TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

61st MEETING

Pages 1 thru 187

Rockville, Maryland
December 11, 1998

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

at

AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

61st MEETING

Friday, December 11, 1998

8:00 a.m.

Double Tree Hotel
Ballrooms I and II
1750 Rockville Pike
Rockville, Maryland

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

PARTICIPANTS

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

MEMBERS

Norig Ellison, M.D.
Richard J. Kagan, M.D.
Marion A. Koerper, M.D.
Jeanne V. Linden, M.D.
Mark A. Mitchell, M.D.
Kenrad E. Nelson, M.D.
Kwaku Ohene-Frempong, M.D.
David F. Stroncek, M.D.
Joel I. Verter, Ph.D.

NON-VOTING CONSUMER REPRESENTATIVE

Katherine E. Knowles

NON-VOTING INDUSTRY REPRESENTATIVE

Donald H. Buchholz, M.D.

TEMPORARY VOTING MEMBER

Paul R. McCurdy, M.D.

CONSULTANT

Mary E. Chamberland, M.D.

GUESTS

William K. Hoots, M.D. (Topic V)
Craig Kessler, M.D. (Topic V)
Margaret Rick, M.D. (Topic V)

C O N T E N T S

P R O C E E D I N G S

Welcome and Opening Remarks

DR. SMALLWOOD: Good morning and welcome to the second day of the 61st meeting of the Blood Products Advisory Committee. I am Linda Smallwood, the Executive Secretary.

Yesterday, I read the conflict of interest statement covering both days of this meeting. This statement still covers today's proceedings. I would just like to announce that, for the presentation and the discussion on the ReFacto Product, we will have, as guests of the committee, Dr. William Hoots, Dr. Craig Kessler and Dr. Margaret Rick.

As I read yesterday, Dr. William Hoots has disclosed that he receives consulting fees from regulated firms including the Genetic Institute, Bayer and Baxter. If there are any other declarations to be made, I would ask that they be made at this time.

I will assume that there are none. Before we start into this morning's session, there are two public announcements that will be made. The first will be from Dr. Mary Chamberland from the Centers for Disease Control and the second one will be followed by Dr. Marybeth Jacobs. These are upcoming workshops and advisory committee meetings.

Dr. Chamberland.

DR. CHAMBERLAND: Thank you, Dr. Smallwood. For those of you who were here yesterday, this is an announcement about an upcoming workshop that is to be held January 14 and 15 in Atlanta. It is a workshop on the potential for transfusion transmission of tickborne agents being sponsored by CDC, the FDA, NIH and the Department of Defense.

The purpose of the workshop is to review current information about tickborne pathogens and their potential for transmission by blood transfusion. We are also looking to identify any research gaps or priorities that need to be addressed and to identify approaches to reduce the risk of transfusion-related infections from tickborne agents.

Further information on both the workshops can be obtained from accessing CDC's website, cdc.gov, under whats new. Also, many of the professional organizations such as AABB and ABC and ABRA have put announcements about the workshop in their weekly newsletter. Additional information can be obtained from me as well as to how to register for the workshop on January 14 and 15.

Thank you.

DR. JACOBS: We want to announce that FDA's Advisory Committee on Transmissible Spongeoform Encephalopathies is going to be meeting on Friday, December

18. The committee is being asked to make a recommendation to FDA concerning possible deferral of blood donors based on potential foodborne exposure to the BSE agent based on geographical criteria in order to reduce the theoretical risk of bloodborne transmission of new-variant CJD.

The committee is also being asked to consider their recommendations in light of potential shortages of blood or blood products. In order to incorporate the point of view of this committee and also the BSA committee, we will be having members and guests from this committee, including the chairman, and from the BSA Committee.

If you would like to be scheduled for the open public hearing, please call Dr. William Freas who is the Executive Secretary. He is at 301 827-1295.

Thank you.

DR. SMALLWOOD: Thank you. At this time, I will turn the proceedings of the meeting over to the chairman of the Blood Products Advisory Committee, Dr. Blaine Hollinger.

Dr. Hollinger.

DR. HOLLINGER: Thank you, Dr. Smallwood. We have two major topics today and the first one this morning that we will start off with is on inadvertent contamination of plasma pools for fractionation. Dr. Tabor is going to give us some insight into that. Some of the stuff that he is going to be presenting was presented last year on risk of

plasma products and then we are going to go into the specific arena of inadvertent contamination with some development of an algorithm at this point.

So, Dr. Tabor?

Inadvertent Contamination of Plasma Pools For Fractionation (HIV, HBsAG, HCV)

DR. TABOR: Good morning.

[Slide.]

This morning we are going to talk again about inadvertent contamination of plasma pools.

[Slide.]

