested alternatives. A couple of manufacturers have not incorporated changes or made changes that are significantly different from those suggested, and we're sending our comments to them in writing. There are five manufacturers that have not submitted anything.

DR. HOLLINGER: Thank you, Dr. Lewis. Any questions for Dr. Lewis?

DR. KASPER: A clarification. Were these comments also to be put on the label of human albumin?

DR. LEWIS: There were various requests. No, these comments were for all plasma derived products.

DR. KASPER: Then if they are to be put on human albumin, are they also to be put on the so-called

recombinant factor 8, which is suspended in human albumin?

DR. LEWIS: No.

DR. KASPER: Why so inconsistent?

DR. LEWIS: The decision was made that the products that had the active component was plasma derived, that these statements would go on the label.

DR. KASPER: Yes or no.

DR. LEWIS: The decision was made that products whose active component was plasma derived would have these comments on the label. It wasn't extended to biotechnology from derived products.

DR. KASPER: Why were you so inconsistent?

DR. LEWIS: I'm going to leave that for Dr. Epstein.

DR. EPSTEIN: Carol, I think you have made a good suggestion, and we will follow up on it.

DR. HOLLINGER: Any other questions for Dr. Lewis? Thank you, Dr. Lewis.

The second committee is with a memorandum that given the committee yesterday on HTLV-I/II, the guidance document that deals with donor screening, with new test kits, testing for either HTLV-I or -II. The presenter today will be Dr. Elliott Cowan.

**Agenda Item: HTLV-I/II Memorandum - Dr. Elliott
Cowan**

DR. COWAN: Thank you, Dr. Hollinger.

In December, 1996, the Blood Products Advisory Committee recommended that donations of whole blood and blood components for transfusion be screened for antibodies to HTLV-II. This was based on the possible association of HTLV-II with disease, and the fact that a test kit containing HTLV-II antigens was under review by FDA.

In addition, the committee reviewed data which suggested that some currently licensed HTLV-I screening tests were statistically equivalent in their ability to detect antibodies to HTLV-II, compared to a screening test that contained HTLV-II antigens. BPAC therefore recommended that currently licensed HTLV-I test kits could be labeled to detect antibodies to HTLV-II following qualification by FDA.

In March, 1997, FDA discussed before BPAC the development of a guidance document to recommend screening for HTLV-II antibodies, and to aid blood establishments and manufacturers of test kits in the implementation of that testing.

FDA has provided a confidential draft guidance document to the committee, and we respectfully request

comments within two weeks.

Thank you very much.

DR. HOLLINGER: I hope the committee has had the opportunity to look at this document.

There is a response to the memorandum by Abbott by Matt Camborzinski(?). Is Matt here? Could you come up here, please.

DR. KOZIARZ: Thank you, Dr. Hollinger.

My name is Jim Koziarz from Abbott Laboratories. What we would like to do for you this morning is very briefly update the committee on some work that has been done by us in conjunction with Dr. Bernie Poisez at State University of New York on the issue of cross-reactivity of HTLV-I/II reagents. Secondly, while we have the podium here, we would like to very briefly update the committee on some of our work on HIV variants as well.

DR. POISEZ: Thank you, Jim.

In the mid-1980s, working with John Sadinski(?) and Shirley Kauf(?) down at CEDS(?), we began to develop PCR assays for HTLV-I and HTLV-II. It became apparent in those studies that we were finding a considerable minority of patients with both HTLV-I and HTLV-II infection that were sero-negative and PCR positive.

This phenomenon occurred to a greater degree if we looked at endemic barriers, and it tended to be skewed towards younger patients, or those recently adopting a risk behavior such as drug abuse. The other observation was that this phenomenon occurred at a greater frequency with HTLV-II than with HTLV-I.

As you know, there are two subsets to HTLV-I, one African strain derived, and the other Malaysian strain. There are two substrains of HTLV-II, A, which is the predominant strain in North America, and B, which is the predominant strain of Paleo-Amerindians throughout Central America and South America.

So the questions we wanted to address over time was how frequent was this sero-negativity phenomenon, and could assays that are predominantly based on HTLV-I African antigens consistently detect HTLV-II both A and B substrains? What we wanted to do over time was select samples at random from endemic groups that were not pre-selected for cross-reactivity.

Earlier this year we published a paper in collaboration with Eduardo Estaban at the University of Buenos Aires at Tangil(?), and with George Ferrer(?) at the University of Pennsylvania, where we studied Indians from

the Gran Chaco. This is a plateau in the northern part of Argentina, southern Paraguay, and Bolivia.

The Indians in this region have fled first the Incas, and became secluded from all other Indians, and also fled the Europeans. There is very evidence of the mixture of either the African or European blood in this group.

They have the highest prevalence rate of HTLV-II infection in the world. Part of this is due to their practice of using wet nurses, who are also used as women for sex such that the prevalence rate of HTLV-II infection among the wet nurses is very high. Some of the Indians also practice polygamy, such that the probability of one man passing the virus to several women is quite high.

The Gran Chaco Indians are divided into the Toba, and the Mataco Mataguaya(?) language groups. The Charodis(?), which are a subgroup of the Mataco Mataguaya have a 50 percent incident of HTLV-II infection, and their perinatal transmission rate from infected mothers to babies is around 30 percent, hence, they represent an excellent group to do these types of comparative analyses, and also an excellence group to study over time for the association of HTLV-II infection with disease.

I can tell you that we have also found that the

HTLV-II infected Indians tend to have a higher incidence of expansion of clonal T-cell populations in their peripheral blood, yet we do not know whether this equals disease or not.

In this analysis we have studied over 1,000 Indians. We have so far done PCR in about 200 of them, so we compare the PCR assay to the serologic assays. I would also want to add that in our laboratory, the PCR assays, the pre-PCR set up is done in a completely separate area, completely separate building, by separate personnel. Then the material is exchanged. The baton is tossed, if you will, to people in the actual PCR area. So there is no contact between the set up people and the actual amplified DNA.

We also incorporate DOMP into our product, and pre-sterilize all samples with uracil n-glucosylase to prevent the contamination of the sample with carryover DNA. We also analyze these samples for HIV and for HTLV-I and none of them have been positive for that. We can cross check with a technique called signature primers for the evidence of carryover, and in none of those samples was there evidence of that.

As you can see, the PCR assay in this group was

the most sensitive, having a 97 percent sensitivity, and a 100 percent specificity. These are various ELISA assays that were used: the Retotek, the Cambridge, which contains recombinant GP21E, and Vironostika, in addition to the Western Blot. We also did the select ELISA which contains HTLV-I versus HTLV-II spiked peptides.

As you can see, all of the ELISA and the Western Blot and the select ELISA, which is not shown there, had roughly comparable sensitivities, ranging from 70 to 74 percent. There was no statistical difference between any of these assays. The Retrotek, however, did have a much lower specificity which was statistically significantly different from all the others.

The data indicate that PCR assay is the most sensitive, but they also indicate, as our other studies have shown, that it is not 100 percent sensitive. We still find samples which we cannot find evidence of peripheral blood HTLV-I or -II DNA in patient populations that are positive by serology.

We have cloned and sequenced the strains from this, isolated them. They are unique HTLV-IIB strain, which is unique to the Gran Chaco as this isolated group would indicate, also verifying that this is probably not due to

carryover.

In our past research, and then published by others, our indication when we looked at HTLV-II positive patients who were PCR positive, but sero-negative, was that if we made a research HTLV-II based whole viral lysate assay, that our sensitivity would go up. If we used HTLV-II antigens rather than HTLV-I our detection rate was a little bit higher.

This we were able to pursue further with the folks at Abbott Laboratories using their newer ELISA test, which is based on a whole viral lysig(?) containing HTLV-I and - II.

The assay results were compared to the Cambridge, Vironostika and Western Blot and select ELISAs. In most instances there was absolute harmony between the two assays, although I would say the signal to cut off ratio of the Abbott ELISA compared to the others tended to be higher, as you might expect, using HTLV-II containing reagents.

We had eight discrepant samples, however, that were all PCR positive, many of which have been cloned and sequenced and again shown to be unique Gran Chaco isolates. Two of the samples were under the Abbott cut off, but were positive in the Cambridge test containing the recombinant

GP21 peptide, and were either a IA pattern Western Blot, which is a 24-21 reactivity, or were actually positive in the Western Blot. So these were Abbott negative, but positive in most of the other tests.

The remaining six samples shown here were positive in the Abbott containing the HTLV-II viral lysate, but negative both in the Cambridge assay and in the Vironostika assay. Two of these were positive on the Western Blot. One had the IA pattern, but three of them had a IB pattern, which is no reactivity to p24, and reactivity to any other combination of antigens on the plate.

In conclusion, the data would indicate that the performance of these assays in this limited, unique population of humans containing a unique strain of HTLV-II is not exactly equal. I would submit that the exact performance in terms of sensitivity and specificity over time in HTLV-II infected individuals needs further study.

Thank you.

DR. HOLLINGER: Any questions of Dr. Poisez?

Bernie, just one thing. Was the Abbott test used on all the concordant samples also?

DR. POISEZ: Yes, it was used -- we have actually about 1,000 samples of PCR only in about 200, and we have

done about 800-900 on the Abbott test. We still have a lot of PCRs to do to get further data.

DR. HOLLINGER: And there is concordance with all the other tests also?

DR. POISEZ: Yes, they actually match up fairly well except for these eight samples.

DR. HOLLINGER: Thank you.

DR. EPSTEIN: Bernie, what percent of North American Type IIs would you think are B?

DR. POISEZ: In our hands -- and I would say that is skewed to getting samples perhaps more from the East Coast if you will. About one-third of our samples are IIB and two-thirds are IIA. The IIB that we tend to see in North America tends to be on the subset of IIB that is closer to these Gran Chaco isolates.

The most distinct IIB that we have found to date is from Gahibo(?) Indians in Venezuela. It's a very unique IIB that branched off way before all the others that we see in North America branched apart from each other.

So it's roughly about one-third of the samples that we have had. I would say that we have worked up probably now about 10,000 HTLV-IIB samples.

DR. HOLLINGER: Thank you. I think we will go on.

I'm sorry.

DR. DEVARE: I'm Sushil Devare from Abbott Laboratories. I just want to give a brief update about one of the hues which was also discussed at the December 19, 1996 meeting. We addressed whether HIV variants are detected by the HIV-I and HIV-II screening test which are currently in market, and what has been in them, trying to improve the detectability of HIV-I group samples, which are now quite critical in terms of detection.

At Abbott Laboratories we have been collecting samples from many HIV endemic areas of the world. So far we have built up a large panel of samples which is shown in the first transparency. We have 343 samples of different subtypes of Group M, and other samples are detected by an assay which is currently under review, which was submitted in September 1996.

We have also have looked at 28 Group O samples. Here we have 28 Group O samples which have been screened using the assay which was submitted in September 1996, which has the ability of detecting Group O samples well. As you can see in this transparency, we can detect all the samples.

We continue to collect more samples and characterize them. By the way, all these samples have been

characterized by sequence analysis, including all the subtype samples which were on the previous transparency. So we can really collect more samples, and we would like see how the sample performs and supports the data in terms of detectibility of all subtypes.

Thank you.

DR. HOLLINGER: Dr. Nelson.

DR. NELSON: Two questions. On that table, 2156, is that a positive sample? What does that mean?

DR. DEVARE: That is a positive sample which is very near the cut off. It is very near the cut off so it can go flip flop. That was predicted also at that time.

DR. NELSON: It looks like it is so near that it is below in one run.

DR. DEVARE: I agree with you. That's the reason why in the future assays it will be a good idea to incorporate specific reagents from Group O.

DR. NELSON: I didn't understand on your first slide, you have a number of mixed samples. What is that? Is that people with infection with two viruses?

DR. DEVARE: That's right. Typically, what we do is --

DR. NELSON: You found that many people?

DR. DEVARE: That's right. What we are finding is -- typically we look for the GAATTC specific sequences, and in the same sample we look at the envelope specific sequences. We PCR amplify in both the regions and then sequence characterize. Based on analysis, we can say which subtype it is.

Now in these regular samples we have found the A of GAATTC and B of envelope. Similarly for A and F, you have a mixed population, and A and D, and so on. Now this could be due to recombination and the other thing of recombinant R. Maybe these people are infected by two different strains, and we PCR amplify both the sequences.

DR. NELSON: This was based on sequencing or HMA?

DR. DEVARE: It was based on the sequence analysis and [unintelligible] analysis.

DR. HOLLINGER: Thank you very much.

It's my understand that the memorandum was primarily just for the committee's interest. It is not going to be discussed further. So we will move on to the next presentation by CAPT. Mary Gustafson on uniform blood labeling.

Agenda Item: Uniform Blood Labeling - CAPT. Mary Gustafson

CAPT. GUSTAFSON: Thank you.

This committee was first presented with a discussion of uniform blood labeling in March of 1995. At that meeting the committee was asked if it thought FDA should support the blood industry's transition from use of a uniform blood label incorporating A-B-C code-a-bar, bar code symbology, to a uniform blood label utilizing ISDT128 symbology. The committee recommended that FDA support the transition. In December 1996, the committee was provided an update on the progress of this transition.

Briefly, the history of uniform labeling for blood and blood components dates to the 1970s. An industry initiated effort resulted in design of a blood label to be used by all blood suppliers in the U.S. This label format included information fields with information encoded in bar codes. The bar code selected at that time was a variation of code-a-bar termed A-B-C code-a-bar.

In the late 1970s, a document providing guidelines for uniform labeling utilizing A-B-C code-a-bar was presented to the FDA. In 1985, FDA revised the regulations for blood labeling to accommodate use of a guideline for uniform blood labeling, and adopted the industry document as that guideline.

Although the regulations as currently written do not require use of any automated symbology, the regulations provide in 21 CFR 606.12 C13 that the container label may bear encoded information in the form of machine readable symbols approved for use by the director, Center for Biologics Evaluation and Research.

The preamble to the final rule of the 1985 regulation revision stated that at the time, code-a-bar was considered to be the only acceptable bar code, but that others would be considered based on data supporting usability and safety.

By the late 1980s, the code-a-bar symbology began showing its age. With increases in component variations, increased blood sharing, and use of centralized test laboratories the code-a-bar symbology showed that it was not sufficiently reliable or flexible for continued use. Additionally, the uniform labeling format established did not provide for uniformity in the donation number, nor did the numbering system provide a guarantee that donation numbers would be unique.

At that time, an international effort sponsored by the International Society for Blood Transfusion to select automated technology and labeling parameters began. In

1989, the ISBT working party for blood banking automation selected a form of code 128 to be the new automated symbology. The code, with specific data identifiers for blood component use is termed ISBT 128.

Work to develop a new uniform label in the United States was first undertaken by the Information Systems Committee of the American Association of Blood Banks. More recently, an independent organization, the International Council for Commonality and Blood Banking Automation was formed with the sole purpose of supporting, promoting and maintaining a uniform label utilizing ISBT 128.

Since 1991, there have been numerous public meetings, work shops, presentations and publications designed to educate, elicit participation and input, achieve consensus and discuss transitions.

Work also began on an industry document describing the uniform label and symbology to replace the ones designed using code-a-bar that was presented to the FDA in the late 1970s, and adopted as a guideline in 1985. A draft of the new document was presented to FDA in the fall of 1996.

An industry sponsored workshop was held on December 11, 1996, to discuss the draft document and reach consensus. Few concerns were voiced about the document

itself; the labeling format or the bar code symbology. The major of concerns centered around costs and implementation strategy.

The Blood Products Advisory Committee was provided an update on uniform labeling the following day, and advised that FDA had received the industry document, with the request that FDA consider adopting it as a guidance to replace the 1985 guidelines. The committee was also advised of the process for guidance development, including publishing the availability of the document in the Federal Register for public comment.

Since the December workshop there has been considerable pandering and angst in the blood community concerning transition to ISBT 128. It is as if the parties most affected by change are waiting to see who is going to blink first. Software vendors need to develop code and modify software, but they seem hesitant to move without assurance that the code will be acceptable to customers and the FDA.

Blood centers are hesitant to convert to ISBT 128 labeling until they are sure their customers have made modifications necessary to read the new code. Transfusion services are waiting for a variety of reasons, including

fear that it will be an expensive, unnecessary change if suppliers don't actually adopt the change.

Perhaps it is time to revisit the reasons why change was considered desirable and necessary. These reasons include flexibility, security and safety. While it is true that FDA's current regulations for blood labeling do not require use of encoded symbology, we do have regulations that require blood unit traceability from the donor to the recipient, and we do have regulations requiring process control in blood bank operations.

We view the transition to ISBT 128 labeling an important step in insuring traceability and process control. Our reasons include the improvements afforded by the ISBT labeling and donation numbering, security and accuracy.

One of the disadvantages of code-a-bar is the susceptibility to substitution errors, and the lack of space to incorporate a check character to reduce the likelihood of such an error. In 1987, the Automation Identification Manufacturers, AIM, conducted a study of bar code symbology. Of seven codes examined code-a-bar performance rated at the bottom. It was found to be more likely to prevent substitution errors, short read errors, and autodiscrimination errors than other codes examined.

In a comparison of substitution errors with code 128, code-a-bar resulted in errors in 1 in 170,000 characters, compared with 1 in 600,000 to code 128.

Information was presented to this committee in 1995, by the Department of Defense concerning the susceptibility for error with code-a-bar. In Desert Shield/Desert Storm the U.S. military contracted with numerous civilian blood suppliers to ship blood to the Persian Gulf.

In theater operations the military found thousands of labeling mistakes. These included: bar code substitution errors; absence or use of unstandardized donation identification start codes; improper or incorrect start codes in FDA registration number; general noncompliance with the 1985 labeling guidelines; and duplication of donation numbers. All of this resulted in misidentification of units, requiring manual data entry and unit renumbering, and increased opportunity for undetected error, and a decrease in productivity.

Besides the general improvements in readability and accuracy of code 128 over code-a-bar the ISBT 128 labeling structure includes use of a built in check digit. The incorporation of a check digit improves accuracy if

manual data entry is needed. With appropriate software this check digit can insure that the unit number was manually entered into the computer correctly.

Another distinct advantage offered by the ISBT labeling is the donation number format. In one field information is encoded identifying the blood collection center, the year of collection and a six digit consecutive number. This improvement virtually eliminates the fear of a testing laboratory transfusion facility or plasma fractionator receiving units from different sources with identical duplicate identification numbers.

It will eliminate the need for transfusion services to renumber units of blood received from suppliers. This is a practice that is common now, and introduces the potential for error and loss of traceability.

Other advantages that I will not discuss in detail include: better definition of product code; ability to encode more information regarding additional testing performed on a unit of blood, which may include such things as CMV testing and red blood cell antigen screening; improved autologous blood labeling; and inclusion of encoded expiration date and time.

In summary, we strongly support the industry

transition to the new labeling format. The industry consensus document with revisions resulting from our office's review of the draft document, and other comments received by the International Council on Commonality in Blood Banking Automation following the December public meeting was received by us the week before last. It is in our review sign off channels for publication of comment.

We do not anticipate show stopping comments. This change is not new or unexpected. The late Joel Solomon(?) wrote the first article about the need for change in 1989. The blood community has had nine years to think about change. It is now time to stop thinking about change, and begin changing.

The blood community should not feel that they must wait until the consensus document is officially blessed as an FDA guidance. Based on information we have about ISBT 128 we are prepared to approve individual applicants to begin labeling with ISBT 128. To insure uniformity and an organized implementation, we feel the guidance is a helpful tool, but is not critical to our approving use of the code.

Mr. Chairman, members of the committee may have comments. Dr. McCurdy related to me yesterday, concerns about labeling banks' core blood for transplantation. The

size of the bags used for freezing appear incompatible with the length of the donation identifier label.

My flip response to him yesterday was that the bags are obviously too small. I do not have an answer for his concerns today, but discussions with people more computer literate than I should result in a workable solution.

Dr. Holmberg and I spoke very, very briefly before this session. Dr. Holmberg attended the recent ISBT working party on blood banking automation. He shared with me that this is an issue that was discussed, and a working group has been formed to address the concern. Additionally, Dr. Holmberg may want to comment on the status of transition within DOD.

DR. HOLLINGER: Thank you, CAPT. Gustafson.

Dr. Holmberg?

DR. HOLMBERG: Thank you, CAPT. Gustafson. Let me just say that when I do wear this uniform, I do represent the surgeon general of the navy, as the head of the navy blood program. I also sit on the North American Technical Advisory Group for the International Council on Commonality for Blood Bank Automation.

At the current time there are two tags, if you

will, that have been formed internationally; one in Europe, and one here in the North American continent. At the present time, the Pacific Rim nations are also trying to get their tag together, and that is primarily being orchestrated by Australia.

We have very seriously looked at this problem that has been presented to us as far as cored blood, and this is the beauty of the International Society for Blood Transfusion's working party on automation and data processing is that first of all, we realized that there was a need for commonality throughout the world, and secondly was that to try to develop commonality in automation.

As CAPT. Gustafson mentioned, the Department of Defense came across a lot of errors in Desert Shield/Desert Storm. Anywhere in this nation at the present time, with the configuration of the blood facility identification and the unit number there could be multiple unit numbers floating around.

At the present time, that unit number is associated with the facility ID. The beauty of ISBT 128 as CAPT. Gustafson mentioned with the AIM study -- and by the way, this AIM study was not ever published, however, the International Council on Commonality for Blood Bank

Automation is attempting to get that data from AIM.

There are also attempts to try to repeat that study. When that study was performed, there were a lot of manual manipulations with that study to scan the different types of bar code symbology. The label manufacturers have told us that there are mechanisms available now to scan and eliminate the variables. So we are going to be repeating those studies so that we can have more data. Clearly it shows that code-a-bar does have a lot of inherent errors, and substitution errors are very well established.

One of the things that I think somebody mentioned yesterday about automation, that especially with the automated procedures that we talked about yesterday with medical devices, and that basically people are just going to put things into the computer or rely on what the computer says or what the micro chip says.

I think that that is one of the major problems that I foresee even now with code-a-bar, is that when blood bank workers are scanning products into the computer, they listen for the beep of the scan, and they don't look up at the screen to see what the number has been. There are numerous substitution errors presently with code-a-bar, and we within the DOD also have to make modifications when we

receive blood in from other locations.

A study that was just recently done in California indicates that only 28 percent of the blood centers and hospitals are computerized, however, we do see a lot of problems with the start codes; places that are not computerized, but still have code-a-bar on their labels, and the labels have really never been verified to say whether those bar codes really encoding the right information.

As far as the DOD is concerned and the transition, the DOD plans to be ready for ISBT 128 by the end of 1998. We have also sent notice to the American Association of Blood Banks, the Americas Blood Centers, and the American Red Cross that at that time we will require that the contracts that we have with those agencies, that ISBT 128 will be necessary for our transition.

We have received responses back from all of those agencies, and they say that they recognize the direction that we are going. I have to say that the conversion to ISBT 128 is not an inexpensive transition. It will be very expensive, however, that is the initial cost. I believe by the maintaining of product codes, and the core blood is a good example of why we need an organization to maintain the product codes.

Also the software development and the standardization in the international community, and as far as the military is concerned, standardization across through NATO, through the other countries that we interchange blood products with, it is very important for us to make this transition.

To address the issue as far as the cored blood, we did address that in the working party meeting in Edinburgh last week. The size of the blood bags or the sample bag is critical. We have looked at different ways that we can alter the label. There is a task force that is investigating that currently.

Again, the beauty of ISBT 128 is that it will have not only the country where the collection was taken, but also the registration of the facility and a unique number, so that anywhere in the world, whether you are shipping cored cells or a unit of blood, you could tell where that product came from.

So we do realize that the bar code itself is larger, however, the added safety feature as far as the check digit is very important.

DR. HOLLINGER: Thank you very much, Dr. Holmberg, for that evaluation. We appreciate it.

DR. NESS: Just one brief statement as the industry representative. I just wanted to commend the FDA for making a strong statement in this issue. This has been festering around in the blood community for a number of years, and I think this statement will help everybody get off the dime and do the appropriate thing. I think this is a very timely statement.

The only thing I would also hope is the FDA might do is it is my impression that even though this started as an international effort, and the United States participants are still committed to doing this, there seems to be some slacking off internationally of some other countries who were originally involved, and now seem to be less interested. I would hope the FDA would use its clout to whatever extent it can to make this an international effort, so that the technology can be fully realized.

DR. HOLLINGER: Thank you, Dr. Ness.

We're going to move on to the open committee discussion of the topic which is inadvertent contamination of plasma pools for fractionation. The initial talks will be to brief the committee about this issue. It will be followed then by an open public hearing, followed by a break at that time.

So I believe Dr. Tabor is going to introduce the topic, and then we will move on after that.

Agenda Item: Inadvertent Contamination of Plasma Pools for Fractionation, A. Introduction - Edward Tabor, M.D., Director, Division of Transfusion Transmitted Diseases, OBRR

DR. TABOR: Good morning.

I'm going to discuss the very vast and complex issue of inadvertent contamination.

Inadvertent contamination is defined as the presence in a plasma pool or in a plasma product derived from such a pool of a unit of plasma from a donor who was thought to have met all donor acceptance criteria at the time of donation, including negative tests for viral infections, who was subsequently found to have an exclusionary risk factor or a reactive screening test.

In addition, inadvertent contamination now has to include those situations in which a plasma pool itself has been found to have an explained reactive test following pooling.

It is important to differentiate between an adverse event and inadvertent contamination. In the case of an adverse event, the existence of contaminated pool is

discovered based on information obtained from the recipient. In this situation the product is recalled.

In the case of inadvertent contamination, the information is derived from post hoc information on the donor or on the unit, the pool, or in some cases on the final container. The disposition of those products is the topic of today's discussion.

As I said, this is a very complex topic, and there are many different types of inadvertent contaminations. Today we are only going to discuss those that are shown on this slide in yellow. Inadvertent contamination can include situations in which a positive risk factor or history is revealed after pooling. It involves situations in which the tests that are required were performed incorrectly or in which the results were recorded incorrectly.

It can involve situations where a donor sample is tested later or in another location by another method and found to be positive, or where a pool sample is for reason tested later, or elsewhere by another method and found to be positive.

Inadvertent contamination can exist where a more sensitive test is developed and applied to previously collected and pooled materials. There could be situations

where a blood donor has donated whole blood and the red blood cells are discovered to have transmitted infection to a recipient at a time after which the recovered plasma has been pooled.

In addition, there could be situations where post-donation disease symptoms in the donor indicate that there was infection present, or prior donation was learned to have transmitted infection.

Today we are going to limit our discussion to those viruses for which we have tests available to detect them, and to those viruses for which inactivation procedures are available. That is, we are going to limit our discussion to HIV, HBV and HCV. This in order to try to put a boundary around part of the topic, so that we can try to achieve results in the time we have available.

At a future BPAC meeting, probably in September, we will deal with issues in which revision of the donor history of risk factors is the defining factor, or where transmission of disease by a prime donation is the defining factor. At a future BPAC meeting we will also deal with other infectious agents, and we will touch on look back issues related to inadvertent contamination, and the impact of nucleic acid testing, although that will be touched on

briefly today also.

The history of inadvertent contamination regarding hepatitis B virus is shown on this slide. In 1973, the first third generation test for detecting hepatitis B surface antigen became available, and their implementation in blood collection was required by 1975.

Between the year 1975 and 1979, the concept of inadvertent contamination was recognized. Also in this period the concept of high risk and low risk products for transmitting hepatitis B was defined. This was based in part on a re-analysis of the sera collected in volunteer studies in the early 1950s, and retested with the newly available serologic tests in mid- to late-1970s. Also on the clinical experience that was accumulating with these products.

Then in 1983 to 1985, two of the high risk products at that time, antihemophilic factor and Factor IX complex were subjected to viral inactivation. This was done largely because of HIV, but it had a positive effect on eliminating the risk from hepatitis B virus also.

The history of inadvertent contamination with regard to hepatitis C virus is shown on this slide. Hepatitis C virus infection, which makes up the vast

majority of non-A, non-B hepatitis was recognized as a major transfusion problem in 1975.

In 1981, my laboratory showed that hepatitis-c virus, or that is non-A, non-B hepatitis could be inactivated by heating it 60 degrees for 10 hours. This was also shown in 1983, by other laboratories, including that of Dr. Hollinger. In 1988, the hepatitis-c virus was first identified, and in 1990, assays to detect antibody to hepatitis C virus were licensed.

Throughout these years the concept of high risk and low risk product was maintained for hepatitis C virus based on extrapolation from epidemiologic similarities to hepatitis B virus, and to a consistent experience with various products in a clinical setting.

This slide shows the history of inadvertent contamination with regard to HIV. Between 1981 and 1983, the disease AIDS was recognized. During these years its viral etiology was hotly debated even by expert virologists. In 1984, the virus itself was discovered, and again the concept of high risk products and low risk products persisted based on parallels between HIV infection and HBV and non-A, non-B hepatitis.

In 1985, the anti-HIV assays were licensed for the

first time, and by 1985 to 1986, experimental fractionation studies and experimental inactivation studies showed that HIV could be eliminated by the manufacture and inactivation of some products, and it supported the application of the high risk/low risk concept for HIV.

To a great extent the risk of inadvertent contamination comes from window period donations. These data that are well known to many of you from an article by Dr. Scriber(?) show the number of window period donations that could be expected per million donations of whole blood. While these figures may not be exactly the same as you would expect from plasma donors, they do give you an idea of the risk. His data show that there would be two window period of donations per million units for HIV; more than nine per million units for HCV; and more than 15 for HBV.

Now there are some issues with regard to inadvertent contamination that I would like you to keep in mind. I would like to point out also that these are not questions for the committee that I'm showing at this time.

First of all, inadvertent contamination as a concept really came into existence when we could first test for viruses. Prior to that it was an issue that did not exist. It is possible that the issue will be reborn with

every new assay that we develop and require for testing blood and plasma.

I would like you today to think about what the impact of viral inactivation and removal is on possible inadvertent contamination, and whether risk assessment can be used to determine the disposition of products so affected.

Should the impact of product shortages be considered in determining regulatory action for inadvertent contamination?

Should the pool be destroyed? What about in process product or final product that is still in inventory? Should product that has been distributed be recalled?

We need to define some of the regulatory terms that we'll be using in the discussion today. Quarantine is defined as the sequestering of in process materials that are possibly unfit for their intended use.

The terms used for final product -- unlike the term "quarantine," which is for in process materials -- the terms used for final product are actually defined in the federal regulations. Stock recovery is when a firm removes a product that has not been distributed yet. Market withdrawal is when a firm removes a distributed product for

a minor violation or no violation, and it is used in situations where FDA would not take legal action had the firm not done so.

The term "recall" is when a firm removes a distributed product that FDA considers to be in violation of the laws that FDA administers, and it is used for those situations in which FDA would take legal action if the firm did not recall the product.

I would like to just mention that the availability of the highly sensitive nucleic acid tests, including PCR have changed the way in which we can investigate cases of inadvertent contamination. Once an implicated pool has been identified and quarantined, it becomes possible not only to test it with the currently required viral marker tests, but to use nucleic acid tests to detect virus in the pool and in the final product.

However, at the present time there are still serious problems with the use of nucleic acid tests in evaluating inadvertent contamination. Most of the available tests have not been validated for testing pools of plasma or final products.

Most of the available tests are qualitative and not quantitative, and it is necessary in investigating

inadvertent contamination to do quantitative assays to make sure that the amount of virus detected in the pool or product, if it is so detected, is consistent with the amount that could get there after going through the process of dilution and removal resulting from the manufacturing process.

Finally, the most serious problem with any nucleic acid test is the fact that when you have something that is by far the most sensitive available test, you have a difficult time proving that what you have detected is really there. It is necessary to have some sort of algorithm for confirmation of the result.

At the present time, this could involve testing the material again, using a different primer set. It could involve testing a different aliquot of the sample. Or it could involve, in the case of a possibly infected donor, obtaining a follow-up sample to test with the same method.

As we proceed with our discussion, we should realize that we may have a better situation ahead of us in a few years. Nucleic acid testing of plasma pools is the hot regulatory topic of 1997, and will surely be in place to a large extent before too long.

In addition, I think it is very likely that in a

few years we will achieve the technological capability of applying nucleic acid testing to individual units. When that time comes, I wonder whether we will eliminate many of the types of situations that we now call inadvertent contamination, although we will never fully eliminate that due to human error.

Before we move on to the other presentations, I would like to go over briefly the questions for the committee so you can keep them in mind during the discussion. I'll just read them.

1. When notified of inadvertent contamination of a fractionated pool with units reactive for HIV, HBV or HCV should FDA: (a) uniformly quarantine for recall all products as violative; or (b) determine regulatory action based an assessment of product risk such as considering the impact of virus removal or inactivation?

2. Considering the recommendation made in question 1, should FDA modify its actions based on the possibility of product shortages resulting?

3. If products affected by inadvertent contamination of a plasma pool by units reactive for HIV, HBV or HCV should not be distributed, then (a) should any distinction be made between in process and final products;

(b) if so then, under what circumstances should in process products be quarantined?

4. Should a different approach be taken when there is a known positive unit, or when it is a question of a positive pool, or a different approach for one type of product or another?

5. Under what circumstances should previously distributed products be recalled?

Thank you.

DR. HOLLINGER: Thank you, Dr. Tabor, for that introduction.

MS. PIERCE: Dr. Tabor, when you talk about positive pools, just to clarify, is that before or after an activation technique has been done?

DR. TABOR: Well, the concept of inadvertent contamination, as I said, has really been in existence since the mid-1970s. At that time, the only inactivated products were albumin and PPF. Since the introduction of other activation procedures, the concept and its application have been changed somewhat.

Now you are asking about -- I believe you are asking whether it is still inadvertent contamination if it has been inactivated?

MS. PIERCE: No, no. When you are talking up here about the pool being contaminated, are those tests done on the pool before or after inactivation?

DR. TABOR: Let me try to answer it. As you know, individual units that are donated, are tested as required by regulation. If these are all negative, and the donor histories are appropriate, these are pooled together to make a large pool, which is then processed to produce the products you are familiar with.

Theoretically that pool should be negative, but there are situations where it could in fact be positive unbeknownst to the people who are preparing. For instance, the technician could have incorrectly done a test, and that might be discovered in an audit later. Or there are situations now where some groups are actually testing the pools using PCR, and they may discover a positive pool.

The pool at that point has not been subjected to inactivation procedures. Now with some exceptions -- and we can discuss this later in some of the other talks, and I think particularly after Dr. Lynch's talk -- in general, inactivation is done on the final product, for reasons that we will discuss.

MS. PIERCE: I just wanted to clarify that.

DR. TABOR: Yes.

DR. HOLLINGER: Thank you, Ed.

The next talk is on current procedures by Alice Godziemski.

Agenda Item: Current Procedures - Alice Godziemski, Consumer Safety Officer, Division of Inspections and Surveillance, OC

MS GODZIEMSKI: Well, Dr. Tabor gave a definition for inadvertent contamination, but how does the FDA apply it? This term has been applied by the FDA for situations in which one or more plasma pool or plasma units did not comply with all applicable FDA regulations and guidance, and is used to manufacture plasma derivatives.

Now the plasma can come from either recovered plasma or source plasma. The noncompliance is due to the fact that the collecting facility has learned subsequently that the donor was unsuitable, or the unit of plasma was improperly tested.

Current procedures that are employed in CBR is that the Office of Compliance, Division of Inspections and Surveillance has the responsibility for processing the correspondence concerning the advertent contamination of plasma pools used to manufacture plasma derivatives.

This information comes via two ways. We either learn about it from a recall that has taken place, or directly from the fractionator. Usually the fractionator or manufacturer in this case requests release of final products under Title 21, Code of Federal Regulation, Part 640.120.

We use previous case precedence for or direct consultation with the scientific staff to make a decision, and based on that decision and outcome either a 640.120 alternative procedure letter, or a disapproval letter is issued.

Now what does Title 21 CFR 640.120 say? Well, it provides alternative procedures that blood, blood components and blood products may be licensed, collected, tested, labeled, stored and distributed in ways alternative to those specified in the biologics regulation, only upon approval of the director, CBER.

So probably everybody wants to know what kind of situations has CBER disapproved and approved? CBER's current procedure is for unit suitability problems, we have a repeat reactive viral marker test, positive confirmatory test for reactive supplemental test, no final products or intermediates are suitable.

A repeat reactive biomarker test indeterminate or

nonreactive, confirmatory or supplemental test, with no further testing done on the donor -- this is also a situation where no final products or intermediates are suitable.

The last case would be a repeat reactive, initially reactive or untested biomarker test with no further testing done on unit or donor.

So all of these situations would be prohibit final products or intermediates from being released or from further processing. The rationale for this is that there is potential for infectious disease transmission, and the FDA regulations prohibit its use.

On the flip side, for unit suitability problems, if we have seen a repeat reactive viral marker test with negative confirmatory or non-reactive supplemental test, but additional testing was done on a donor, and from that additional testing the donor meeting re-entry criteria. In these situations all final products and intermediates are suitable for release and for processing.

The same way for initially reactive, untested, incorrectly tested biomarker tests, where further testing was done on a donor or the unit, and that testing is negative. This also results that all final products or

intermediates are suitable.

The rationale for this is that the negative further additional testing that was done is strong evidence against infection in the donor. Also, the viral inactivation process for the derivatives is also considered, which will be discussed later in this presentation.

To put this in terms that I believe that it would mean more to everyone, let's look at actual precedent cases that have come across CBER's desk. CBER has issued disapproval letters for the following cases:

A unit tested repeat reactive for anti-HIV by EIA; the donor previously tested repeat reactive for anti-HIV-1 by EIA and Western Blot positive; a unit tested repeat reactive for anti-HCV by a multi-antigen assay, and tested positive for anti-HCV by supplemental test; and also the unit tested non-reactive for anti-HIV-1, but the donor previously was repeat reactive for anti-HIV-1 and Western Blot positive.

CBER has issued approvals in cases where a unit tested non-reactive for anti-HIV-1, but the donor previously tested repeat reactive for anti-HIV-1 by EIA and Western Blot either negative, indeterminate or not tested; where the unit tested non-reactive for anti-HIV-1, but donor

previously tested initially reactive for anti-HIV-1 by EIA and not retested in duplicate as required by the manufacturer's instructions; or the unit tested non-reactive for viral markers, but the donor was previously incorrectly tested for anti-HCV.

In these cases, other factors played an important role in the decision-making process such as the nature of the event and the product; the documentation of the manufacturing process; and the robustness of the viral elimination procedure. All decisions considered the benefit versus the risk factors. The clinical benefit of having the products available outweighed the theoretical risk posed by the inadvertent contamination.

Just to give you some numbers of what we have seen, and it's kind of on the down swing. For fiscal year 1995, there were 12 requests that were approved in the Center for Biologics. In 1996, we only saw nine, and to date in 1997, we have only seen two requests.

That's how CBER handles inadvertent contamination.
Thank you.

DR. HOLLINGER: Any questions from the committee?

If not, we will go to the next speaker on risk assessment, but Dr. Kimber Poffenberger.

**Agenda Item: Risk Assessment - Kimber
Poffenberger, Ph.D., Regulatory Scientist, Division of
Transfusion Transmitted Diseases, OBRR**

DR. POFFENBERGER: Good morning.

The questions that you have been asked require you to tell us or give us some guidance on inadvertent contamination. That is primarily, how should the action that we are going to do, be taken? Should there be a uniform action, or should there be a risk assessment or some evaluation perhaps on a product-by-product basis?

My goal is to give you a perspective on risk assessment for plasma products, and I'm going to do that from the basis of risk into the plasma pool, and Tom Lynch will follow and talk about inactivation processes as they go into products.

I'm going to give you a perspective on risk assessment. In order to keep things simple, because risk assessment is a highly complicated subject no matter what you are talking about, I'm going to use as a yard stick, the nucleic acid amplification techniques that have been in use for a good number of years now. Those techniques will be used to talk about how much virus may or may not be present in a pool.

So today when I speak about risk assessment, what I'm talking about is the risk that a plasma pool will contain a unit infected with HIV, HBV or HCV. I'm going to give you some estimates of the viral load that may be in that pool. I'm going to separate the discussion of risk into two areas: the area of background or unavoidable risk, which is inherent in a plasma pool, that is for a pool that contains only screening test negative units; and then I'm going to talk about the risk from something that we would call inadvertent contamination, that is, a pool that we know has a screening test positive unit, or we suspect has a screening test positive unit.

The methods that are used to evaluate risks to plasma pools fall in two categories. The first category, and probably the most effective is the direct method. That is, follow-up of the recipient. Has the transmission occurred?

The other two categories for which most of the data is available are long-term surveillance of donors, and additional testing of donor units. That is, in this case by nucleic acid amplification. These two things, the surveillance numbers, and what we now know about the length of the window period and the progression of disease in

individuals all combine to give us a fairly statistically significant method for evaluating risk.

What are the sources of risk that a pool of plasma may have virus in it? The primary source that I have listed here is the window period; that is, a donation made when a donor is infected and viremic, but has not sero converted, and hence their unit will not be screened out.

There are also immuno-silent infections. For instance, there may be some chronic HCV patients who become antibody depleted during the course of the infection, and yet still have detectable HCV viral RNA.

There may be donors infected with viral variance. There may be testing errors, where you get a false negative result for a unit. That can be due to a lot of different reasons.

The first three sources are lumped into the subject of background or unavoidable risk. That is something that we cannot screen out at this time. The bottom two sources, testing error and processing error, some of them possibly may be unavoidable, but a lot of them would be termed inadvertent contamination. I'll go on to talk about the numbers.

Dr. Tabor gave you a brief discussion of the risk

that a window period donation may be made. This table comes from material that has been presented at least in part at the AABB meeting last fall. It has been modified somewhat. It comes from the Red study, from American Red Cross studies, and it also comes from information from some plasma product manufacturers who have been screening pools with nucleic acid amplification. So there is a composite of information here.

The numbers are broken out for the four different sources I discussed before: window period, viral variance, immuno-silent or atypical sero conversions, and test errors. What I would like you to notice from this slide is the total risk -- this is per million units -- for HIV is about 1.6 per million units from these studies; for HCV it runs from 10 to 110 units; and for HBV it is about 16 units.

The window period comprises the majority of the risk from these unavoidable risk sources for HIV and HBV. It may also compromise the majority of risk for HCV, but that is a sort of moving target at this point. Some manufacturers who are screening plasma pools have seen pools that are positive for HCV RNA, but when they go back and check the donors, they remain negative for HCV antibodies.

There have been preliminary look backs on some of

these donors and the units that they had previously donated, and as yet there has no record of sero conversion in the recipients of those units, so at this point we do not know whether the incidence of HCV RNA means that there is infectious HCV in those units. That's why the numbers range so large for HCV at this time.

From this slide you can see that for HIV and HBV definitely the window period is the largest source of risk, and for HCV it may also be the largest source of risk.

This slide now is a summary taken from many different papers, presentations, in-house FDA information and information from some manufacturers to try and pin down what is the relative viral load that you would detect in a unit of plasma.