In June, 1997, BPAC considered the issue of inadvertent contamination of the type where it is discovered, after pooling, that a unit entering the pool had, in fact, had a positive test for hepatitis V virus, hepatitis C virus or HIV. Then, in September, 1997, BPAC considered the type of inadvertent contamination in which it is discovered, after pooling, that despite the fact that all donors whose units entered the pool indicated in their questionnaires that they had no risk factors for any of the viral infections that, in fact, they had either forgotten to answer affirmatively to one of the questions or, for some other reason, were discovered to, in fact, be part of one of those risk groups.

There is a third area of inadvertent contamination

that we have not previously dealt with and that is those agents for which there are no tests and, in some cases, no inactivation procedures.

Today, we are going to revisit the issues discussed in June, 1997--that is, those types of inadvertent contamination in which a test has been discovered to be positive. I am going to present to you information about the epidemiology of transmission of these three viruses by plasma derivatives and information about the kinetics of inactivation of these viruses.

A large part of this is material that I presented in June, 1997 but there has been a substantial renewal of the membership of BPAC since that time and it has also been a year and a half since I have presented it. So I am going to present that with some newer information as background and then I will show you a draft flow chart or algorithm that represents the current FDA thinking about dealing with this type of inadvertent contamination.

We would like to get input from BPAC. We would like to have some discussion. I would like to emphasize that the algorithm is still in a draft form and has not been seen by very many people at FDA although we have worked very hard on it. So we would welcome your input.

[Slide.]

This flow chart shows an outline of the

manufacturing processes by which the most commonly used plasma derivatives are made from plasma. Antihemophilic factor and factor IX products come off very early in the process and then, down at the bottom, are immune globulin, plasma protein fraction and albumin which are made from plasma by a combination of Cohn method 6 and Oncley method 9 cold-ethanol fractionation, the method that is used for almost all immune-globulin products approved in the United States.

[Slide.]

Early on in the use of these products, a concept of high- and low-risk products was developed based on experience primarily with transmission of what we now know is hepatitis B virus. There were some products that frequently transmitted hepatitis and some that never did.

When hepatitis C virus and human immunodeficiency virus were recognized to be risks associated with certain plasma derivatives and blood transfusion, the concept of high- and low-risk products was extended to these viruses based on their epidemiologic similarities to hepatitis B and based on observations and recipients of the products.

The concept of high- and low-risk products has evolved over the years since inactivation procedures were introduced for products such as antihemophilic factor and factor IX. At present, we can divide the products into

three groups. In the first group are products that are subject to inactivation and for which we have a very long history of safe use. This includes albumin and PPF which have been used for forty to forty-five years with a very high degree of safety.

In the second category are products which are inactivated but for which we have a much shorter history of their use in the inactivated form. This includes antihemophilic factor, factor IX products, alpha 1 protease inhibitor and thrombin III.

Then, in a third category, are the immune globulins which, until recently, were not subjected to inactivation but, nonetheless, had a very good safety record particularly after the introduction of screened plasma. Today, all of the intravenous immune globulins are inactivated and the vast majority of the intramuscular immune-globulin products are subjected to inactivation as well.

[Slide.]

Albumin has been heat stabilized for most of the years that it has been used. Heat stabilization was developed during World War II to permit the use of albumin in desert areas and it was recognized very soon that this heat stabilization permitted heating at 60 degrees for ten hours to inactivate viruses.

[Slide.]

The safety of albumin was recognized quite early. For instance, in a study conducted by Paine and Janeway reported in 1952, they studied 237 albumin recipients who received albumin from 92 lots. They expected a very high rate of hepatitis which was defined by the presence of jaundice at that time because testing for the viruses was not available, and they expected to find jaundice in 39 percent of recipients because of the high prevalence of icteric plasma in the donor pool and because of the large number of units entering the pool.

In fact, of the 33 recipients who received only albumin, there was no jaundice observed at all and, even in 204 recipients who received albumin plus other products, only two had jaundice.

[Slide.]

Volunteer studies were conducted in the '40s and '50s that also showed that albumin and, particularly, heated albumin, was safe with regard to transmitting hepatitis B. Gellis, in 1948, reported studies in which an infectious plasma was put in an albumin preparation and heated at 60 degrees for ten hours.

When this was inoculated into ten volunteers, none of those volunteers receiving the heated material developed hepatitis whereas three of five receiving the unheated

material developed clinically recognizable hepatitis.

[Slide.]

Studies conducted by Murray also showed the safety of albumin. Rodrick Murray was the first and only director of the Division of Biologic Standards which was a direct forerunner of today's CBER. One of the investigators in this study--in fact, the principle investigator, Dr. John Oliphant--believed that beta propiolactone could be used to inactivate viruses in plasma products. When this method failed and three volunteers died of fulminant hepatitis, Dr. Oliphant committed suicide.

Nevertheless, the studies of Rodrick Murray and his group were very important in establishing our knowledge of the safety of heated albumin. They conducted studies using a pool of infectious plasma which later was shown to have an HBsAg titer of 1 to 100, and on the basis of infectivity studies in human volunteers, had an infectivity titer of $10^{7.5}$ infectious doses per ml--that is, each ml of the plasma pool contained over 10 million infectious doses of hepatitis B virus.