What we are talking about here, and I really have to emphasize this, is nucleic acid copies per ml. That is the yard stick I am using today to talk about contamination of units. When you are talking about nucleic acid copies, you are not necessarily talking about infectious doses, however, nucleic acid amplification is the most sensitive technique we have right now, so that is the one I chose to discuss.

You can see I have separated out the categories

into units in the window period and sero positive units. For HIV and HCV the peak viremic phase typically occurs prior to sero conversion for antibodies. That's why the ranges spike up very high; HIV for the range is from 10^3 to 10^7 , and we have tested occasional samples which go up to a 10^8 range for HIV nucleic acid copies.

In brackets for the categories I have listed what is the predominant range, that is most of the units tested will test in that range. For HCV in the window period the range is from 10^3 to 10^8 again, and typically you see a little bit greater than 5 times 10 to the sixth load. HBV ranges from 10^3 to 10^6 , with occasional spikes to 10^7 .

Sero positive units on the other hand for HIV tend to fall in a lower range. They don't spike up so high, 10^3 to 10^6 is the typical range. For HCV, 10^3 to 10^6 also.

For HBV it gets a little complicated. I have included in sero positive units, units that are reactive for hepatitis B surface antigen, and that reactivity tends to coincide with the peak viremic phase. So the spikes here will range up to 10^7 and sometimes 10^8 . Typically, once you have come off the viremic phase, most HBV infected patients will be cycling between a load of 10^3 to 10^5 copies per ml.

So as you can see, there is a pretty large range

here, but I am going to try to use these numbers to give you some perspective on how much virus may be in plasma pools. In order to do that, I'm going to use the upper end of the range, so that we know that I'm talking about the most virus that would be going into those pools.

This is a summary slide of the unavoidable risk going into a plasma pool. That is for pools containing only screening test negative units, what is the number of infected units predicted per pool? I have that listed in the column in the left under each viral category. On the right, the column gives the maximal number of nucleic acid copies for ml if you would have a single infected unit in that pool.

I have chosen pool sizes of 60,000 units or 10,000 units. A 60,000 unit pool might be typical of a pool of recovered plasma donors. A 10,000 unit pool might be typical of a pool of source plasma donors.

As you can see, the number of infected donor units expected for HIV reflects back to the 1.6 in 1 million units I reported a few slides back. The maximal number of copies you would get in that 60,000 unit pool would be about 1,700 copies per ml for HIV. It goes up to 10,000 copies per ml for the smaller pool size. For HCV the maximal copy number

would be about the same as for HIV. For HBV the copy number would be slightly lower.

Now I want to emphasize that this information is using the maximal load that we have ever detected using a nucleic acid amplification test. That is the risk from an unavoidable contamination. That is, a single unit in the window period got into the pool. The ranges for maximal level is from 10^2 to 10^4 copies per ml.

What I want to go on and talk to you about now is the risk and the viral load that may be there in pools containing a single unit that has tested positive for the viral marker. Before I talk about the actual viral numbers, you heard from Alice that there are different incidents that may indicate that a pool has been inadvertently contaminated.

In particular, we may receive information that a single unit which tested repeat reactive is in the pool, but because of certain circumstances, no further testing was done. In order to know how much risk there is in that pool, you need to know what is the rate that repeat reactive donors confirm as positive units.

The top line in white, listed as volunteer donors, gives some of the most recent numbers from volunteer donors.

This is primary information from Red Cross surveillance. Eight percent -- I'm sorry, the categories have shifted over. The first column is HIV. The second is HCV, and the third is HBV.

For volunteer donors, 8 percent of HIV repeat reactivities EIAs will confirm as positive; 61 percent of HCV repeat reactivities; and 50 percent of HBV repeat reactivities.

Source plasma donors, I have that asterisked here, because I did not get recent data for this. What I have used is prevalence data that was reported from studies conducted between 1984 and 1992, that were discussed at the 1993 workshop on safety of plasma donations. So I'm sure there are better and more recent numbers that someone may care to comment on later.

For HIV, the number of repeat reactivities which confirm as positive for HIV was 63 percent; for HCV, 96 percent; and for HBV I didn't have sufficient data to give you a good number. So that's the risk. You know if you hit a repeat reactive, you've got a 1 in 12 chance that that is actually a positive donor.

Now the second section of this slide is giving the viral load in copies per ml if a definite positive unit has gone into the pool. Here again I have used the same pool

sizes, and I have given a range of viral load that is taken from the range of viral load that was detected in sero positive units. In this case the range, when you have a repeat reactive unit in a pool is from 10^{-2} copies per ml up to 10^4 copies per ml.

So now you have an idea of how many copies per ml may go into a pool if the single unit comes in. We have to make decisions about risk to a product based on this information and the consideration that there may be more units there.

So I set up some numbers giving a worst case scenario. In this case, I envision this someone on the order of chance of happening as that volcano that erupted in L.A. in that movie, but in any case, it's possible. In this case I have assumed that more than one infected unit went into the pool, ten infected units went in. Each of these units were at the peak viral load that we have detected so far.

In that case, I have given, going down vertically, and on the left in white are the numbers for the 60,000 unit pool, and in red are the numbers for the 10,000 unit pool. We're talking a 10^3 to the 10^5 range of nucleic acid copies per ml in these copies. This is nucleic acid copies, and

not infectious doses.

This is just to give a summary and give you your full perspective here. So coming from the worst case scenario, the maximal load will be 10^2 to 10^5 viral nucleic acid copies per ml. A typical case would be somewhere around 10^{-2} to 10^4 copies per ml. In any case, we have got these copies sitting in a pool.

The pool then goes on to be made into product. It undergoes fractionation, which separates the virus into different components. It also undergoes inactivation. All these factors combine to give a total clearance factor for each product that is made from that plasma pool.

The clearance factors that we have defined and that have been validated so far combining all three viruses across different products range from 10^{10} to 10^{17} . Tom Lynch will be talking about that later.

What I have done here is a little elementary exercise. If you take your maximal load of 10^5 copies, and you divide by the 10^{10} or the minimal clearance factor, the highest load you would expect in a very worst case circumstance would be 10^{-5} copies per ml into the pool. If one dose is equivalent to 1 liter, that would bring you to 10^{-2} copies per dose.

So that is the very, very upper limit that we are talking about here if you have a contaminated unit in a pool. I would like to emphasize that the risk to the recipient is going to be several orders lower because in particular, clearance factors are based on infectious dose removal. It is known that copies of virus -- there are always multiple copies of virus that are needed to make one infectious dose of virus.

If we expand this calculation to include the 10^{17} clearance factor, what you are left with is for the different products, the very upper limit of contamination will range from 10^{-9} to 10^{-2} copies per dose.

So you can see that while the risk is not zero, it is very low, but it will vary because of many of the input variables, and because of the differences in product manufacturing and clearance. This data has been primarily derived from indirect data, but is reinforced by direct data tracking of transmission of disease to recipients.

I think I will end here and let Tom talk to you about our information on inactivation.

DR. HOLLINGER: Any questions? There is a lot of data. It would be nice if the committee would have had this information some time before this meeting in order to act

properly.

Yes, Dr. Nelson?

DR. NELSON: I didn't understand some figures, but one that came up was your hepatitis B at 50 percent. Now HIV and HCV both have confirmatory or second tests, but when you do hepatitis B surface antigen, that is considered positive. Are you saying that 50 percent of people that are hepatitis B surface antigen are not infected with hepatitis B?

DR. POFFENBERGER: I probably didn't separate that out very well. I'm sorry, I think we are talking about anti-core reactivity at that point. I'm sorry.

I would have to confirm that. I would have to look at my notes on that, because that information came primarily from Sue Stramer(?) at the Red Cross.

DR. NELSON: I would think the core might even have more false positives than 50 percent.

DR. POFFENBERGER: Possibly.

DR. LEITMAN: I actually had the same consideration. I don't understand the HBV confirmatory data, 50 percent for repeat reactive. Maybe you could clarify that.

DR. POFFENBERGER: I'm sorry, I can't hear.

DR. LEITMAN: It's not my experience in our blood center of HBSAG repeat reactive has a confirmatory rate of 50 percent. I'm not sure I understand what does it mean to have a confirmatory rate of 50 percent? What is the confirmation that you use?

DR. POFFENBERGER: Oh, I'm sorry. That is the rate where your repeat reactive is indeed a positive unit. Those are the numbers I was given based on incidence numbers from Sue Stramer. She couldn't be here, so I can't really discuss it.

DR. NELSON: Unless this represents hepatitis B surface antigen that also has antibody, in other words complex, but I wouldn't think it would be 50 percent. In other words, again, it might not be infectious.

DR. POFFENBERGER: Where would you all expect the number to be?

DR. NELSON: Ninety percent.

DR. POFFENBERGER: You would expect it up at 90 percent. Then I would like to say that I should probably update some of that information. We can correct that later, but I would want to check that.

DR. HOLLINGER: The other thing, the copies you said for the sero positive samples for HBV you have as 10^3

or lower?

DR. POFFENBERGER: No, 10^3 was the lower limit.

DR. HOLLINGER: And the usual number is what?

DR. POFFENBERGER: It's hard to have a usual number. What I said was once you have gone through the peak viremic phase, there is some fluctuation after that. There is more limited data for HBV, but the range is generally from the lower limit of detection; 10^3 is the lower limit of detection for most of the assays, but you would see anywhere from 10^3 up to about 10^5 .

DR. HOLLINGER: For HBV?

DR. POFFENBERGER: Yes.

DR. HOLLINGER: There are huge numbers of virus circulating with HBV -- in the millions. I mean 300 million. You are talking about something else.

DR. POFFENBERGER: Yes, that is seen. The number went up to 10^8 also. We have also seen up to 10^8 .

DR. HOLLINGER: This 10^3 is way too low for an average number; even 10^5 .

DR. POFFENBERGER: I wasn't projecting the range. That's the range. It's not the average. I don't believe that I gave the average as 10^3 . You think 10^5 is too low for the average?

DR. HOLLINGER: In my opinion it is. You're seeing hundreds of millions of particles. Many of these patients have, as I said, probably even 100 pico grams, and a pico gram is about what, about 3.3 million. So 3.3 million is at the -- the lower limit is 330,000 with the hybridization technique, which is a fairly insensitive technique. So 100 pico grams would be also 330 million, and that's not a very large amount.

So anyway, as I said, I think this data needs to be --

DR. POFFENBERGER: All right, for the HBV data I would like to emphasize that that was the weakest part of the data, and I was looking at somewhat limited numbers. This is data from people who have made donations. This is donor unit screening, and that is where those numbers came from. That is why I included that 10^8 . When all the calculations were made, the 10^8 number is what was used, not the number that was given in brackets.

DR. LEITMAN: I have a question that ties this last presentation and the prior presentation together. In the prior presentation the kinds of requests from plasma pool or fractionation manufacturers that were disapproved were pools in which there appeared to be a breach in

manufacture, in that units that clearly tested positive were allowed to enter the pool.

Were those picked up on simple clerical process review, or were those picked up by PCR testing of pools?

DR. POFFENBERGER: I don't know about these particular cases. It sounds like we don't know how they were picked up.

DR. HOLLINGER: Thank you very much.

The next speaker is Thomas Lynch, who will talk to about viral inactivation of plasma derivatives.

DR. FINLAYSON: Could I make one more comment?

DR. HOLLINGER: Sure.

DR. FINLAYSON: I have a question and a comment. Dr. Hollinger, were the numbers for HBV that you were citing from patients? So the difference between patients who are sick and patients who present themselves with as blood donors could conceivably be different?

DR. HOLLINGER: Yes, many of these actually were detected as blood donors in the first place.

DR. FINLAYSON: The second thing that I perhaps can give an answer to the question that Dr. Leitman asked, far and away the most common situation in which an

inadvertent contamination is revealed is by an audit of records. In other words, either the blood establishment itself or an FDA inspector, or an outside group that is being used as part of quality assurance goes over the record and finds something that in fact tested out positively, was recorded as negative.

Now in the somewhat distant past we were faced with situations in which an audit showed a mechanical testing error, that is a setting of a machine was at a different setting, and in fact things that were read that is below the cut off, should in fact have been above the cut off. That is the typical scenario.

DR. HOLLINGER: Thank you.

**Agenda Item: Viral Inactivation of Plasma
Derivatives - Thomas Lynch, Senior Staff Fellow, Division of
Hematology, OBRR**

MR. LYNCH: Thank you, Mr. Chairman, committee members.

This morning I want to provide an overview of viral inactivation methods, and the procedures for validating them. After this general overview, I want to give you some idea of the actual application of these methods, with particular instances of individual products.

This is not intended to be a comprehensive survey of all manufactured products for which viral inactivation clearance methods are applied, but just to give you a flavor of how these methods work in practice. Of course any risk assessment must be done on an individual product, on a case-by-case basis.

Now clearance steps in manufacturing are only one element in the total safety profile of any product, but they make an essential contribution. They have proven very effective with respect to the viruses at issue today, hepatitis B, hepatitis C and HIV. In fact, screening and testing cannot entirely eliminate the possibility of window donations entering a manufacturing pool and the manufacturing stream.

The safety of products made from such pools depends on the effectiveness and the reliability of the viral clearance methods incorporated into the manufacture of those products.

Now clearance is a general term. It may include methods that either inactivate or remove viruses. They are typically associated with one or more manufacturing steps that may either have been specifically designed and incorporated into the process to clear viruses, or may have

their primary purpose in the production of product, but as an added benefit, are effective in removing viruses.

Now the effectiveness of these steps is demonstrated by validation studies, which I will describe in a moment. The reliability of these methods depend on assuring that the production methods and practices conform to the validated process.

With respect to the actual methods, inactivation includes a variety of heating protocols under different schedules, depending on temperature and condition. They are listed here; as well as chemical methods, including solvent/detergent, which is an example of a technique that is specifically intended to inactivate virus.

Also included: the effect of ethanol, which is used in the fractionation process itself, or low pH, which is incorporated in the manufacture of some immune globulins. Although their primary intent is to produce product, they also are effective against some viruses.

With respect to removal, again there is partitioning during purification. Ethanol fractionation is one general example; chromatography is another. While these are basically production methods, they also are effective in partitioning some virus away from the product.

Now filtration is a removal method that is coming into use just recently, that is again specifically intended now for viral removal. The name refers to the small pore sizes of these filters, but it must be remembered that absorption may also play a role in their function.

Now validation of any particular clearance step or method starts with the selection of the method itself. This is almost always dictated by the characteristics of the product. The product must survive the method without damage or significant change. Once that method is selected, the production scale process must be scaled down to a laboratory model. This is required because the introduction of viruses into production facilities is considered undesirable. So a laboratory model was constructed with which to perform the validation.

Then the starting material that feeds into the step is spiked with a marker virus. Where possible, relevant viruses may be used, but usually model viruses that are selected to represent some characteristic or multiple characteristics of a virus of concern are used.

The operations performed and the virus titers or concentrations in the starting and ending materials are compared. This gives you a measure of the steps' capacity

for virus removal or inactivation.

Finally, to make sure all of this has some bearing on actual manufacturing practices, compliance with GMPs assures that the methods are applied faithfully, and consistent with the validation studies that have been performed.

I want to highlight two elements in this step, because they play key roles in the reliability of the data that is available to us on the effectiveness of these clearance procedures. First of all, the scale down is intended to construct an accurate model of the production process. So it goes without saying that certain physical parameters -- time, temperature, pressure, so on -- should remain constant, while the other physical dimensions are changed, but in proportion to one another -- volumes, load, surface area, and so forth.

Now this accomplishes basically a miniaturization of your manufacturing process, but having done all this, one must still verify that your laboratory model performs as an accurate replica of your production scale. So the capacity, yield, purity and so on must be demonstrated in the laboratory procedure before proceeding to the actual validation study itself.

With respect to the virus titrations, Kimberly alluded to the fact that very high tiders of virus are used in these studies. This increases the dynamic range of the assays that one is using, but it also contributes to the safety factors that are the result of these validations. The range of viruses that can be used are often dictated by which viruses are available in sufficiently high tider stocks.

The assays that are used to measure the virus must be validated. Most studies today are conducted with in vitro infectivity models that measure such things as cytopathic effect or plaque assays. Animal models are more rarely used, although in the past models such as the chimpanzee have been used. Biochemical assays -- it must be verified that the measure, be it PCR or an immunological-based assay does in fact reflect the infectious particles present in the inoculant.

Finally, the study itself must have certain design features -- of course positive/negative controls, and the evaluation methods must be adequate. With respect to removal methods, it is considered essential that the overall recovery of virus and the distribution of the virus over the process step be determined.

Similarly, when one is validating an inactivation method, it is equally important to demonstrate the kinetics of this inactivation. These two elements measure what is sometimes termed the robustness of the process.

I apologize for this. This is a bit hard to read, but the point is that of the three viruses in question today, only HIV-1 is used directly in the validation studies. For hepatitis C there are two fairly well recognized and established model viruses, bovine diarrhea virus, and Zeliki(?) forest virus that are related to the hepatitis C virus, but for which in vitro assays exist.

There really isn't a good related in vitro assay model for hepatitis B. In the past, chimpanzees, primate models have been used. There is also another animal model based on the duck hepatitis B virus, but by and large the use of a range of other envelope viruses that may be resistant to one inactivation procedure or another provide supportive data that all of these viruses are effectively inactivated or removed by the process step in question.

What one gets out of a validation study is a numeric measure that is sometimes referred to as a clearance factor. This is a proportional reduction in virus concentration. So because it is only proportional, you can

never formally demonstrate that virus concentration goes to zero. As Kim alluded to, the proportional reductions can reach almost astronomical numbers. So while a virtual zero is not achieved, in fact the removal or inactivation often approaches it.

Also it should be borne in mind that the effects of multiple clearance steps in a production process may be combined if and only if each has been independently validated, and each is based on a mechanism that is independent from all other inactivation or removal steps.

Before moving on to the examples, I want to emphasize the critical importance of this tripartite assurance system that provides the safety of manufactured products from inadvertent contaminations, or the background risk associated with pool products.

It is of course the production process itself that provides the safety, but our knowledge about that process depends on information gained from a laboratory model. To assure that that model reflects what we are relying on, the scale down to construct that model must be adequately validated.

The measurements made with a model, the titration studies themselves, the methods must be validated, and the

results must be accurate and possess a high degree of confidence. Once one has validated a certain extent of clearance, the assurance that that safety factor is in fact achieved on a lot-to-lot, day-by-day basis depends on the application of good manufacturing practices.

I want to talk about a couple of examples from several product categories. Albumin and PPF are the first. They are in fact the exceptional products, because they are subjected an inactivation procedure that has been conducted for many years, that is mandated in the CFR.

Immune globulins, both intravenous and the immune globulin human, that is the intramuscular product, and the coagulation factors will follow.

This is just to remind me to tell you that for some of these products -- all of these products are derived from plasma pools that are subjected to ethanol fractionation to produce on one hand immune globulins, and on another hand albumin. So these two product categories are exposed to ethanol.

Whereas the coagulation factors, Factor VIII and Factor IX are drawn off the process before the addition of ethanol. That is something also to keep in mind. You will see ethanol crop up for the immune globulins and albumin,

but not for the coagulation factors.

Albumin and plasma protein fraction; they are exceptional because they are subjected to the mandated inactivation procedure. This is sometimes, but erroneously known as pasteurization, but because John Finlayson is here, I will call it 60 degrees for 10 hours.

The second exceptional aspect to these products is that the validation that is available in the public domain has been done primarily as scientific or academic studies, rather than the product-by-product related validation studies that will characterize all the other products.

Now we know that removal of some virus occurs during fractionation. That is true for hepatitis B, hepatitis C and HIV. We also know that inactivation during heating occurs by a variety of studies, including the early studies by Drs. Gellis and Murray, and more recent studies actually from CBER with HIV.

What is interesting to note, at least to me, hepatitis B, although there is some removal of virus during fractionation, it is known that these products, if not heated sufficiently, are still capable of transmitting this virus. This was established many, many years ago. So the combination here of the fractionation and the 60 degrees for

10 hours is what renders these products safe with respect to hepatitis B, and I suspect that the same argument obtains for hepatitis C and HIV.

In any event, it is important to bear in mind that since the heating of final containers of these products has been initiated, there have been no confirmed transmissions of hepatitis B, C or HIV, and that is really a remarkable safety record to my mind.

Moving on, another product category that has had a long safety history, the immune globulins. I'll start with the intramuscular preparations. Recently inactivation procedures have begun to be incorporated into these products as well.

Now I'm going to show you a series of tables that look very much like this. The numbers are exponents, log tens of the reduction or inactivation factors. Individual steps are identified over here, and then where appropriate, the cumulative clearance factor is given on the last line.

The little symbols here, greater than indicates that during the validation study virus was removed below the limit of detection. This is the sole example where this occurs, but it's a good example; clearance of an order of magnitude, a factor of ten or less is not generally

considered to be significant. So we are talking about significant, truly major reductions in viral titer.

This product, two purely production steps were validated, the ethanol fractionation and treatment of the product with pH 4 and pepsin. The cumulative reduction factor for HIV is about 11 logs, and for BVDV, this is our hepatitis C model 4. Zelicki forest virus, another hepatitis C virus greater than ten logs.

Another intramuscular preparation adds an active viral kill step using solvent/detergent. This has been validated out to about five logs using HIV and simbus. Overall clearance for this product over four viruses is about 10^{10} to 10^{11} .

Intravenous immune globulins, in this case we have both ethanol fractionation and pH 4, so production steps, and solvent/detergent. The validation of BVDV or hepatitis C model is around 11 logs, and HIV around 17.5.

Another intravenous preparation uses heating at 60 degrees for 10 hours, and this is instructive because of the possible relationship with albumins. HIV, 13 logs -- those should be greater than 13 logs. BVDV, around 10 logs or better.

Moving onto the coagulation factors, this product is also pasteurized. Again, an enormous amount of HIV is cleared, about 16 logs, and anywhere from 10 to almost 15 logs of other envelope viruses have been validated for this product. Again, it is a combination of several purification steps that are lumped together and heating.

Another, Factor VIII, solvent/detergent this time, and a terminal dry heat step, plus one of the chromatography methods. Total validated reduction for BVDV or hepatitis C model, about 17 logs; HIV 12, and a substantial clearance of other model viruses.

Factor IX, in this case we've got a couple of process steps that have been validated, at least for some of the viruses. Active kill with solvent/detergent and a nanofiltration step, and the total reduction of HIV-1 is about 12 logs; VSV simbus from greater than 5 to about 12 or more.

Finally, the last one of these. Here we have a product that relies on filtration, as well as the purification itself, and again the cumulative reduction ranges from about 10^{10} all the way up to 10^{14} . I think that is enough of that.

The conclusions from all of this is of course that

viral clearance during manufacturing is important, because that goes without saying. We know the effectiveness of these methods simply because they have been validated, but there is also supportive data based on the clinical experience with these products, which since the institution of effective, robust inactivation methods has been on the whole, good.

The validation of viral inactivation or removal methods provides a quantitative measure of their effectiveness. That quantitative measure can be used to perform risk assessment.

With that I think I will stop and entertain any questions.

Thank you.

DR. HOLLINGER: Thank you, Mr. Lynch. Any questions? Yes, Corey?

MR. DUBIN: I need to be corrected if I am wrong. The picture painted seemed very good, but I heard things that just astound me; (a) I heard that since the 60/30 petri process went into effect, there has been no HIV transmission.

I would point out the Armour(?) first generation heat treat, which went off to Canada, and had roughly 7

known sero conversions right away, and I see Dr. Epstein shaking his head yes, and had a number of sero conversions here in the United States, but the majority of the Armour heat treat was shipped to Canada. That's one thing in the presentation that I think was wrong.

I have to ask the question why we have had I believe it is 19 recalls this year alone. We have had some major incidents. I have spent more time on the phone this year notifying the community of various recalls, albeit some of them were minor risks, and we agreed with that assessment by FDA and the manufacturers.

I get this picture that we've got this beautiful, smooth inactivation system, just flowing along, and we are reducing logs of virus, and then I start hearing things that aren't true. I think we've got to look a little harder. I see things about the picture that still trouble me.

I raised with this committee two meetings ago a question about regulations, and who had read them and seen them. I am still probably the only one who has digests and knows the recall, looked back at notification regulations fully. This is the kind of thing that is up vis-a-vis when this system breaks down, and these are the kind of things that need to be considered.

I am just boggled if the system is working so well, and we're inactivating these products so well, somebody talk to be about all the incidents that have happened this year. I don't understand why they would miss something so obvious as what happened with the first generation Armour heat treat, which we all know that, because not only has it been discussed and written about, it has been litigated.

MR. LYNCH: Yes, you are certainly correct about the early generation inactivation methods. There is no question about that. These were not included in my presentation, because those methods are no longer used. Also not included are some of the methods in developments, things coming down the pipeline.

This is a very active area of research, and I anticipate new methods being incorporated into the manufacture of these products as time goes on. They do not exist now, so it would be incorrect to place any reliance on them.

DR. HOLLINGER: Could you answer the -- one of the questions was did you apply these treatment criteria that you did now to that method Mr. Dubin is talking about? What kind of cumulative responses did you get using these same

viral loads in that procedure?

MR. LYNCH: Could you clarify that question? I'm not sure I exactly followed it.

MR. DUBIN: Let me go back. I don't understand something. You just tried to answer my question, but the statement made to the committee was since the onset of the 60/30 heat treat process there has been no transmission of HIV.

MR. LYNCH: One has to be clear on this. This is heating and solution at 60 degrees for plus or minus a half a degree for 10 to 11 hours. The methods that you are alluding to are quite different.

MR. DUBIN: They are, but it should be stated clearly when you make a blanket statement like that without clarifying it.

MR. LYNCH: I'll let the statement stand. I believe it is accurate.

DR. KASPER: I think that where we are getting some confusion is on the first slides, the one that Mr. Dubin was objecting to, and I saw said, what, what? You were talking about albumin and gamma globulin or something like that. You were not talking about coagulation products, if I remember that first slide correctly. Perhaps you are

right that the 60 degree for 10 hours, there has been no transmission in albumin, but you have to be very careful.

The other thing we need to be very careful is not just to say 60 degree, 10 hours and let it drop. Do you mean dry? Do you mean moist? Do you mean in solution? Because there is a tremendous difference. Dry is inadequate for coagulation products; in solution is adequate.

MR. LYNCH: You are absolutely right. The compendial method, by the way, the CFR methods are heating and solution.

DR. HOLLINGER: Corey, what was the process that was used where there were transmissions?

MR. DUBIN: Armour first generation.

DR. HOLLINGER: At what?

MR. DUBIN: Which was different. It was 60/30, but I believe the duration was different.

DR. KASPER: Dry heat.

DR. HOLLINGER: Have you used that technique in the same methods that were used here? What kind of cumulative response did you show with that? That would be important, because we are basing a lot of what we are saying based upon some modeling, not necessarily what is going on

in the product. So it would be important to know a product that was treated in a certain way that seemed to result in transmission, therefore what kind of numbers would you get under the same circumstances?

MR. LYNCH: There is actually two parts to a complete answer to that question. First of all, the viral titration methods have become far more sophisticated in the last ten years than they were when several methods were put in place that proved to inadequate.

The dry heat treatment at relatively low temperatures is an example that given the technology of the time, appeared to be adequate, but in fact transmitted virus. When that was re-examined after this incident, it was clearly demonstrated that it was not capable of killing virus to the same extent as some of the methods that are in current use today.

DR. HOLLINGER: What kind of numbers could you put?

MR. LYNCH: I hesitate to do that. I just don't recall. Does anybody?

DR. FINLAYSON: The highest claim that I ever saw for that 60 degrees celsius, 30 hours in the dry state was a 6 log kill. That was a number that was much higher than

most of the data for that value that I saw.

Dr. Epstein wants to make a comment, and after he comments, I will reply to something.

DR. SMALLWOOD: Before Dr. Epstein speaks, may I just remind everyone if you have not spoken before, please state your name so that we may have it correctly recorded in the record.

Thank you.

DR. EPSTEIN: I think there is a distinction that needs to be made that may be helpful when we talk about logs, clearance or reduction, which is the presence or absence of a virus residual in the experiment. In some experiments the clearance is limited by the input virus. If you can't get in more than three logs or five logs, then certainly you can show clearance of more than three logs or five logs. That limitation characterized many of the early experiments.

The second point, however, is that in some of the studies when you put in five logs, you end up with the detection of two logs, and you claim you cleared three. The FDA has very consistently since the 1980s regarded experiments in which there was a detectable residual as far less comforting than experiments in which you clear all the

virus you put in. Unfortunately, that is not reflected in these data, because you can't for the most part, tell which is which.

The second point that I would make specifically about the 60 degree, 10 hour dry heat process is that the experiments that were done, were done over a long period of time and by different investigators. There was a lot of inconsistency.

In retrospect, data have come to light suggesting that there ought to have been more concern in prospect with the validation studies because of virus residuals, and because there was evidence of far less effective virus kill, comparing that particular process to other processes that were concurrently under study. These had to do with the degree of purity in the product.

We know that there is a very large impact, not just by the physical state, such as Dr. Kasper pointed out, but also by the milieu. So I think that we are not prepared this morning to review the history of that tragedy. I think that Mr. Dubin's point is quite well taken. We do not wish to mislead the committee in thinking that all heat is equal or all purification is equal. That is not so. That is why you see a complex data array here.

What we are saying, however, is that the processes that have been in place since 1987, have an excellent track record. I think if you will let us complete the presentations on clinical surveillance, I think that will complete the picture. What you have seen now are the laboratory data, and to be sure, they have their limitations.

DR. HOLLINGER: Can we also assume that we look at cumulative levels. We have added these up as if the virus which is remaining after one treatment is maybe the same as the virus initially in terms of resistance and so on. So can we honestly say that because one procedure takes out five logs and another takes out four that we have got nine logs of cumulative protection, or is it perhaps that there may be differences in the virus response?

DR. EPSTEIN: No one can assert that for sure. The concept that was put forward, and was on the slide is that if the procedures are different, that they operate on different biochemical or physical principles, then there is rationality in summing, the idea being that they operate independently, and therefore they should have a cumulative effective. There is no proof of that, however, it is true in various model systems.

MR. DUBIN: I have no desire to dredge up anything and rehash it as you know, Jay. I have not done that here. I don't intend to do that. I'm glad to see the presentation finished. I just want to underline when I hear things that rock me out of my chair, I want clarification. When I see a difference between what I see in the presentation, and what is happening on the ground day-to-day, I want to have a chance to discuss that when the presentation is done. It has nothing to do with dredging up the 1980s. It has to do with 1997, and what has happened between January and this moment in 1997.

DR. HOLLINGER: Thank you. I think we will go ahead and finish. I think Dr. Tabor is going to also update the committee and the others on the epidemiology of transmission of viruses by plasma derivatives.

Ed, could I ask that the committee receive copies of the presentations, certainly by Mr. Lynch and Dr. Poffenberger in terms of their slides and so on, so we could have them.

DR. TABOR: Sure, we can do that.

DR. HOLLINGER: Thank you.

DR. TABOR: I don't know if it is going to be done today though. It might have to be initiated now, but we'll

get them to you soon.

DR. HOLLINGER: What we're going to do after having this last talk here, instead of having the open hearing, for those of you who have to go, we're going to take a break for probably 20 minutes. Then we'll come back for the open hearing and the final committee discussion.

Agenda Item: Epidemiology of Transmission of Viruses by Plasma Derivatives - Edward Tabor, M.D.

DR. TABOR: I'm going to talk to you about the epidemiology of the transmission of viruses by plasma derivatives. The products that we're talking about all come originally from a plasma pool which is first subjected a freezing process, and from the cryo-precipitate is derived the anti-hemophiliac factor, and from the supernatant after a variety of steps, Factor IX.

Then the material is, as you have heard, is put through a series of fractionation steps involving different concentrations of ethanol, leading eventually to fraction 2 from which the immune globulins are derived, and fractions 4 and 5 from which PPF is derived, and albumin from fraction 5.

It is reasonable to group these products into categories according to different risks. In the case of

albumin PPF we have two products that are subjected to inactivation, have always been subjected to inactivation and have an extremely long history of use in this form; greater than 45 years.

In a second category we have products which have been inactivated for a shorter period of time, namely antihemophilic factor, Factor IX, also alpha-1 protease inhibitor and anthromen-3(?).

Finally, in a third category, the immune globulins. At the present time all of the intravenous immune globulins undergo viral inactivation -- I'll discuss that further later -- some of the intermuscular preparations also do; and all of the remaining are tested by HCV RNA tests prior to release.

Heat stabilization of albumin was developed in order to improve the physical stability of the product itself for military use in North Africa during World War II. It was very soon recognized that this had some value for viral inactivation. As a result, the product was heated at 60 degrees for 10 hours.

As I said, albumin has been heated prior to release for more than 45 years. With regard to hepatitis B virus there has been no transmission of hepatitis B virus by

albumin during this 45 year period. In addition, HBV has shown to be inactivated in albumin in volunteer studies, which I will describe in a few minutes.

With regard to hepatitis C virus, heating at 60 degrees for 10 hours has been shown in chimpanzee studies to inactivate the virus.

For HIV there has been no known transmission by albumin even in the years prior to screening for anti-HIV. More recently, a study by McDugal(?) showed that a full five logs of infectivity of HIV can be inactivated at 60 degrees in as short a period of time as 10 minutes.

In 1952, Payne and Jamesway(?) published a study in which they looked prospectively at 237 recipients of albumin involving 92 albumin lots. The prevalence of hepatitis B virus was so great at that time that they would have expected jaundice to occur in 39 percent of albumin recipients, or for that matter recipients of any pooled plasma product if it had not been inactivated.

In this study 33 of the recipients received only albumin, and none of them received jaundice. Among a further 204 recipients who received mainly albumin, but also small amounts of blood and thrombin(?), only two had jaundice. This really showed that albumin did not transmit

clinically recognizable hepatitis.

In 1948, Gellis made a preparation using infected plasma that was known to transmit hepatitis, mixed it at 20 percent solution in albumin. This material was then heated at 60 degree centigrade for 10 hours, and injected into 10 volunteers; none of them developed clinical hepatitis, whereas three of five of those injected with the unheated preparation developed hepatitis.

In a series of three studies conducted by Roderick Murray, who was a former director of what is now the Center for Biologics Evaluation and Research -- and two of those studies are shown in this slide -- in three studies he showed that heating at 60 degrees centigrade for 10 hours fully inactivates what is now known to be the hepatitis B virus in albumin.

Dr. Murray used a plasma pool that was later shown to have 7.5 logs of infectivity for hepatitis B virus. That is, theoretically as little as 1/10 millionth of an ml of this material could theoretically transmit hepatitis B.

In the first experiment, shown at the top here, he showed that heating at 60 degrees for two hours and four hours did not inactivate hepatitis B virus.

In the second experiment, heating albumin prepared

from this plasma pool at 60 degrees for 10 hours, and inoculating 3 ml of that into 10 volunteers resulted in prevention of hepatitis. That was not only prevention of clinically recognized hepatitis, but later shown to be no hepatitis B transmission at all when serologic tests were applied to the stored samples.

Inoculation of 100 ml of this heated albumin preparation also did not transmit hepatitis. The unheated albumin, when 3 ml were inoculated, did not transmit hepatitis to any of 10 volunteers, but inoculation of 100 ml of the unheated albumin into each of 10 volunteers still transmitted hepatitis to two of them, and the unheated plasma transmitted hepatitis to five of ten recipients.

What this study showed was that there was a fair degree of elimination of hepatitis B virus solely by the preparation of the albumin, but if a large volume was given, it was still infectious, and the heating removed the remainder.

A third study not shown here was conducted using a produced called Stable Plasma Protein Solution, which was a precursor of PPF, and that also showed that 60 degrees at 10 hours eliminated hepatitis B.

In a study in 1972 by Soulier in an effort to

develop a fairly roughly designed heat inactivated vaccine against hepatitis B, it was shown that heating a fairly low titer preparation in the HBSAG titer was 1:16, heating that preparation at 60 degrees for 10 hours eliminated hepatitis, but when a higher titer preparation was heated at 60 degrees for 10 hours and inoculated into seven volunteers, six of them developed hepatitis B.

This inability of heating alone to inactivate hepatitis B virus in a serum preparation was confirmed in chimpanzee studies by Shikada(?) in 1978. Shikada concluded that heating alone caused a four log reduction in hepatitis B virus based on the length of the incubation period.

Pattison reported an incident in which two lots of PPF had transmitted hepatitis B virus due to an error in the heating process. In this particular situation, the material was subjected to heating of the final bulk, and it turned out that there was a small portion of the container in which the material was sequestered and was not adequately heated.

Following this incident, all materials -- and this was in 1973, and published in 1976 -- were subjected to heating in a final container. In an analysis of this episode, recipients of albumin from what was possibly the same donors, but certainly the same donor pool or donor

base, did not transmit hepatitis B to any recipients.

Immune globulins, with almost no exceptions, have never transmitted hepatitis B. There have been volunteer studies showing no transmission, and there have been certainly no transmissions by either IM or IV preparations in the 25 years that these materials have been made with screened plasma.

Prior to the introduction of screening for hepatitis B virus there probably was also very little transmission of HBV by immune globulins, however, in 1979 I reported a case, which probably is the only report of transmission to a number of recipients of hepatitis B by a lot of immune globulin that was prepared by plasma that had been collected before the introduction of third generation screening.

That particular lot of immune globulin had detectable titters of HBsAG when examined later, and very, very low titters of anti-HBs. In this regard, it should be noted that prior to the introduction of screening almost all lots of immune globulin had anti-HBs titters of less than 1 to 100, but beginning in 1979, when a group of lots were studied in our laboratories at Biologics all lots had greater than 1 to 100 anti-HBs.

In 1953, Dr. Murray conducted volunteer studies using the same plasma pool, with 7.5 logs of infectivity for hepatitis B. The material was prepared into immune globulin using Cone method 6, and method 9. This material did not transmit hepatitis B to any of 10 recipients, whereas the untreated plasma infected two of five recipients.

Now as you know, beginning around 1973 to 1975, all donors were screened with third generation assays. Certainly after 1972, all donors were HBsAg negative by whatever tests were available at that time.

In a study by Dr. Hoofnagle it was shown that prior to the introduction of screening 78 percent of immune globulin lots had detectable HBsAg that could be identified in the lots in the form of HBsAg anti-HBs immune complexes. In lots studied from the period after 1972, there were no complexes, and no HBsAG.

Despite the fact that many lots of immune globulin made before 1994, contained HCV RNA when examined recently, intramuscular preparations of immune globulin have not transmitted HCV. Evidence of this includes follow-up studies of recipients of intramuscular immune globulin. For instance, immune deficient patients who receive weekly injections of immune globulin. One study in the U.K. with

individuals who had received weekly injections for 10 months, and another study in Sweden with individuals who had received weekly injections for up to three years; none of them developed hepatitis C virus.

There also was no transmission of hepatitis C by intramuscular immune globulins made from the same donor base as the infectious lots of the intravenous preparation Gammagard, which I will describe in a few minutes. Only a few of the manufacturers of immune globulin are currently inactivating the material, and that is in part because the material has never transmitted the viruses, but since 1994, HCV RNA has been sought by PCR testing of final product of the intramuscular preparation as a final safeguard.

The situation with intravenous immune globulin is somewhat different. There was an outbreak in 1993 of hepatitis C virus transmitted by Gammagard. There, however, was no transmission by any other U.S. licensed intravenous immune globulin, and there has been no transmission since 1994. Viral inactivation procedures were put in place beginning in 1994, by some manufacturers, and were universal by 1995.

The Gammagard incident involved the transmission of HCV to 23 of 210 recipients of the product; none of 52

recipients of other IG IVs developed HCV infection. Nine lots were implicated out of 43 lots received by these individuals that were screened by second generation tests. The transmission was dose related, and it was related to the amount of HCV RNA received. It only occurred in recipients of HCV RNA positive lots.

In a very elegant series of studies conducted by Dr. May Ling Yu(?) at CBER and Dr. John Finlayson it was shown that the cause of this outbreak was the introduction of screening plasma using second generation tests for anti-HCV, which removed the ability of the anti-HCV to inactivate any virus that was present. The solution of this problem was the introduction of viral inactivation methods for this product.

Immune globulin has not transmitted HIV. There have been no sero conversions in recipients of either the IM preparation, the IV preparation, or hepatitis B immune globulin made from anti-HIV positive pools during the period 1982 to 1985, when AIDS was already present in the community, but screening tests were not yet available.

It has been stated, at least by some investigators, that the fractionation process can remove 10^{15} infectious doses of HIV, and in most cases infected

plasma only has at most 10^5 infectious doses per ml.

Finally, it has not been possible to culture HIV from immune globulin lots, although in fact it is very difficult to culture HIV from plasma derivatives anyway.

Antihemophilic factor and Factor IX, which used to be very high risk products for hepatitis B before the introduction of inactivation, have not transmitted HBV. This has been true for all U.S. licensed products that are made from screened and properly inactivated materials since 1987.

Lots of antihemophilic factor made after the introduction of testing for anti-HCV and after the introduction of inactivation, which also incidently inactivated HCV have been negative for HCV RNA, and have not, as far as we know, transmitted HCV.

I would like to thank Dr. Michael Souci(?) of the CDC for providing us with data from a CDC surveillance study. In the portions of that study dealing with 1993 to 1996, there were no confirmed sero conversions for HCV in any of 71 hemophilia treatment centers. This represents about 50 percent of the hemophilia treatment centers nationwide, and probably approximately 35 percent of all hemophiliacs.

Studies of AHF made from plasma pools that are positive for HCV RNA have shown that the resulting product does not contain detectable HCV RNA. This is product that has been subject to inactivation procedures.

There have been no sero conversions to HIV in recipients of only viral inactivated products made from screened plasma when those inactivation processes have been done correctly. Again, in the CDC surveillance study from 1993 to 1996, there were no confirmed sero conversions to HIV in any of 71 hemophilia treatment centers.

In summary, there has been no transmission of HBV, HCV or HIV by any U.S. licensed plasma derivative since the introduction of effective virus inactivation procedures, when those procedures were carried out properly. In essence, I believe this means since 1987 for most products, with the exception of IG IV, for which it would be since 1994.

Thank you.

DR. HOLLINGER: Thank you for that summary.

Are there questions for Dr. Tabor or for anyone else right now from the committee? If not, it is 11:22 a.m. We will reconvene here at 11:45 a.m.

[Brief recess.]

DR. HOLLINGER: I'd like to call this meeting back to order please.

We are going to go into the open public hearing now. There have been several people who have asked to speak. I would like to ask if you would come up to the microphone up here. We would appreciate it.

The first speaker is going to be Bill Hartin from Alpha Therapeutics.

Agenda Item: Open Public Hearing

MR. HARTIN: Hello, I'm Bill Hartin with Alpha Therapeutic Corporation. I'm here to tell you about an incident involving potential contamination of a plasma pool or pools. I will try to describe the situation, and how we dealt with it.

Alpha Therapeutic Corporation has been conducting an extensive internal investigation following a report by the National Institute for Biological Standardization in the U.K. The report was of anomalous HIV antibody reactive results for plasma pool samples.

The investigation began on the February 14, 1997, when Alpha management first learned of the report. The investigation has been conducted in close concert with the US FDA. The investigation has been vast in scope, and has

encompassed all aspects of the implicated plasma pools. This includes individual donor unit tracking, testing, pooling and processing.

Throughout this investigation, Alpha has attempted to maintain a high level of communication and information flow between Alpha, its subsidiaries, its customers, and the US FDA, as well as various other regulatory agencies.

Alpha's primary goal has been the confirmation of consistent safety and quality of its products, and the rapid resolution of the issues surrounding the reportedly HIV antibody reactive plasma pool, and the apparent testing discrepancies.

As I mentioned, we learned of the report on February 14, and it involved discrepant results associated with two lots of albumin. The first lot of albumin was prepared from four plasma pools. Three of those four plasma pools with this lot of albumin were found to be slightly positive on an Abbott HIV-1/2 Third Generation Plus test, and this kit is not licensed in the United States, so it cannot be used for donor screening. In addition, in the U.K. they were using a modified cut off value such that it was half the cut off value recommended in the appropriate direction insert.

The second lot of albumin was prepared from two plasma pools. One of those two plasma pools was considered positive for anti-HIV reactivity under the same conditions, and in the same place.

So we have six plasma pools. All six, you will notice as I go on, were investigated, but only four of them were implicated as a result of a reactive test. I might mention of course that all six were tested and were found negative by the Genetic Systems test system.

FDA and NIBSC scientists performed general amplification testing on samples of all six plasma pools associated with these two lots of albumin. All were negative for the presence of HIV RNA. Although we have conducted intensive investigations, to date we have not found a conclusive cause for the aberrant test results.

This is a complicated timeline, that I will just point out a couple of things. On the same day that we became aware of the incident, we were in close contact with FDA and had identified all of the final products that were made from all six lots.

At the time, there was only one coagulation product in distribution, a Profilnine complex factor, and it was in concert with the FDA, that we agreed to place that

lot on a quarantine basis, even though this lot was manufactured from one of the two lots that were not implicated in the testing.

Immediately we began by reviewing our records, particularly our test records, and started with the plasma pool test results that were received, as well as the controls that were run at the time, and all were non-reactive. We looked at the individual donor unit initial test, along with their controls, and each one of those also were all non-reactive.

We do PCR testing on all of our final products that are made. So we reviewed the PCR test results for each of the products that were made from these six plasma pools, and again, no anomalous findings; all were non-reactive.

We did a batch record review for the products that were made, and again, found no significant aberrations. By the way, FDA did their own independent review of those batch records and found the same thing.

Then we began our series of repeat testing. We started by testing the six plasma pools that were involved. We retested them with the Genetic Systems test, and all six were found to be non-reactive. We went on to test with other test systems and found that five of the six were also

non-reactive with other test systems, but that one of them, batch number 6230 was reactive or just over the cut off with the Abbott and with other test systems. These findings that we found were confirmed both by FDA, by NIBSC and by many other outside laboratories.

Almost immediately we identified all of the reactive units that were identified during the time frame, and with the same shipment, to verify that in fact the known reactive units were culled and quarantined. So we, together with FDA, verified the physical presence of the known positives that were culled, or verified the certified documentation for their destruction or sale as a known reactive unit. The investigation of these units confirmed that all known reactives were properly culled and reconciled.

A thorough review was performed by senior management of all cGMP procedures applicable to the collection, sampling, identification, transportation, testing, result reporting, receiving, inspection and clearing of donor plasma units. A similar review was conducted independently by FDA.

The review traced the path of an individual donor plasma unit from collection at the plasma furesis(?) center,

through sample testing at the ATC Memphis laboratory;
receipt of test results by the plasma furesis center;
receipt, inspection and clearing of plasma units by our
Temple warehouse, to plasma unit pooling at the Alpha
manufacturing facility.

Only cleared units are transported from the Temple
warehouse to the valley manufacturing site. During each
step of the procedural review, focus was kept on individual
units from plasma pool 6230 to confirm that all appropriate
procedures were followed. Neither Alpha nor the FDA found
any significant procedural deviations or failures that would
compromise product integrity or account for the reported
testing discrepancies.

An extensive review of the Memphis testing
laboratory was conducted. This review focused on sample
handling procedures, and specifically those employed during
the handling of the samples associated with the six plasma
pools. The sample handling review included all aspects of
the testing, tracking and result reporting of each
individual donor sample.

The investigation also included a review of all
applicable testing error reports and deviations. A review
of all invalid test results for the past 14 months was also

conducted. A review of the validation, calibration and maintenance was conducted for all equipment utilized in the processing of donor plasma samples.

The robotic pipe headers are tested weekly for precision with an absorbance measurement based on dye transfer. These pipe headers are tested monthly for accuracy by gravimetric methods. All accuracy and precision testing was within specification. A complete review was also conducted of the College of American Pathologists proficiency testing for the personnel performing the previously mentioned testing. All of this information was gathered and reviewed concurrently with FDA.

We embarked on repeat testing, because we keep back up samples of each unit of plasma. We prioritized the repeat testing in consultation with FDA. We started by looking at the look back units that were contained in these six plasma pools. What we found is we found some discrepancies between the Genetic Systems and Abbott tests. All of the look back units were negative or non-reactive with the Genetic Systems test, but two were just over the cut off with the Abbott test.

We have been attempting to find these donors, and to get a current reading of their current test results.

We next prioritized with the idea of dealing with donors who did not return for a subsequent donation, because donors who have been in the pool, but also donated subsequently and tested negative were very unlikely to be the causative agent in this case.

So we started with new donors who did not return for a subsequent donation. There were 335 of those, and all 335 were non-reactive with the Genetic Systems test, but one out of the 335 was reactive by Abbott. There was a tracking down of the donor and some further testing by both Alpha and FDA that included some PCR testing on the individual donor.

As I say, we found the donor and tested, and found him to be non-reactive by all systems. So this was assumed to be a false positive result with the Abbott test on this.

We then went on to finding the back up samples for all repeat donors who did not return for a subsequent donation. There were 470 of them. None of them tested positive for either the Abbott or the Genetic Systems test system.

We are in the process of doing a protocol that we have agreed to with FDA regarding the remaining 10,000 units, who are donors that had come back and tested negative in subsequent donations.

I want to talk about viral inactivation.

Immediately the batch production records, as I mentioned, were reviewed to insure that the viral inactivation steps were performed according to our procedures and licensing requirements. For the coagulation and immune globulin products, the primary inactivation step is solvent/detergent treatment. For albumin products the primary inactivation step is heat treatment at 60 degrees for 10-11 hours.

The viral inactivation validation information was reviewed for each product. This is the viral inactivation data. Alpha has conducted viral validation studies to assure a margin of safety in our plasma derivatives. These studies are performed by spiking a known amount of virus into product samples, and recreating the actual production process on a smaller scale.

The effect of the product sample on the virus detection system, as well as the ability to show that the experiment fairly and accurately represented the manufacturing processes are important to the validity of the experiments. Alpha has typically conducted viral inactivation validation for the solvent/detergent method at worst case conditions, for example, at lower temperatures.

We have also studied the kinetics of the

inactivation which show that there is no detectable virus at the 30 minute time point. Our process is six hours.

The reduction factors for HIV are in excess of approximately six logs.

Alpha has also reviewed the reports from clinical studies and pharmaco-vigilance for all products. There have been no reports of HIV sero conversion with any U.S. licensed coagulation product in over 10 years, and no confirmed reports with U.S. licensed albumin or immunoglobulin products.

Alpha has received no post-marketing reports of HIV sero conversion with our currently licensed products. Furthermore, we have ongoing clinical trials with Alphanate, AlphaNine and Venoglobulin-S in which recipients are tested periodically for markers of HIV and other viral diseases.

In some of our blinded clinical trials we have administered albumin as the placebo control. There is no evidence for HIV sero conversion with our products in these carefully controlled clinical studies.

The antibody test results for plasma pool 6230 appear to be consistent with the inadvertent addition of a strongly antibody reactive donation into the plasma pool. The investigation focused primarily on three types of errors

that could account for the reactivity observed with samples in plasma pool 6230: an error in handling of contaminated units; misidentification of sample units; a test error.

With respect to the first type of error, reactive unit handling, Alpha and the FDA have independently reviewed procedures, documentation inventory for handling of positive units. To date, neither Alpha nor the FDA can find any evidence of a mishandled unit.

The possibility of a mislabeled sample has been thoroughly investigated and is highly unlikely given the double lined identification of positive units. This is a diagram of the bottle we use to collect our plasma. The middle is just a top view of that bottle.

At the time we manufacture the empty bottle, the sample vial is an integral part of that bottle. In addition, there is a serial number that is imprinted on the sample vial and the identical serial number is printed on the bottle.

So at the time of use, after the plasma bottle is filled up, the bottle is inverted and a sample moves down to the sample vial. Just before that, we put on the bleed number label on both units. It is only then that the sample vial is sealed and disconnected from the bottle, and the

tubing in between represents the back up sample that may be used later.

When a positive result is found at the laboratory, the plasma center is called with the bleed number of the positive unit. The plasma center then has to read the serial number, which is a different number, that has been imprinted on the bottle, read back to the laboratory. There it is confirmed to have the identical serial number, so we feel very confident with this system.

There are rare occasions when the sample collected in this tube is, for one reason or another, not satisfactory to do the testing, in which case we call on the back up sample, the tubing to redo that. In the case of the lots in question here, over 99.6 percent of the samples were able to be tested with the integral sample tube.

Test errors could be caused by the following type of defects: test kit defect; pipe heading error; or test kit sensitivity to reactivity. There have been several studies published that try to estimate the likelihood of test errors including test kit defects. Utilizing the data in Michael Bush's publication, we have calculated for Alpha the expected error rate would be about 1 in 15 million. Thus, we could have expected a false negative test maybe

once every three to five years.

Another source of error could be pipe heading errors. The validation studies in the weekly and monthly calibrations as I mentioned, have been reviewed with no obvious sources of error. Reviews of deviation and test error reported from the Memphis lab have further failed to elucidate a reason for the apparent test result.

Test kit differences appear to be one area to consider, however, even with differences in dilutional sensitivities, it is difficult to believe that any test kit would miss a strongly reactive unit. With the additional testing, it does not appear to be a different subtype of HIV that is not detected on the Genetic Systems test. Although we have tested the samples thought to be most at risk for a false negative result, we have not yet found a sample that could explain the apparent positive result.

In conclusion, the cause of the apparent reactive unit in plasma pool 6230 may be due to a testing error albeit very rare. Alpha continues to evaluate samples in order to better determine the sources of error. In the meantime, Alpha has committed to a number of redundant systems to prevent the possible reoccurrence of a testing error:

1. We of course continue to do the individual unit testing by the Genetic Systems.
2. We continue to do the p24 antigen testing on individual units by Coulter.
3. We have instituted what we call some mini-pool testing. After the individual unit testing is completed, as it has been in the past, 64 units are pooled together and a test is done on that pool utilizing the Abbott antibody test.
4. We also continue to do plasma pool testing by Genetic Systems, but we also do that manufacturing pool testing with the Abbott HIV-1/2 antibody test. In fact, we use a similar cut off that is used in NIBSC, that is 50 percent of the cut off published in the direction insert.
5. We continue to do a final container product testing by PCR for not only HIV, but HAV, HBV and HCV.
6. We have just recently begun clinical trials for plasma mini-pool testing for both HIV and HCV using PCR technology.

Alpha has been conducting this investigation to confirm the consistent safety and quality of its products and to rapidly resolve the issues surrounding the reported HIV antibody reactive plasma pool, and the apparent testing

discrepancies. Alpha will continue to work in cooperation with FDA and world regulatory authorities to bring solution and closure to these issues. Alpha's investigation will continue until every avenue has been explored, and the best possible prevention strategies have been implemented.

Alpha is committed to employing the most appropriate, accurate and advanced technology available to assure the safety and quality of its products.

DR. HOLLINGER: Dr. Kasper?

DR. KASPER: Could I clarify a couple of things, please? I take it in my ignorance I have never heard of Genetic Systems. This is a laboratory I gather? This is a laboratory. Although I got confused a moment because of the name, Genetic System, I thought maybe this was a genomic or nucleic acid test, and it isn't. I take it, it is an antibody test, and this just the name of this particular laboratory?

MR. HARTIN: That's exactly right.

DR. KASPER: In this page where you say repeat testing of look back and reactive units, what was it that NIBSC identified? The entire lot? What were you able to cull it down to? What was reactive to less than a lot? To a particular pool? To a particular donation?

MR. HARTIN: When we sell products, in this case two lots of albumin, we submit samples of the plasma pool or pools that were used to manufacture that product. They tested the plasma pools and they reported the results that I had told you about.

Does that answer your question?

DR. KASPER: So when it says reactive units produced some discrepancies between Genetic Systems and Abbott, that means the plasma pool?

MR. HARTIN: No, I'm sorry. That was we looked at look back units that happened to be in these pools, the six pools that we investigated. Any look back unit that was contained that, we called for the back up sample and did some repeat testing on that unit.

DR. KASPER: If these were reactive units, that means unit of plasma. They were dealt with; not included in the pool. You were trying to see whether the test system Genetic Systems uses and the test system that Abbott uses give you the same results, and they don't always? There are discrepancies?

MR. HARTIN: That's correct.

DR. KASPER: Thank you.

DR. HOLLINGER: Thank you for those points.

Yes, Dr. Leitman?

DR. LEITMAN: This is not directly relevant to what was just presented, but while we have a representative of a manufacturer up, I was told by my pharmacy in my institution that they could no longer get 5 percent albumin for therapeutic use about four to six months ago, and only 25 percent was available, which is a major inconvenience for procedures like therapeutic aporesis(?). Can you edify us as to why there is an absolute shortage of 5 percent albumin? Is it related to --

MR. HARTIN: You are certainly right, there is and has been a significant shortage of albumin. I believe a major factor in that shortage is that one of the major manufacturers had discontinued operation temporarily.

DR. HOLLINGER: Okay, thank you very much, Mr. Hartin.

DR. SMALLWOOD: Before the next presenter comes, I just wanted it to be entered into the record that some of the members of the committee reported having received an advance copy of the presentation of the next presenter directly. So we just wanted that to be publicly clarified.

Thank you.

DR. HOLLINGER: I think when you have to send to

the committee, while you can certainly do so, there are no laws that prevent you from doing that, it certainly would be better to send them to Dr. Smallwood, who then could see that all the committee receive these pieces of information.

The next speaker then is Dr. Jean-Jacques Morgenthaler from the Red Cross Foundation Central Laboratory Blood Transfusion Service in Switzerland.

DR. MORGANTHALER: Good afternoon. I would like to give the ZLB's position regarding the risk of products prepared from inadvertently contaminated plasma pools.

I'll start with a description of a recent event which involved ZLB. On 11 December 1996, an American blood bank told us that one of their whole blood donors now tested confirmed positive for HIV-1 or -2. His or her previous donation had been obtained on 10 January 1996. The incident was recorded at ZLB; the plasma of the donation of 10 January 1996, traced; and the FDA informed of what products were involved.

On 30 December 1996, the FDA reported to ZLB that the blood center had conducted a look back at their donation of 10 January 1996; it was infectious; and had unfortunately transmitted HIV to the recipient of the corresponding red cell concentrate.

On 11 January 1997, the FDA asked ZLB to halt distribution of the product involved. They also requested samples of the plasma pool and of the final products. At the same time, they announced a directed inspection to review the records of the batches involved. This inspection took place from 15-20 January 1997, and concluded with no observations. It therefore confirmed ZLB's own review of the batch records, which had shown that all the relevant SLPs were adhered to.

Both ZLB and FDA initiated PCR testing in plasma pool samples and in final products. National Genetics Institute in Culver City, California carried out a test for ZLB. They were negative in the starting material, and in the products. According to verbal information the samples also tested negative in FDA assays.

The incident involved two batches of intravenous immunoglobulin product and two batches of 5 percent albumin, plus a number of intermediates, so-called precipitate GG, and one IV IG bulk, which is still ready for filling.

Of the 5,961 bottles of IV IG that were made, only 120 were delivered. The rest is still stockpiled at the distributor. In contrast, only 94 of the 6,337 bottles of albumin that were produced were returned after market

withdrawal initiated by our distributor, which is to say, most of the albumin had already been used.

Let me now turn to policy issues. Rather than simply discarding the products involved, ZLB aims at developing a rational and scientifically sound procedure. ZLB's policy for dealing with this type of incident is based on a reasoned approach for evaluating the safety of the final products. The approach is intended to minimize and [unintelligible], and it is based on the following premises.

Thoroughly validated virus inactivation procedures demonstrate complete inactivation of viruses. The two products under consideration were never reported to have transmitted HIV, HCV or HBV even before testing for anti-HIV and anti-HCV was introduced. There might be differences between recovered and source plasma regarding availability of the retention samples and the transfusion of unfractionated components.

The infectious dose, the minimum number of vital particles required to transmit disease is often not known with certainty. Product rests essentially on up front screening measures and validated manufacturing processes, not on potentially haphazard communications.

Since zero risk is not an obtainable goal, the

ethics of destroying large amounts of end products in return for the immeasurable safety increase is questionable. Recall of products prepared from an inadvertently contaminated pool is ineffectual, because many products have already been used. This scope of recalls is at best, fuzzy both with respect to infectious agents and the time frame involved.

PCR testing, particularly in the mini-pools is a sensible goal, but doubts concerning the accuracy of the method will prevail, as will discrepancies between laboratories.

The ZLB has validated production processes for IV IG and albumin. Elimination factors for various viruses can therefore be used for risk assessment. It was already mentioned that the batch reviews did not reveal anything abnormal. The results of the virus validation studies therefore, apply to these batches.

The following calculation is based on worst case assumptions, i.e., the lowest element elimination factors were used. It should also be mentioned that all virus validation studies are incomplete in the sense that no manufacturer attempts to validate all process steps, but rather limits the studies to the most relevant steps.

For albumin and IV IG we have calculated a theoretical virus load expressed as genome equivalent per gram of final product as a function of an assumed virus load in the starting pool.

We have set a load of one genome equivalent per 1 million grams of final product as an acceptable limit for a safe product. This is the dotted line. We realize that this is even more conservative than it appears at first sight, because considerably more than one genome equivalent may be required for detection.

This limit is reached in the case of albumin with a load of approximately 50,000 genome equivalents per ml of plasma pool. The limit is far out of range of the graph with respect to IV IG.

Since the detection limit of PCR is in the order of 100 genome equivalent per ml we still have a very wide safety margin with both drugs. We therefore cannot find any scientific rationale why the two products discussed above should not be released.

In conclusion, there must be a significant number of contained donations that are incorporated into plasma pools without ever being detected, because some donors do not return for further donations. A manufacturing process,

therefore, has to be robust enough to eliminate a moderate virus load generated by infectious donations which escape screening.

It is the validated removal and/or the inactivation of viruses through the manufacturing process which guarantees the safety of the final products. Our goal is to evaluate all like cases in a similar way, and to reach a consensus with the authorities as to a rational and scientifically sound procedure.

Thank you.

DR. HOLLINGER: Thank you very much.

Any questions from the committee for Dr. Morganthaler?

If none, then we will proceed on with the next speaker, Dr. Robert Hostoffer, from the Immunodeficiency Foundation.

DR. HOSTOFFER: Good afternoon. I'm Dr. Robert Hostoffer. The Immunodeficiency Foundation asked me to testify on behalf of the patients with immunodeficiencies.

I am a pediatric immunologist. My practice is part of Rainbow Babies and Children's Hospital, a major pediatric tertiary care center in Cleveland, Ohio. There I manage a clinic solely devoted to the diagnosis and

treatment of patients with primary immunodeficiencies.

The Immunodeficiency Foundation, through a national survey of physicians and patients estimates that some 20,000 immunodeficient individuals receive IV IGG, both children and adults. Our clinic is the largest of its type in Ohio, managing approximately 200 IV IGG infusions per month. These 2,400 yearly infusions take place in doctors' offices, patient homes and other institutions.

Immunoglobulin infusions replace what nature has omitted, a protective umbrella from infections. Indeed, without these infusions, these patients would experience at least 10 ear or sinus infections, two pneumonias, one or more life threatening infections per year. In addition, accumulated damage from these infections would lead to hearing loss, lung destruction and eventually death.

As you can see, these infusions allow our patients to move through their bacteria laden environment freely, without risk of endangering their live from serious illness. Therefore, the importance of these treatments to our patients' health and welfare cannot be overstated.

Issues discussed by the committee are grave concerns to our patients, because of the finality of the consequences, and are subsequently shared by the physicians

like myself, who are charged with responsibility of their care. We have heard these concerns from our patients, and they are focused five issues: safety, availability, cost, patient notification of withdrawals and recalls, and pool sizes.

Immunoglobulins have been used broadly over the past 20 years. The immunodeficiency patient population has experienced an almost unblemished safety record with these products, however, I must mention that the relatively recent transmission of hepatitis C through IV IGG products created a sense of vulnerability within our patient population that acted as a wake up call on the issue of blood safety.

The circumstances accounting for the transmission of HCV to immunodeficient patients highlight the unique health concerns of these patients and their special vulnerability to infectious agents in the plasma pool. We must remember that these patients are extremely vulnerable, because their immune systems are missing or incomplete.

The main concerns for our patients are unknown or not well understood viruses or viral agents for which screening mechanisms and elimination processes have yet to be developed. The recent recalls and withdrawals related to CJD have frightened many of our patients. Thus,

contamination of IV IGG is a disastrous occurrence for our patients.

In this context, effective patient notification of recalls and withdrawals, and the subsequent avoidance of those recalled lots is of paramount concern. Unfortunately, there have been many instances where our patients have received recalled lots even after formal notification was initiated.

One particular problem is the variety of infusion sites. As I have pointed out, most patients receive their infusions at one of three places -- physician offices, home and other clinical settings such hospitals or proprietary infusion clinics. The specific lot numbers in some instances are not recorded at the infusion sites, thereby making identification of those potentially infected patients impossible.

We have instituted a policy of lot recording at our institution, but infusions that are performed not under our auspices still remain problematic. Therefore, we feel that a standard method of lot number recording be instituted, and that an intense education program be directed towards pharmacies, physicians, other dispensing NTs, and also directed towards patients. The

Immunodeficiency Foundation is eager to assist in this process, and this would decrease the morbidity and mortality associated with our patient population.

Since our patients rely on IV IG month-to-month, issues of supply weigh heavily. Despite advance ordering by our department, there have been multiple occurrences when shipments of IG IV have been inadequate to treat our entire patient population. This has forced us at times to triage or split doses. None of these choices are acceptable. The supply of IG IV to these patients in our opinion, should be guaranteed in order to prevent unacceptable outcomes and death.

IG IV is a highly purified blood product. The product is costly. Indeed, the total cost for one year of infusions for a child may be as high as \$12,000, and for an adult approximately \$24,000. In most cases insurances may cover the cost, almost, but not completely.

Our patients are still left with a significant monthly payment. In other cases, insurances do not cover or approve therapy despite multiple submissions. Additional problems are met by our patients when insurance is lost due to job change or job loss. Some of these problems may be resolved with the Kassebaum-Kennedy health care bill, which

goes into effect next month, however, implementation of this legislation remains questionable.

In my practice I am aware of a multitude of patient problems related to insurance cost and reimbursement. While affordability of insurance may be improved with new legislation, lifetime insurance caps remain a major concern within the immunodeficiency population.

The cost of monthly infusions over the lifetime of the patient can cause them to reach their maximum coverage amount within a number of years. While this committee is not concerned with insurance reimbursement of cost, the issue must be raised because supply and industry regulations directly affect the patient's pocketbooks.

The amount of protection supplied to a patient by each lot of IG IV is based in part on the pool size from which a lot was obtained. Because not all individual donors will be exposed to the same bacteria, development of immunity in the normal host varies. Therefore, a pool or spectrum of immunity against bacteria may only be provided from a large pool of donors.

These concerns may be unique to the immunodeficient population, and we recognize that at the

first blush our perspectives may vary from other patient groups receiving other plasma products. The IDF has assured me that they will work closely with all patient groups to insure the best results for all affected parties.

The science will need to be closely reviewed to determine the number of donors required in a pool to maintain acceptable antibody levels. Such decisions, based on fact are required to insure the effective IG IV therapy for our community.

I want to leave with a perspective of one of my young patients and that of his family, a five year old boy who I will call John. John was diagnosed with X-linked agammaglobulinemia, Bruton's, at six months of age. Because of early diagnosis and the availability of specialized care centered around monthly infusions of 20 grams of IG IVV, John can expect to lead a relatively normal life, with an average life expectancy.

Given the state-of-art in treatment, John may receive over 800 infusions of IG IV during his lifetime. John is one of 20,000 primary immunodeficiency people who are facing this scenario. John and other patients like him are especially vulnerable to the quality of the blood supply.

Primary immunodeficiency patients like John bellwethers for the safety of the plasma pool. This substantial patient group ought to be monitored and studied for infusion-related infections. They should be part of a surveillance protocol currently in use, and above all, they should have a formal voice on this committee. This not only serves their own interest, but even more importantly, serves the broad public health interest.

In summary, patients with primary immunodeficiencies are a special group of individuals who rely on monthly IV IG infusions to maintain their existence. Issues such as safety, availability, patient notification of recalls and withdrawals, cost and pool size directly affect their infusions and subsequently their lives.

As an immunologist, their lives are my responsibility. I would like to take this opportunity to thank you for allowing me to voice their concerns.

DR. HOLLINGER: Thank you.

Are there any questions for Dr. Hostoffer?

In your practice, have you seen any cases of HBV or HIV or HCV outside the Gammagard?

DR. HOSTOFFER: Well, we haven't had any HIV or hepatitis B, but we have had two patients with hepatitis C

related to infusions.

DR. HOLLINGER: With the Gammagard?

DR. HOSTOFFER: Yes.

DR. HOLLINGER: So that's the only thing that you have seen in that period of time?

DR. HOSTOFFER: Yes.

DR. NELSON: I wonder if you would elaborate a little bit on the issue of pool size. I have heard ranges of 10,000 to up higher. What would be an optimal pool size for this population?

DR. HOSTOFFER: That would be hard to really determine. I don't know. We would have to really look back and do some studies on that, because diversity in each individual varies. I think that you would have to look at it a lot closer than what my estimates would be.

DR. NELSON: Let me state it the other way. What is an inadequate pool size for this population?

DR. HOSTOFFER: That would be additionally hard to say, but it takes a lot of work. I think we need to look at those issues and come down with some sort of number that would be agreeable to all populations using these plasma pools.

DR. HOLLINGER: Thank you.

The next person who has asked to speak is from the National Hemophilia Foundation, Mr. Bruce Ewenstein.

DR. EWENSTEIN: Mr. Chairman, members of BPAC, good afternoon. My name is Bruce Ewenstein. I'm a practicing physician in Boston, a hematologist, who runs a hemophilia treatment center, and also co-chair of the blood safety working group of the NHF. It is on behalf of the NHF that I would like to take this opportunity to offer some brief comments pertaining the questions before the committee.

Let me begin by saying that we believe that these questions are of the utmost importance. They go to the heart of the mission, we believe, of this committee, and are of vital interest to the NHF and its members. Regrettably, we were not afforded the opportunity to preview much of the important data that was presented here today, nor did we have sufficient notice of the specifics of the questions that have been put to you.

We do appreciate the comments of the chair in this regard, and urgently request that in the future information be available to the committee and to the public at the earliest possible time, especially for questions or issues for which public comment is being sought. Consequently, I

will have to confine my remarks I think to some of the general principles and perspectives that we at the NHF believe should guide these discussions.

First and foremost, we believe that safety, not fault, is the overriding issue here. Consumers of products are more concerned with the risk to their health than to a somewhat arbitrary distinction between avoidable and unavoidable events, or to the entity or entities at which such events took place.

Second, the principles of effective notification and the public's right to participate in their own health care decisions are intimately connected to the questions before you today. Until an effective primary notification system is in place, it is hard to envision how patients would be informed about the technically violative products that are to be released, or allowed to remain on the market based on health hazard assessments.

Third, the choice before the committee taken to its essence is between possibly contaminated product and no product at all. Clearly, neither choice is desirable. You all probably feel as uncomfortable with having to make that decision as consumers would be.

Clearly, scientific methods should be employed,

but we need more information; information about rates of occurrence and projected impacts. For example, data were presented today indicating two favorable actions taken by FDA with respect to inadvertent contamination this year, but what was the denominator, and what was the impact of those decisions?

Can we really say that all efforts have been taken to date to achieve an irreducible minimal level of error in screening and testing. Utilization patterns can be modified. For example, we can delay elective orthopedic or other similar procedures to minimize impending shortages, so that safety is not sacrificed for supply, but reliable, objective data pertaining to product availability and stocks must be available to the public and to the FDA, and we're not convinced that such data are currently available.

Maximum effort to reduce the number of inadvertent contaminations, and to limit the impact of these sometimes unavoidable errors through mandatory limits on pool size represent at least two approaches to extricate all of us from what must clearly be an uncomfortable choice of supply versus safety.

Finally, from my own communications with patients at our treatment center, I can say with regret that the

recent disclosures of lapses in GMP have once again diminished the confidence that many patients have in the manufacturers of Factor concentrates. Their concerns speak to the need to maintain our current triple layered safety net of screening, testing and GMP.

To disregard known defects in one or two of these layers requires assumptions be made about the absolute integrity of the remaining layer. Such assumptions are not readily made by consumers and some treaters at the present.

To conclude, the questions before you are critically important to the NHF and its members. We urge that you take ample time to review the data presented today, and to seek more detailed comments from consumer groups and other members of the public in your deliberations.

Thank you for your time.

DR. HOLLINGER: Thank you. You might also add to your triple safety net, surveillance as well.

Any questions for Dr. Ewenstein? If not, we will go to our next speaker, Mr. Edward Burke, a consumer for the hemophilia community.

MR. BURKE: Thank you and good afternoon.

My name is Edward Burke. I am a 39 year old hemophiliac. I'm a Factor VIII severe, and I'm a 12 year

survivor with AIDS that I contracted through blood products in the eighties.

I'm very pleased to have the opportunity to speak to you all today. I'm also pleased to see friends of the hemophilia community on your board, Ms. Bea Pierce and my good friend, Corey Dubin.

Today as a person with hemophilia and representing as a consumer, the hemophilia advocacies out there, the National Hemophilia Foundation, the Committee of Ten Thousand and the Hemophilia Federation to express our concern over the issues being brought to you today.

We believe that the FDA should be applauded for their policy on quarantine. Blood products which have been in question for their safety, because the product has been traced back to a donor in question is essential, and in fact it should be enforced, and improved upon.

We hope the FDA continues inspections of GMP and of SOP, because these inspections have revealed inadvertent contamination, issues such as: bacteria in albumin, temperature variations, vacuum problems, saline backwash procedures, and cracked vials, of course alluding back to the bacteria in albumin.

Although we have been assured by industry that the

viral inactivation methods are fail safe, as a community member it gives me great concern as to the safety of these products, and whether GMP and SOPs are being taken seriously considering the gravity and the tragedy of the 1980s, and the underlying policy, wait and see.

We believe that the FDA is on the right track in assuming its fiduciary responsibility of regulatory enforcement. We feel that when the FDA introduces safety guidelines, they must be adhered to. The FDA must again, have the availability to enforce their role.

It is our belief that if a member of industry cannot market a product because of GMP or SOP errors, that industry will be taking greater efforts to make sure the product is safe.

If the FDA were to decide to release inadvertent contaminated product, then a specific warning label or an insert should be added to the release product. This allows the consumer to make an informed decision. We, the consumers, demand a better process of notification, and we don't want to have to depend upon our physicians or organizations, although we do appreciate their efforts. We want a means of notification by direct mail or a phone call.

Also, I can't find the words to tell you how

strongly that I feel that I hope that the FDA will be able to convince industry to initiate a limiting pool size. I'm happy because I heard today that the government reform and oversight committee will be holding a hearing on July 31st on limiting pool size.

It is important to me and to the hemophilia community. I'm a last member. I grew up with two brothers with hemophilia. I buried my younger brother in February of this year, one of the thousands of hemophiliacs who have died. We are here asking industry and everyone involved with the blood industry to work together so that we can prevent this from ever happening again.

I have two questions to put to you. Are the GMPs providing enough safety through the quarantines and/or recalls so the public should not be concerned? Or are the quarantines and recalls due to inadvertent contamination reflections of serious infractions of the regulatory process and pose a serious problem to the public?

Thank you.

DR. HOLLINGER: Thank you very much for those thoughts. Anybody on the committee have a question for Mr. Burke?

The last speaker under the open public hearing is

Douglas Bell from the IPPIA. Could you tell us what all those letters stand for too? I know it's the International Plasma something.

MR. BELL: I am Douglas Bell, director of public affairs for the International Plasma Products Industry Association. We represent the commercial producers of plasma products.

The underlying issue with inadvertent contamination is the need for manufacturers to be able to interdict, and when possible, retrieve units of plasma which are determined to be unacceptable for whatever reasons. The plasma industry is and has been examining this important safety issue. In an attempt to increase the safety and quality of plasma-based therapies, IPPIA has promulgated a series of voluntary standards which take effect in 1997.

These standards are designed to interdict and cull out these units. Center, donor and unit management, combined with state-of-the-art virus testing technology create a web of protection to insure the highest degree of safety and quality in our products, and significantly reduce the potential risk of inadvertent contamination.

First let me highlight some of these voluntary standards. First, as I had said, the focus on center

management. The first step in reducing the risk of undetected pathogens entering the manufacturing process is to manage the quality, recruitment and retention of the donor population at the centers. The IPPIA voluntary standards establish a maximum allowable viral marker rate incidence of disease in the plasma donor population.

The next area of the voluntary standard is donor management. Under the IPPIA voluntary standards plasma from one time donors, the group that is widely acknowledged as the most likely to be at risk, will not be used to make plasma-based therapies. Only donations from those individuals who test negative on two separate and sequential occasions, and on each and every subsequent occasion will be used.

I think that was highlighted early by another individual focusing on the first time donor situation. Under our standards only repeat donors will be used.

The next area of focus for the voluntary standards is unit management. Under the voluntary standards all donations will be held in inventory for a period of at least 60 days. During this time, if a donor sero converts and subsequently tests positive, the earlier donation can be retrieved from inventory and destroyed.

Finally, the last area of emphasis of voluntary standards is testing technology. The voluntary standards also require all plasma use in the manufacturing process to test negative through genome amplification testing for HIV and hepatitis C. GAATTC procedures such as PCR are more sensitive than the antigen or antibody detection methods currently employed to screen collected plasma.

PCR is therefore capable of reducing the window period in which potentially infectious units may enter the plasma pool. IPPIA believes that PCR testing will greatly enhance the safety of our products, and we are working closely with the FDA to gain regulatory approval for the state-of-the-art technology.

Finally, IPPIA believes that through our voluntary initiatives and our leadership through these initiatives to reduce both the real and theoretical risks resulting from the window period, and through a cooperative dialogue with all the involved parties, we will make strides toward our mutual goal, a safe and adequate supply of plasma-based therapies.

Thank you very much.

DR. HOLLINGER: Thank you.

Dr. Kasper?

DR. KASPER: Could I ask for a clarification? If there will be no one time donors, and plasma units will be quarantined at least 60 days, it's at least 60 days until the donor returns?

MR. BELL: Correct.

DR. KASPER: Then there will also be no last time donors? If somebody donates three times, and doesn't show up a fourth time, will the third unit be discarded?

MR. BELL: Under the voluntary standard it is for the first time donor, which we have no history on, so the focus is on having at least one repeat donation to come back to, so we have that history.

DR. KASPER: Just so I understand, so then if you have a quarantine say on a donation, and the donor never shows up again, how long is the quarantine?

MR. BELL: It is a 60 day inventory hold. This is a baseline standard, by the way. Manufacturers will vary from manufacturer to manufacturer. This is the beginning process and the consensus that was agreed upon as a baseline.

DR. KASPER: Thank you.

DR. HOLLINGER: It probably sounds like it would be a reasonable idea not to use that donation, doesn't it,

if the person does not come back again? It could be just as important of a risk.

Anybody else, any other questions?

DR. NELSON: I think that does sound like a good idea, but I wonder what the frequency of that is. In other words, the window period would have expired by the time they came back for the 60 day donation in most instances. I just wonder how frequently the person would not have a terminal donation in a pool. Is that practical? It sounds like a great idea.

MR. BELL: As I said, these are voluntary standards that industry has come forward with. We welcome and invite comment from the BPAC and from all the interested parties on these standards, but as I said, this is our attempt in moving forward to raise the level, to raise the bar beyond which the regulations require. I think this is something that we are showing by virtue of example, our leadership to the industry on how to improve the safety of the products.

That information, to my knowledge, is not available.

Agenda Item: Open Committee Discussion, Committee Discussion and Recommendations

DR. HOLLINGER: If there are no further questions from the committee, this will end the open public hearing, and we'll move into the committee deliberations on the questions for the committee.

So the first question is, when notified of inadvertent contamination of a fractionation pool with units reactive for HIV, HBV or HCV, you're asking us two parts actually. Should the FDA uniformly quarantine or recall all products as violating? That would mean they just remove them. They would not be used, as I understand it.

Or, they would determine regulatory action based on an assessment of product risk, that is the impact of virus removal or inactivation of other factors related to the release of that product eventually, or not to release it eventually.

I would like to open this up for comments for any of the committee members.

DR. LINDEN: I just don't really completely understand the question. If we could get clarification before we start. The various speakers talked about what seemed to me a much larger universe of what inadvertent contamination could be of improper testing of various things.

So I gather we are only talking about a small portion of the total inadvertent contamination situations, and that seems to be limited to reactive or only these three analities, the way I'm reading it. I just wanted to clarify that we are talking only about reactive, not confirmed positives? So there may be initial reactives here?

DR. HOLLINGER: Dr. Epstein, would you please fill us in. I know we are talking about the three viruses primarily, but the issue I think has to do with are there other reasons here, such as errors or things like that?

DR. EPSTEIN: Yes, we deliberately narrowed the scope of the presentation and questions today in the hopes that we could begin to develop recommendations for a much larger set of things. It is our full intention to come back to the committee, perhaps as early as the next public meeting, to discuss other situations of inadvertent contamination such as post-donation information on positivity for risk factors.

Then of course there is also the issue of infectious diseases for which we don't test or have no inactivation. So we have limited it. That is deliberate. What we are talking about now is evidence of reactive tests.

Now it is true that you may wish to clarify that

one set of actions might be appropriate if there are confirmed positives, and a different set of actions might be appropriate if we only have unconfirmed screening result, and no additional testing. We deal with many, many such variations, as was suggested by Ms. Godziemski's presentation. You will have that opportunity in a later question.

What we are really trying to ask you in question 1 is should all the subtleties simply be ignored? In other words, if there is technical violation and we learn of it, should we simply have a uniform recall or quarantine policy? If not, then we are in to some kind of domain of assessments, and we will query you, what are reasonable considerations.

MS. PIERCE: I have some concerns here. A lot of information was presented on the slides which we did not have access to prior to the meeting. As well, information was given to us prior to the meeting that was elaborated on, and some of that had to do with the actual incidences of contamination; positive units that did get into the blood supply.

I am feeling a bit of an imbalance here in terms of issues on that other side. I would like to know if

anyone has any idea of the number we are talking about in terms of these inadvertent contaminations over denominator and the numerator, and what kind of a time period are we talking about, consequences.

A lot of the information that we have seen has documented that there has been no transmission of these different agents, but I think that also needs to be tempered by the fact that some of these are only 35 percent of a population, and there is no documented transmissions. There have been some transmissions that have been questioned, but there are other risk factors involved.

Also the issues with the violations of the GMP and withdrawal and recalls; that data also has not been presented. So I'm feeling uncomfortable looking at all this data, and in this small time frame, trying to get a balance of what would be an appropriate response.

DR. HOLLINGER: Yes, Corey Dubin?

MR. DUBIN: A couple of things. Let me say this first. I think in response to what you said, Jay, I understand the need for subtleties and to look at situations, and I think we are sensitive to that, because frequently they can affect larger issues of supply, and we need to be cognizant of that at the same time.

I think one of the difficulties FDA has had is uniform application of standards and guidelines, whether they be the recall notification and look back standards or others. In discussions with Deputy Commissioner Pendergast, she certainly informed us that the move now is to really apply in some uniform way, standards. I'm kind of caught in that dilemma of seeing that difficulty that has occurred.

That said, the other difficulty I have is I feel a sense of operating in a vacuum on some level with the committee right now. These are really serious questions that for me as a representative of the hemophilia community on this body, these cut to the core of not only our safety and security, but the perception of security out there today.

We are asked being asked to answer these questions at a time when I am aware of things going on out there that I'm not sure the entire committee is aware, and when we are talking about inadvertent contamination, it is hard for me to feel comfortable when I'm not sure the committee has been briefed on what is happening with Baxter and Humanetics and the collection equipment and contamination with saline, which speaks quite directly to these issues we're now talking about. So I share Bea's discomfort, because I feel

a sense of operating in a vacuum.

Then my other dilemma, as I said was I see the need for subtlety. I would be crazy not to. Supply is an important issue for us. I also see the lack of uniform application and the problem that that has been.

The last thing I would say is I sit in front of me with a GAO report, with an inspector general HHS report, and I'm not sure these reports have gone to the committee members, and these reports speak to these issues directly. I think if the committee is going to make informed decisions, which is what I think we all agree we are here to do, these reports need to be digested by members of this committee.

REV. LITTLE: These are just some general comments, but if we are talking about a triple or a quadruple safety net if we include surveillance, it seems that a system of checks and balances doesn't really work if you are only putting consideration or heavy emphasis on one part of that system. That what I have seen addressed in most of the presentation, when we are talking about the heat treatment, and the final solvent process.

The other thing I have serious concern about -- I do have concern about supply. I guess the bottom line would

then be if a consumer had to choose a product that was clearly labeled saying this product was inadvertently contaminated due to et cetera, I wonder -- each situation would be different -- as to whether or not the consumer would say yes.

If I were in the situation -- I do receive IV IG - - and I were in the situation where it were a matter of my being on a ventilator, and this was the absolute only product left, I might say yes. If it were the situation where I would feel having some weakness in arms and legs and saw this, I might say no.

My concern is also how is this inadvertently contaminated supply then distributed? Who gets what? I would like to think that in the best of all possible worlds there is no distinction made, but I'm not so sure about that, just based on life experience with all the different injustices that exist in our society.

The final thing I want to say is that one of the presenters talked about there is no scientific rationale to suggest that we should not put some of this product back. I realize that we are a scientific committee here, but I think that the reality is that we have to look at these situations with two sets of eyes, and maybe three sets: one, a

scientific rationale; but certainly these numbers and algorithms and everything else have human faces attached to them. I very much appreciate the speakers who got up to help us flesh out some of these human faces.

Whether it affects 10,000 or 10 people, these are human lives, and we just have to always keep that in the forefront.

DR. HOLLINGER: Dr. Nelson?

DR. NELSON: The thing I don't have a sense of is not being someone who treats patients with hemophilia or immune deficiency, is it seems like the current system is working in terms of safety, except for the Gammagard situation, since 1987 or something like that.

Maybe it isn't if there is a lot of problem with availability or difficulty in getting the key product. Other than the albumin situation that Susan brought up, nobody has talked about this part of the equation. How has the current blanket recall or quarantine algorithm affected availability? How many people have had to go without critical product when they needed it?

That is clearly part of the equation. It has not been presented by anybody. We don't have any data on that as far as I know.

DR. HOLLINGER: Mr. Dubin?

MR. DUBIN: Let me try at least to respond at least from the Committee of Ten Thousand's perspective, and how we view it. There is no question that vis-a-vis lipid envelope viruses, HIV, HCV, we have seen a marked change in the situation. There is no question about that. I think that is a given, and I think we are very clear about that.

I think there are some lurking emerging threats that have got our people really on edge, and that people like Bea and myself or Dr. Kuhn(?) are trying to sort out and report back, Dr. Ewenstein, Dr. Kasper. I think those are things that we are concerned about.

I think in terms of whether it is working, I will give you an example in terms of availability. There was a global monoclonal Factor VIII shortage, in part because of what happened at Sention(?). What happened at Sention was a bit of a shocker to this community, that it would happen in 1996 or 1997, given all we have seen.

I think as some of this stuff about the current collection problem with Baxter, the Humanetics problem has gotten out, people have said, well, you guys, what are they not telling us? We know that temperature deviation is not a giant risk to us at all. We understand that. People say,

but what does it mean?

So I think in some ways the system is working. I think where we think it is breaking down, and I think what is contained in some of the reports I have identified is that there are serious problems in enforcement of GMPs, SOPs and that that is where we need to adjust this system.

If we looked at 19 recalls; 17 look pretty substantial, regardless of looking at how violative each one is, I think that indicates to us something is not working right, whether it is an enforcement question or there is a breakdown somewhere.

I think that is the growing sense in the community. I think what we are saying to the manufacturers is certainly what I said at the ABER(?) meeting was, let's look at a new paradigm, where FDA, us, Congress, CDC all get together, because I think everyone in this room shares one goal, a safe blood supply. I don't think there is anybody in here that doesn't share that goal.

We work in this whole paradigm of distrust, and somebody doesn't want to tell somebody this. I think we keep banging our heads up against this issue of well, you guys if you keep this junk up, there is not going to be enough of this stuff on the market, and it is going to be a

problem.

To make intelligent decisions, to participate as part of intelligent decisions, that data needs to be forthcoming, and we have not had it. Not only have we not had it, FDA has not had it. A comment off the cuff a year ago from a guy from CCBC was don't feel bad, Corey, we can't get anything out of the fractionators either. So you guys aren't alone on this issue.

So I think that is what we keep batting our heads against is how can we make these decisions about emerging threats, about current threats, about policies when we don't really as a body, understand what the implications of a given decision will be.

DR. HOLLINGER: Jay, do you have a response?

DR. EPSTEIN: Thank you. I just wanted to remark that there is an issue of which side of the coin you look at. Certainly as the FDA steps up surveillance and enforcement, as it has been admonished to do in the wake of the AIDS era, there will be more and more withdrawals, recalls, notices, many of which are being taken on a precautionary basis.

I think that as you analyze the recent recalls, and you cite 19 in the last two years or year and a half,

the vast majority of those have not been actual contaminations or known transmissible disease. We certainly had bacterial contamination of albumin. We certainly had transmission of hepatitis A.

Many of these recalls have dealt with things like CJD, where the risk is theoretical, or they have dealt with GMP breakdowns, errors, accidents and other deviations which have not clearly been translatable into product risk, but where the risk assessment was remote risk. Nonetheless, the products have been recalled. Should we look at this as a good thing or a bad thing? I think that that it is important that that perspective be understood.

At the very same time, and also in the wake of the AID era, the agency has been pursuing far more conservative policies regarding acceptable, or I should say unacceptable risk. This has contributed also. It is the basis on which we have had a withdrawal policy for CJD, but it is also the basis on which the change that you heard with respect to inadvertent contamination.

The fact that there was an era of our history when hepatitis B proven positive unit in albumin or immune globulin was not regarded as a basis of a quarantine or a recall. We have told you that that policy has changed, and

we now would act against the product.

This represents once again, a change toward a far more conservative mindset. What we are really asking the committee is based on considerations of safety and effectiveness, is there a way to fine tune these policies? I understand that issues of supply have been brought up; issues of ethics have been brought up, but that the committee has a charge to look at safety and effectiveness, and to advise us scientifically.

We have other fora at which we seek to be advised societally. I know that that's a problem, because it is often very hard to disentangle the issues. What we are trying to ask you is can you advise us on the safety question? I understand also that the point has been made that the safety issue becomes clouded if there are GMP breakdowns. That is certainly true.

We are not asking you to make a judgment in the face of GMP breakdown. We are saying if GMP has not been violated, if the validating procedures which are appropriately in the SOP are being followed, and we make these observations, then what? We will be back to you at a later day to ask the even hard questions of what do we do now when there is a deviation? How shall we assess

deviations?

Of course what you also need to understand is that although we may take the time in the advisory committee to deliberate and come to good recommendations which we can translate into criteria, it doesn't relieve the agency of the need to make judgments in these matters currently when they happen.

We are faced with these circumstances and these decisions all the time. I agree with Corey; we would like to move to an environment in which we have clearer actions based on well articulated principles and criteria, but that is what we are asking you to help us generate. That's the questions are being brought here.

DR. VERTER: I started out with one set of remarks, but after listening to the last speaker, I probably have to expand it a bit.

Once again, from my perspective the committee appears to be faced with what on the surface seems like a simple question, but in fact for me at least it is a very complex question for which I feel I have very little information. Actually just listening to the last speaker there were three Ss involved in my problem; four if I add the word simple.

I can answer this question yes just from a safety -- just blanket yes, do it. On the other hand, as Rev. Little brought up, it's not so simple.

DR. HOLLINGER: Yes, do it what? Recall?

DR. VERTER: Yes, quarantine, recall, the whole gamut. Rev. Little points out that there are choices that maybe individuals need to make if the supply is limited. Maybe if the down fall is my pinkie is going to ache, then I'll take the risk. On the other hand, if I'm going to get HIV, maybe I'm not willing to take the risk, and how does that enter into the picture? So supply is definitely an issue.

The most difficult for me is the science. Although we heard a lot of things today and a lot of numbers put up, in retrospect after thinking about them, I'm not sure what any of them mean. I'm particularly concerned about the word "inadvertent." I don't know what that word means after sitting around and listening to everything today.

Does inadvertent mean that a product is manufactured and 10,000 units were sent out, and of those 10,000 units say 1,000 of them have been used, and from that one contamination has been noticed? Now would that

inadvertent mean that the contamination was due to something that happened after it left the manufacturing plant, or because of the use of 10,000, instead of a big pool.

When you get down to a smaller unit, it is more likely that the contamination is going to be picked up, so that in the remaining 9,000, there maybe another 10 or 100 units that are contaminated. So I need someone to clarify for me what they mean by inadvertent.

DR. HOLLINGER: Dr. Tabor?

DR. KASPER: I think it is defined right here. Something that happens after it is distributed, and donor gets sick. That's the donor event, and we're not talking about that.

DR. TABOR: Actually, what Dr. Kasper is saying is right on the nail. I would like to also say that we wrestled with the term "inadvertent contamination" before putting this on the agenda. There have been efforts in the past to change the name for this type of episode, but the euphemisms were just more confusing than the term that had been used for the last 20 years.

Basically, inadvertent contamination means a pool or product made from a pool is discovered sometime after the point of pooling to contain a unit that should not have gone

into it.

DR. VERTER: That means that it was in there at the end of the manufacture, it just couldn't be identified, right?

DR. TABOR: That could be the case, or in some cases you might be able to identify it, but at the time of pooling, it was not known to have been inappropriately in there.

DR. VERTER: The implication for that is that it is the receipt of that unit by the person that is later found to be contaminated or infected --

DR. TABOR: No, this does not involve information that you have obtained from giving this product to a person.

DR. LEITMAN: Dr. Tabor I thought explained this pretty clearly. At the beginning there were three points that went into the definition of inadvertent contamination. At the start of the manufacturing practice, there is a contaminated unit either because it is a window period donation, because it's a sero silent donation, or because it's a donor event, which is essentially the same as a window period donation down the line let's you know that even though every cGMP process that tests, that screens, that goes into eliminating that, could not work.

It is not in the ability of the current system to have detected that unit. It is a true inadvertent. That is no manufacturer's fault, it is just the state of the science.

Now that is different than the situations we heard about from the early FDA presenter where there is a testing error, where there is a repeatedly reactive or Western Blot confirmed unit that enters the pool. The net result is the same. There is a contaminated -- let's take HIV for example -- unit, and that unit has 10^3 , 10^8 variance per ml, so it really doesn't matter if it's a window period or sero silent or silent positive, that contamination is in the same concentration.

The end result is the same. At the start of the manufacturing process, you have this contamination that was part of the pool. So that's the background to this.

I object to the comment that the science can't tell you anything. If you truly believe that science doesn't tell you anything, then we can't vote scientifically as a committee, which is our charge, as Dr. Epstein just told us was our charge. I find that the scientific data is meaningful and is compelling, very compelling to me.

The window period instance of HIV in the recovered

plasma data, which is 60,000 donors per pool, 1.62 positive window period donations per million tells me that -- I just did the math earlier -- that one out of every ten pools made from recovered plasma has a window period donation by that model.

So whether I know that that happened through the donor event that the Swiss Red Cross person told us about, or whether I model it, one out of every ten pools has a window period HIV donation in it. We are enormously dependent on the cGMP and inactivation practices that follow that donation, enormously dependent. As Dr. Nelson stated, it seems as if that is working.

There are breaches in cGMP all the time I think; a lot of the time. Corey was referring to them briefly. Something is off by two or three degrees -- I don't know about these. Corey told me them privately. Other small or large breaches, and there are errors that are made, not in testing, because errors are human.

It's my feeling, listening to all the information today is that if a pool is detected after it is made, or during some process of it being made, or a batch or a lot or final vials, if there was inadvertent contamination, that what should happen is everything that is part of that pool

should be immediately quarantined and recalled, but not necessarily destroyed.

What you go to then is an audit or an inspection of every subsequent aspect of the manufacturing process. Where there any problems, breaks in manufacture, breaks in the viral inactivation steps? If there were none identified, then the unit, that batch, all those vials are safe.

DR. VERTER: I understood everything you said except the last four words. I'm obviously missing something. I didn't mean to imply that I didn't see data which was reassuring, but perhaps not absolutely reassuring. After you went through all that, aren't you saying -- I thought what you were saying is that the process inadvertently had a contaminated unit in it. You found it.

You quarantined. You rechecked and you can't find any reason that anything went wrong, but still there was something positive. Why would you then use the remaining units?

DR. LEITMAN: Actually what I meant to say was it was safe for re-release and redistribution. The reason I believe that is whatever I know, we all know was in there at the beginning, has been inactivated. The scientific data

and the epidemiologic data, which is even more strong than the in vitro viral inactivation data is overwhelmingly compelling to me.

DR. NELSON: In other words, that unit would be the same as the 10 percent of the units that we now do not identify as being inadvertently contaminated, because there are donors that were in the window period that we have not identified, but in fact were contaminated, were transfused, and transmission was not identified.

DR. LEITMAN: Even more, they are more safe, because an audit and inspection were carried out to make sure there were no breaches.

DR. NELSON: I agree that this is kind of a tricky question, because we still need to quarantine until we have all the data. This question is not quite stated that way. There has to be a link to algorithm, and you have to go through the whole thing before you make a decision that this one is safe.

DR. LEITMAN: The potential for re-release at the end of is quarantine or recall, but not destroy. It is quarantine, recall, thoroughly evaluate, report to the agency, and then it is possible, likely perhaps that it will be re-released.

DR. MC CURDY: Actually, that was the point that I was going to ask, because there seemed to be a timing issue here. If the B up there includes an immediate hold on what is going on until it is reviewed and a determination made, then I find it easier to make a decision.

DR. HOLLINGER: It is my understanding that under this assessment of product risk, is included all the quarantine of the product until they have an opportunity to review all the things which Dr. Leitman expressed.

DR. MARTONE: I think there are two different issues here. In the one instance you have got somebody in the window period, and you don't know that the pools are contaminated. You use these inactivation procedures and the product goes out to the people, and it's a safety mechanism.

On the other hand, you know the pools have been contaminated. The two may be the same of course, if in retrospect you find somebody sero converted, but I think it is a different issue when you use a product that you know that had been contaminated versus you are using a product that might be, but your safety net is the inactivation procedure.

DR. LEITMAN: I think that's an emotional difference.

DR. MARTONE: No, I think it's an ethical one.

MS. PIERCE: I would like to clarify. The first page of what we got in the mail said that we were not talking about window periods, and we are mixing it here. I just wanted to be clear that we were talking about the inadvertent as defined as something that was positive --

DR. LEITMAN: Can we ask Jay Epstein to clarify that one more time please?

DR. EPSTEIN: The answer is that the inadvertent contamination as described by Dr. Tabor and recapitulated by Dr. Leitman may come to our awareness in a variety of ways. Sometimes it may be because of subsequent revelation of a positive or reactive test result. Examples of that instance would be for example, delayed reporting through an audit that a positive unit or reactive unit was released through error. It was received by the fractionator as negative, but in fact a reactive unit had been distributed through some error, and there are all kinds of errors that might have caused it.

Another example might be that downstream testing was performed, such as an antibody test on the pool, or a PCR test on the pool. So although you might not have specific knowledge of an improperly utilized unit, you

nonetheless have a positive result affecting the pool, which implies that a reactive unit was pooled, but you don't always know how it happened.

There is the other instance, however, in which there was no positive test result or reactive test result. That the pool unit was a window period unit. That instance also can come to light, however, and you heard presented by the representative on behalf of Swiss Red Cross of a case in which a donor who had denied risk factors, donated in the window period; had negative tests; and it was learned that his transfusable components transmitted HIV, red cells and platelets transmitted HIV.

The plasma from the very same collection had been pooled in a fractionation pool. Now there is no positive test in that case, as was correctly stated. Antibody tests, antigen tests and PCR tests on the pool and on the final product all are negative. We would nonetheless regard this as inadvertent contamination, because you have subsequent knowledge of potential or actual contamination.

MR. DUBIN: To clarify a point, I understand there are a realm of issues around ethics, but I want to sift those away, because I want to focus on what the subject matter is, and I want to understand in staff's presentation

this morning that there is no question that the data and the studies and the technology of viral inactivation vis-a-vis lipid envelope viruses is exactly what was presented this morning, and is effective, and is efficient.

We understand that, and we are not trying to turn a scientific issue into an ethical issue or anything else. I think what we are saying is we were presented a picture of viral inactivation that was very true. I think at the same time we have a picture of the enforcement of the GMPs and the SOPs that make sure that technology is being applied correctly that allows the safety net, the layered net to function properly.

I don't think in my mind that is an ethical or an emotional question. It is a hard core regulatory question. If you have the technology that will do the job, are the manufacturers following the standards that have been established to allow that technology to do what it can do?

I agree Jay, that as the agency steps up, we are going to see more. I grant you that point well. I think if we look at the substance of some of the things that have happened, there is a problem with the way the puzzle is fitting together, and that is what we are articulating, in a purely regulatory enforcement sense, so that the technology

that we know works, can be put to work, and we know it is working.

So if there is an inadvertent contamination somewhere earlier in the system like with what is happening with Baxter at the collection stage, and the tests are changed because of saline contamination, that that will be picked up in the viral inactivation phase.

I think it's pretty strong that we hear that the Chicago office suggested pulling Baxter's license. This is what is out there. Our people hear this. If that is not what happened and they come to me, or they come to Bea, and they say, find out about this. We're nervous about this. What does this mean?

So I think we want to be clear that we are onto the science and regulatory issues, not ethics and emotion. We are focused on what is on the board, and what was on the board this morning.

DR. HOLLINGER: No, I think those are important issues. The way I hear it here is that you have to have these good practices all the time, and no breakdowns. That's what you really want. In this case what they are saying is here you know that something has been contaminated. Now by having the quarantine and the setting

aside, you have an opportunity now to go back as best as possible, and make sure that there hasn't been any breakdowns along the whole line.

Now once you establish that, then I think you go and look at all the of the data. The safety data, at least for albumin and immune globin and IV immune globulin as we know it today is very safe. I think imperceptible potential for transmission. I think at that point then I think one can say that will work quite well.

DR. LEITMAN: I'd like to take the opportunity to change the phrasing of question 1 to the following: when notified of inadvertent contamination of a fractionation pool with the unit containing, instead of reactive, because containing covers all the parts of contamination; that a. Immediately and uniformly quarantine or recall all products as a first step. Then determine regulatory action based on an assessment of product risk, e.g., all the other subsequent steps of cGMP virus removal or inactivation.

I want to also say that I'm not quite as black and white as I sound sometimes. I think there is a world of difference in inadvertent contamination due to true inadvertent contamination, window period, sero silent, donor event, absolutely unavoidable inadvertent contamination.

On the other hand, where there is a major breach in manufacturing practice, so that a positive test unit gets in, I am so upset I'm angry, but the bottom of the effect is the same, it is a uniform treatment of such units after you know of that.

DR. HOLLINGER: Would you include part of the quarantine of the final products or the processes before at some stage, molecular evaluation of the product, nucleic acid determinations and so on, to consider release of that product?

DR. LEITMAN: As we have seen, the PCR can be negative because of the dilution effect as in the Swiss Red Cross case. So that's not 100 percent.

DR. HOLLINGER: I understand that, but we have a viral inactivation step. If we are talking about a contaminated product that then would be given to people without any viral inactivation, that's a different story, and yes, that would make a difference. Assuming at the very least, should the product be free of any detectable nucleic acid on the current sensitivities of the test that are available today?

Or that is, would it make a difference of whether you would release it eventually if you found them to be

positive for HPV DNA or HCV RNA or HIV RNA? Would it make a difference of whether you would eventually release those lots?

DR. NELSON: Is your question saying that if the thorough review of all evidence was that the good manufacturing process was followed?

DR. HOLLINGER: Yes.

DR. NELSON: If that is the case, yes, but if there was a problem with the manufacturing process, you wouldn't release it on any test.

DR. HOLLINGER: Absolutely, I would agree with that.

DR. KHABBAZ: My comment is that I like your suggested rewording, but I would like ask the FDA if that rewording would work for what they are trying to do? If I understand correctly, in trying to enunciate some principles and action. I guess the action often precedes confirmation that a unit contains a virus. There is a time frame when you have a reactive test on the unit, and is that --

DR. HOLLINGER: It seems like (A) could be left just the way it is, but you could add Dr. Leitman's statement to (B), which then would uniformly quarantine all products as a first action, then determine regulatory

action.

DR. LEITMAN: I took the word "violative" out, because violative means you destroy it in my mind. You remove it, because you don't know whether it should be destroyed. So your first safety -- you have to remove it, but it may possible that you have demonstrated that it is safe after that.

DR. NESS: It seems to me that what we are trying to do is write further regulation for FDA, and also rewrite their questions at the same time. It seems we are avoiding the fundamental question that they are trying to pose to us in this question, which is if there is an inadvertent contamination which has been defined by the presenters earlier on, does this committee feel that that product is forever lost from use? Or can it be reviewed, based on the available scientific technical GMP review audit, all of those kinds of processes, and potentially be used for patients?

I think that is what they are asking us, because if we saying (A), it cannot be used, then the rest of our points and discussions are moot. I for one, as the industry representative, think that the FDA has put forward some compelling arguments that there are circumstances were

inadvertent contamination occurs and the product is safe, based on every available piece of evidence that we now have. Therefore, I for one feel confident that they should be able to make those decisions.

DR. HOLLINGER: Thank you. Are there some additional comments? Dr. Kasper.

DR. KASPER: I just wanted to comment on Dr. Leitman's rewording in that the way we have it up there, notified of inadvertent contamination would also cover the situation such as was described at length by Alpha. We still don't know whether that Alpha pool contains truly positive units. What we have is too many tests, and you know if you do five or six different brands of tests on something, one of them may be positive, and that's just the nature of laboratory testing.

So we have a big problem of tests, and are they always -- what do you do when five tests are negative and one is positive? Who do you believe? I think this is a major issue on the Alpha, and it is probably going to be a lot of other issues. You can't say that this is a truly contaminated pool. It is a suspect.

So I think that the FDA perhaps also wants guidance on what do you do with a suspect, when there is a

test.

DR. HOLLINGER: This is a critical issue here. On the other hand, I think that Dr. Ness has sort of indicated, and I think he is right about what these questions are really about. I would like to pose it as a question right now.

DR. EPSTEIN: I would like to request that the question (A) be left alone for the reasons stated by Dr. Ness, which was the exactly the reason that they were cast as they were, however, I accept Susan's suggestion that 1B be modified to ask whether in that instance there should be uniform quarantine of products followed by determination of regulatory action based on assessment of product risk.

I think that we have heard many comments from the panelists that that is a more rational framework. I would caution the panel, however, that FDA does not currently have the regulatory authority to mandate such quarantines, although they have been voluntarily complied with.

I would also accept the suggestion that instead of talking about units reactive for HIV, HBV or HCV, we use the language containing or likely to contain to contain HIV, HBV or HCV. Let me say that in using the word "reactive," we were deliberately lumping the cases in which we had

confirmed positivity, and the cases in which we had evidence and lack of confirmation.

I understand that that has caused some confusion that we may have knowledge of a window period case in the continued absence of any reactive test. So we can erase that confusion by saying containing or likely to contain, understanding that that will subsume window periods without reactive markers, reactive markers without confirmation and confirmation.

Now let me say that our original intent was to ask again only a narrow question, what if you have a marker, because I think that it is possible to have different considerations when you do and don't have a marker, but I think that the broader context is correct that it is either containing or likely to contain.

So if I could just read these for clarity, and I guess if anybody has a grease pen they could mark it up. When notified of inadvertent contamination of a fractionation pool with units containing or likely to contain HIV, HBV or HCV should FDA: (a) uniformly quarantine or recall all products as violative; or (b) uniformly quarantine products then determine regulatory action based on assessment of product risk.

DR. MARTONE: I don't like that word "containing."
It doesn't give me any sense of the viability of the organism. The organism could be there; its DNA could be there, and it could be dead, so I don't like the word "containing."

DR. HOLLINGER: So you like reactive better?

MR. DUBIN: Dr. Leitman also used the word "immediately" and uniformly. I wanted to hark back to that was what she proposed on part A.

DR. HOLLINGER: The fact that they say containing or likely to contain -- that's the way I think he put it, likely to contain, which could mean that there is nothing there.

DR. MARTONE: I think if you took the average person on the street and said would you be willing to receive a product containing HIV, they would say no, but it doesn't mean the same thing that I think we are trying to get at here.

DR. HOLLINGER: Does anybody else on the committee feel strongly about it?

DR. KASPER: I like reactive. I think that explains the situation better.

DR. LEITMAN: The situation of the donor event

with the reporting of infectious red cells and platelet units and plasma that you know has actively replicating virus or potential for actively replicating virus. It wasn't reactive. That's inaccurate; meaning active virus.

DR. MARTONE: Couldn't the pool still have been mistakenly reactive?

DR. KASPER: That's one of the big problems.

DR. MARTONE: But they don't really contain anything.

DR. HOLLINGER: How many prefer leave it as reactive, raise your hand?

DR. LEITMAN: Could I suggest a third, containing or reactive for, so that would cover the testing.

DR. HOLLINGER: Containing or reactive for? How many would prefer to say containing or reactive for? All those opposed to that suggestion?

Okay, so let's read this question once again, and then call for the question. When notified of inadvertent contamination of a fractionation pool of units containing or reactive for HIV, HBV or HCV, and then the rest of it as Jay has outlined.

MR. DUBIN: The word "immediately" as per Dr. Leitman's suggestion.

DR. HOLLINGER: Under (B) it should say immediately and uniformly.

REV. LITTLE: Did Dr. Epstein say or, or and at the end of (A). Did you use the word "or" or "and?" You kept or.

DR. HOLLINGER: I'm going to call for the question.

MS. PIERCE: I just wanted to clarify (B). The immediately and uniformly would be in there, but the remaining part would remain determine regulatory action based on assessment of product risk, i.e., impact of virus removal and inactivation. I'm not sure what that means.

Does that mean that they could go back and say these viral inactivation techniques have been shown to remove X number, therefore it really is okay, or does that mean that someone will go back and do additional tests? It's just a look back on the information that is already there that has given you the result anyway? Or does it mean additional actions will be taken? I think that needs to be clarified before I can vote on that one.

DR. NELSON: Wouldn't it mean that the review of the situation had found that this product did not shortcircuit good manufacturing processes?

DR. HOLLINGER: Yes, I believe that's what it really means.

DR. HOLMBERG: Can I have a clarification here? I don't understand recall all products as violative. That means to destroy?

DR. HOLLINGER: Yes, that's my understanding. It would be destroyed, or not necessarily destroyed; it could be used for research purposes I suppose, but the usual labeling that goes along with it, but certainly not used for human use.

DR. LEITMAN: Paul Ness said this earlier, but (A) is nontransfusable, (B) is potential for transfusability, depending on further inspection or the review.

MR. DUBIN: But (B) does not contain even a temporary quarantine necessarily.

DR. PILIAVIN: It does as the way we just reworded it. It's been reworded as saying immediately and uniformly quarantine or recall all products as a first step, and then determine regulatory action based, blah, blah, blah, which is in (B). That's what we are voting on.

DR. HOLLINGER: We'll vote on the first part (A), about to quarantine all the products as violative. All those in favor of 1A raise your hand. All those in favor of

1A as listed and corrected on this? So 1A is the product would be destroyed; 1A is basically the product would be not used. Recall is not used.

Let's vote again. All those in favor of 1A raise your hand. All those opposed? Abstaining?

REV. LITTLE: I abstain.

DR. HOLLINGER: Then we will vote on 1B.

REV. LITTLE: I would like to explain my vote. It goes back again to the lack of time to really look at this data and come to what I think is a responsible decision. It's not that I don't disagree with some of this that is going on. I just feel that we have not had the time to really look at the data. Some of that is based on some of the comments you made about the hepatitis C and other things like that. That's why I did vote the way I did.

DR. HOLLINGER: Thank you, Beatrice.

Let's vote on 1B then, which basically is immediately and uniformly quarantine all products, then determine regulatory action based on assessment of product risk. All those in favor of that action raise your hand. All those opposed? Abstaining?

Rev. Little?

REV. LITTLE: I would abstain. Can I explain why?

DR. HOLLINGER: Yes, please.

REV. LITTLE: I would abstain, because I think if that were to happen, that it is also dependent upon what then happens next with regard to labeling and other concerns that I have, so I would have to abstain.

DR. HOLLINGER: Thank you.

DR. VERTER: I would just like to make a brief statement. I voted yes, but with some trepidation, and it has to do with the word "science" that I used before, and the word "risk" that is up there. It is how I feel a bit uncomfortable of how risk will be determined based on the numbers that are available. I have a lot of confidence in FDA epidemiologists and statisticians, but I felt that the data was still somewhat lacking in the models, and not presented very well. That was why I mentioned the word "science."

DR. HOLLINGER: I would agree with that too, Dr. Verter. That is a question that I have too. I'm hoping, and you have stated that this is not just based upon product risk and modeling and so on, but is based on a much broader evaluation of this whole product, as Dr. Leitman has indicated previously. It's not on product risk alone.

MR. DUBIN: I just want to underline again, to me

this question is dependent on the climate out there. Again I want to underline for the record, we are seriously concerned about the enforcement climate right now. I voted the way I did, because I think in a rational, correct climate, this is a policy we need to be looking at, because there are a wide range of issues.

I need to underline it again Dr. Hollinger, we are much concerned that the climate is not what it should be. I think if you read GAO and if you read the IGO, you start to read some of this, you see that is where maybe the problem is lying, and I want to underline.

DR. HOLLINGER: Maybe what we need for the FDA, and Jerry, this is probably something that the committee is troubled by is more specifics of what you really plan to do. I think what you hear from the committee is yes, they feel that these products are safe as utilized with the viral inactivation procedures, but we would like to have a little bit more assurance of exactly what you are going to do and how you are going to do it before it is probably initiated, particularly in terms of looking at quarantine products or looking at GMPs and so on, and how you are going to use risk in all those other things too.

I think that is what some of the committee members

have some concern about giving sort of just an open hand to do in this.

DR. EPSTEIN: I just wanted to remark that I think we hear very clearly the message that we should not be lumping situations in which GMP has been carefully adhered to with situations in which there either is inadequacy of records or evidence of breaches. We also hear very clearly the message that you would like to see vigilance on the latter point. I think we understand those messages.

DR. HOLLINGER: I'm going to ask Dr. Smallwood to read for the record the responses to the first question.

DR. SMALLWOOD: There are 13 members present eligible to vote. On question 1A there no zero yes votes; 11 no votes; 2 abstentions. The consumer representative abstained in her opinion.

For question 1B there were 11 yes votes; zero no votes; two abstentions. The consumer representative abstained in her opinion.

DR. HOLLINGER: Dr. August gave me his paper, and he voted yes on B, if you can accept that.

DR. SMALLWOOD: As stated by the chairperson, Dr. August left his recommendation on question 1B, which was yes.

DR. LINDEN: I would just like to make a comment to urge the FDA to give further consideration to the term "inadvertent contamination." I understand from Dr. Tabor you have already discussed it, but I think part of the confusion and discussion of the committee is related to fact that I think we have different perceptions about what that means. I think some people were interpreting it as meaning it was actually contaminated, whereas I heard people saying from FDA, well it's really possibly contaminated.

Dr. Kasper mentioned it's really suspect, not known contaminated. I think the term implies that it is contaminated, and that's really not what you are talking about. So I urge you to give further consideration to maybe coming up with a different term.

DR. HOLLINGER: Now we have some other questions here of the committee, and I would like to turn to those if you will, please. The second question was, considering the recommendations made in question 1, should FDA modify its actions based on product shortages?

I think that probably had more to do with if 1A had been passed more than anything else, because I presume that product shortages would be taken into account, but it may not. Should it matter? Should product shortages alone

matter in terms of 1B? Should it be one of the factors for determining release of a product?

MR. DUBIN: This one I think is a real difficult one, and just to be a bit reflective, this is part of what killed us in 1982 and 1983 at the BPAC when people said, you know there will be huge product shortages. This is one that really haunts me, and in an ideal situation where we knew enforcement was right on the money, and the climate was where we wanted to be, and there was a lot of trust and a relationship built, maybe, but there is no way I can see this one in this current climate from our perspective at all, because the risk is again --

Before I say the concluding statement, let me insert one more. We still don't know what this means. We still don't have the data to say if X pathogen shows up and we've got to recall X amount of collected plasma, what does that mean for the supply of monoclate P or Baxter's monoclonal or any of it? We don't know, and therefore this to me, is a real danger vis-a-vis new threats, and I can't support it at all.

DR. HOLLINGER: Dr. Kasper?

DR. KASPER: I had been considering the issue of whether one could put a label on a lot in which there had

been some suspected, but perhaps a contamination that might be taken care of by viral inactivation. Given the fact that I have lived through the experience of severe shortage of concentrate in 1988, when there was just a great, big shortage of Factor VIII concentrate, and had to give some patients cryo precipitate from Los Angeles, one of the epidemic cities, which was absolutely not viral inactivated.

So I had to triage my patients, and say to some people I knew who were HIV positive, would you please take cryo, so we can give concentrate, what little we have to the kids that are not yet HIV positive.

So when you have lived through a shortage, you want to have the possibility of dealing with it on a triage basis, however, I doubt that any manufacturer in the legal climate of today would be willing to put out a concentrate with a label saying this might be a little more dangerous than our usual concentrate. I doubt that I could get what I really need.

MS. PIERCE: That's my concern also, is that in the past when that has come up with companies -- and they want to address that -- if they label something as possibly contaminated, we have been told that it will not go out. I think that also relates back to one of the issues we haven't

really talked about, if these inactivation techniques are resulting in "zero" risk, why would a company not feel comfortable labeling a unit as having been positive at one time, and stand on those claims legally?

DR. HOLLINGER: Dr. August, who had to leave early, also was not in favor of this particular reason. His comments were FDA actions should be determined by its assessment of product risk, and not by product shortage.

I would like to also bring this to a vote if there are no other burning issues here. I would like to know on this question -- I would like to read the question and get the vote.

Considering the recommendation made in question 1, should FDA modify its actions based on product shortages? All those in favor of this question, that is, should modify its actions based on product shortages, raise your hand. All those opposed? Abstaining? Three.

REV. LITTLE: Opposed.

DR. HOLLINGER: Could you read the vote please?

DR. SMALLWOOD: The vote on question 2, there were no yes votes, eight no votes, three abstentions, and the consumer representative voted no.

DR. HOLLINGER: There was a third question, but

Jay, if you have no objections, because of the committee, I don't think we ought to cut these things short here. I think we have sort of answered a little bit of what is in three anyway. Is it okay from your standpoint if we pass the third question here for right now, or is there a burning issue that you really want us to talk about? Many of us will still be here, but we need to know what your felling is.

DR. EPSTEIN: Well, I think we have to do what is reasonable. I can understand tabling the question. Let me suggest though that there is a dimension which has not yet come out for discussion, which is that there is the possibility to act against inventories under the control of the manufacturer, and not have product recalls for previously distributed product.

There have been times when the agency has made that distinction, and we seek to be advised whether any such distinction should be made. I think that is an important question. I think it is not implicit in what has already come before. So I leave it to your discretion whether to table it or not, but if it is tabled, we will probably come back to you with it some other day.

DR. HOLLINGER: So let's open it up then at least

for discussion. Are there some comments about this?

DR. SMALLWOOD: Excuse me. On question 2, Dr. Leitman left her vote. Her vote was no to question 2.

DR. HOLLINGER: So three then is if products affected by inadvertent contamination of a plasma pool by units reactive for HIV, HBV or HCV should not be distributed then: (a) should any distinction be made between in process and final products?

DR. PILIAVIN: I don't think we have any information from anything we have heard today that would help us answer this question.

DR. KASPER: Let me say that I don't understand why there has been a distinction made in the past. Suppose there is a pool of plasma, and some of it has been already processed into a lot of concentrate, and that is out there in the pharmacies, but some of it is still in the manufacturer and is being processed, I don't see the distinction.

If you are going to act one way against the stuff that is still in the manufacturer that's going to be recalled, but you are not going to recall the stuff out in the pharmacy, I just absolutely don't understand that. That doesn't make sense. I think we are being asked does that

make sense, and I think the answer is no, it does not make sense to treat it differently if it is already out there; if it has gone through the warehouse door, it's okay.

DR. NELSON: Actually, my understanding, and maybe Jay can correct me on this, the FDA has done this in the past. There is a trial of Hivig(?) HIV immune globulin which was found to be PCR positive for hepatitis C, which was in the middle of a trial in the U.S., ATPG0185. At the same time, there was a grant awarded by NICHD to start a trial in Haiti that was not along with AZT. They would not allow that trial to start, but they did not stop the trial that was in process.

Maybe Jay can correct me, but that's my understanding of what happened.

DR. HOLLINGER: Jay, is that right? Jay is nodding his head yes.

DR. NELSON: That's a situation where it was in the middle of a clinical trial.

DR. HOLLINGER: Go ahead, Jay. Do you have a response?

DR. EPSTEIN: Well, I think these questions 1, 2 and 3 are linked in the minds of regulators in ways that are perhaps not immediately apparent. If we think that the

reactive test or suspect contamination makes the product violative and a health hazard, then we recall it.

The problem comes if you have not decided that it is either violative or a health hazard. You may still have reasons not to want not more of it to be produced and distributed. In that kind of situation we have often asked the manufacturers voluntarily to cease distribution. We have not, however, engaged in recommended or required recalls absent a determination of a violation or a hazard.

What we are really asking is given the complexity of these risk determinations, should we always lump? Or is it ever reasonable in your mind to have the notion that perhaps in situations of remote risk or technical violation, that you may not want more produced, but maybe it doesn't reach the threshold for withdrawing products from the market with all the consequences that that entails.

I would say that there has been some ambiguity within the agency, what is the right course of action. That's why we are asking the question. I fully understand from the scientific point of view that there is no difference between the product in the shippable inventory and the product that left the door, but the issue from a regulatory point of view is, are you or are you not in a

recall mode when you request these quarantines?

DR. HOLLINGER: That is not quite what the question says. The question really says the products affected by contamination should not be distributed. It doesn't say that if they were already distributed, and then what are you going to do about the in house, in process. So your question is a little bit different.

DR. EPSTEIN: Okay, well I think what we have in mind is sometimes you learn about a contaminated pool and no product has been made. Sometimes you learn about a contaminated pool and you have already got intermediates. Sometimes you learn about a contaminated pool, and you have got intermediates, some of which are pending further manufacture, others of which have already been made into finished goods.

Does the committee feel that any distinction should be made about in process material versus final product?

DR. KASPER: I think Dr. Epstein said something very critical here. I don't know if I can get your words exactly, Jay, but he said if it's a technical violation, or he used another term. It was something not really thought to be significant.

Well, what I think we should do is to get rid of those recalls or those submersions. Do you have to be so technical? I think maybe the problem is that maybe the FDA is being picky about some things. If it isn't important, it isn't important.

MR. DUBIN: This kind of raises the flag for me about uniformity of interpretation and standards. If a product is violative, don't we want it out of the system at any level? Are we assessing how violative?

DR. MARTONE: I think he means when it is under active investigation, which is sort of gray area.

MR. DUBIN: In the period when it is under investigation. Is that true, Jay, what Bill is saying?

DR. EPSTEIN: Well, again you have a spectrum of situations. If the product is demonstrated contaminated, it is violative, because it is adulterated. If the product contains units that are reactive, and it is labeled as made from non-reactive units, it is also potentially misbranded; either misbranded with respect to its label, or misbranded with respect to its condition of licensure.

So one can almost always regard products as violative. Now that doesn't mean they automatically have to be recalled if they can be exempted. So we trigger recall

action based on a determination both of violation and health hazard.

The standard for a recall definition is that the agency would act against the product if the manufacturer did not do so voluntarily. That is the distinction between a voluntary withdrawal and a recall. If it is classified a recall it is a statement that the agency would act against the product, and that would be on the basis of it being found adulterated or misbranded.

So what we are really saying is if we think that a contamination or a potential contamination affects a pool, and we are permitted, based on the answer to your question 1B, to engage in a risk assessment, should we allow ourselves any distinctions to be made between in process materials and finished goods?

DR. HOLLINGER: You said something that I hadn't even thought about in that first question, which we have already voted on, but basically I was looking at something that you know something before you get a final product, it is already distributed. Theoretically as you said, you might discover something after the product, at least a portion of it, is already distributed.

We have already said that we believe that should

be immediately quarantined and so on. In some respects we didn't answer the question really about whether the product already out there on the market should be recalled or should there be a market withdrawal in there. For me, I just hadn't perceived that issue. That is an issue also that needs to be thought of.

REV. LITTLE: I just have to put out here I am really uncomfortable at this point discussing this, even though we have been graciously provided with food by an FDA angel. These topics are so important and so big, and at this point I know I need to leave soon, and a number of people have gone. I'm just wondering if some of this could be picked up at another meeting. I feel I can't give 100 percent at this point, and I have to put that out there.

DR. HOLLINGER: It's true, I agree with what you are saying, Rev. Little. I think they would like to hear though even of the ones here if there are any discussions with this, because that would be helpful too, even if the question has to be reformulated next time.

DR. VERTER: Maybe a clarification, but I think what I just heard you say makes me nervous. I thought when we voted on 1B that implicitly included recalling stuff that was out there.

DR. HOLLINGER: Yes, your point is right, and I think that is inherent in what I was thinking about too. It was just something I hadn't thought about until Jay mentioned the possibility that in this long process of preparing things, that something could already have been prepared and distributed, and they might not know about it until after that distribution had taken place.

Is that what the others sort of felt also inherent in that question, that it was not just quarantine, but also recall of the products already out there until something could be decided? Is that the feeling?

MR. DUBIN: It would kind of defy logic to do it any other way.

DR. HOLLINGER: I would think so.

DR. HOLMBERG: I guess I look at number three as being a moot issue. You know if we already decided 1B, I don't see where the differentiation is there. I think we have already answered it.

DR. HOLLINGER: Well, I guess we could vote on 3A, and just let me read it. We'll see what the committee feels like. Considering the recommendation made in question 1, should FDA modify its actions base -- excuse me, I'm reading 2.

If products affected by inadvertent contamination of a plasma pool by units reactive for HIV, HBV or HCV should not be distributed then: (a) should any distinction be made between the end process and final products?

All those in favor that -- should any distinction be made between in process and final products, yes or no? All that want to vote yes, raise your hand. One. All those opposed and say no. Abstaining? Two.

DR. PILIAVIN: I just don't think we have any data on which we could make this decision. I think the question is moot by the answer we gave to 1.

DR. HOLLINGER: Any response at all, Jay?

DR. LINDEN: I would basically agree with that.

DR. SMALLWOOD: Voting on number 3A --

DR. PILIAVIN: You can't do that; 1A we have already voted no on, and it says if so. So now that one is certainly moot.

DR. HOLLINGER: Could we have a reading then of the responses for 3A.

DR. SMALLWOOD: Responses to question 3A, one yes votes, eight no votes, two abstentions. The consumer representative would have voted no. In their absence Dr. August left his vote of yes, and Dr. Leitman left a no vote.

DR. HOLLINGER: Thank you. I think then the B part is clearly moot. If that is the case, then any other burning issues?

MS. PIERCE: I just have a question how the votes of absentees get noted, because they obviously weren't part of the last discussion, which may or may not have changed their minds. I'm just wondering, does that get recorded as the same as all the other nos or yeses?

DR. SMALLWOOD: I made a distinction in my response to the voting. I identified the votes of all those who were present, who were actually counted, and I entered into the record what would have been the voting of those who were absent.

DR. KASPER: If we are to continue a discussion of such issues as we discussed today at another meeting, I think we should ask the FDA to give us some idea of the magnitude of the problem. Mrs. Pierce said give us the nominator, give us the denominator, and we don't have it.

What are all of the issues that are going into it, I think Mr. Dubin also brought up. I would like to see the big picture next time, not just a little teeny window of it, and vote on that, if I could ask for that please.

DR. HOLLINGER: An excellent idea.

If there are no further questions, then I declare
this meeting closed.

[Whereupon the meeting was adjourned at 2:23 p.m.]