In the first study, shown in the top box here, they heated the plasma, itself, at 60 degrees for two or four hours and did not remove infectivity. Needless, to say, the unheated plasma also transmitted hepatitis to volunteers.

But when the plasma was made into albumin and the albumin was heated at 60 degrees for ten hours, either 3 ml or 100 ml inoculated into twenty volunteers was shown not to be infectious whereas the unheated albumin was still not infectious at 3 ml. But at 100 ml, the unheated albumin did transmit clinically recognizable hepatitis to two of ten volunteers.

This showed that the very process of making albumin removes a very large amount of the hepatitis B virus present and that heating at 60 degrees for ten hours removed the small amount remaining.

Murray also conducted a third group of studies of a product called--I think it was called stable protein plasma solution. It was a forerunner of today's TPF. Heating at 60 degrees for ten hours also removed the infectivity and prevented it transmitting hepatitis B to volunteers.

[Slide.]

Studies by Soulier in volunteers, studies which were part of an early study of a sort of crude hepatitis B vaccine showed that heating serum containing hepatitis B virus reduced the infectivity but, when high-titer material was heated at 60 degrees for ten hours, the material was still infectious.

This, again, underlies the fact that just

manufacturing albumin removes a lot of the infectivity but that heating infectious serum alone did not completely remove the infectivity. This was supported by chimpanzee studies published a few years thereafter by Shikata et al. which showed that heating infectious serum at 60 degrees for ten hours reduced the infectivity but did not totally remove it.

[Slide.]

PPF has also, like albumin, not transmitted hepatitis B. Albumin has never transmitted hepatitis B during its forty-five-year history. PPF has only transmitted hepatitis B on one occasion. At one point, PPF from one manufacturer transmitted hepatitis B to 5 percent of recipients.

The reason for that was that that manufacturer was heating the PPF in a bulk container rather than in the final containers. It was discovered that the bulk container had a sampling neck in which some of the infectious PPF was sequestered and was not being subjected to the full benefit of heating.

Albumin made from the same general group of donors as that PPF at the same time did not transmit hepatitis B and, although this is rather soft data, it underlines the fact that albumin is even safer than PPF based solely on the purification process of the albumin.

[Slide.]

Albumin has never transmitted hepatitis C virus. It never transmitted what we then called non-A, non-B hepatitis even in the years before screening tests for hepatitis C virus were available. In addition, studies have been conducted in chimpanzees. There are two reported studies. The first was from my laboratory showing that heating hepatitis-C-virus-containing material at 60 degrees for ten hours can inactivate up to 10^4 infectious doses per ml.

[Slide.]

Albumin has also never transmitted HIV. This was true even in the years when HIV had already entered the donor pool but before anti-HIV screening was available. The reason for this is that HIV is exquisitely sensitive to heating. If you hit HIV-containing material at 60 degrees for only ten minutes, it can inactivate 10^5 infectious doses per ml.

It is worth nothing that the maximum titer found in infectious plasma during HIV infection is 10^4 infectious doses per ml. In fact, it is usually never higher then 10^3 infectious doses per ml. Therefore, heating HIV for only one-sixtieth as long as we heat albumin can inactivate one log greater titer of HIV than is ever found in infectious plasma.

[Slide.]

As I said before, immune-globulin products have a very long history of safety particularly after the introduction of screened plasma. In volunteer studies which I will show you the results of in a few minutes, there was no transmission of hepatitis B by immune-globulin products and hepatitis B, with one single exception, has never been transmitted by either intramuscular or intravenous preparations of immune globulin in the twenty-five years that they have been made from screened plasma.

The one exception involved an outbreak which occurred on Milan, Italy with U.S.-manufactured immune globulin. It was an outbreak that I reported a number of years ago. In that outbreak, the immune globulin that was used had been made from plasma produced before 1973 and which had only been screened by counter-electrophoresis for hepatitis C surface antigen.

The final product, in fact, had a very low titer of anti-HBs as a result of the HBV present in that lot. Needless to say, this has not been a problem since the introduction of screening.

[Slide.]

Murray and colleagues, using the same infectious plasma that I described before with $10^{7.5}$ infectious doses per ml produced an immune globulin using the same method

that is used for almost every immune-globulin product licensed in the United States today; that is, Cohn method 6 and Oncley method 9.

This material did not transmit hepatitis B despite the fact that the starting material had more then 10 million infectious doses per ml. It did not transmit hepatitis B to any of ten inoculate recipients whereas the starting plasma in the control portion of this study transmitted clinically recognizable hepatitis to two out of five inoculated recipients. It is very likely that more than two were, in fact, infected with hepatitis B.

[Slide.]

We don't really know why immune globulin is safe but one of the theories is that the high titers of antibody found in the pool inactivate any virus that enters a pool from another unit. In support of this, there is a study published by Hoofnagle et al. which showed that in immune-globulin products made before the introduction of screening--they studied products from 1962 to 1971--they could find hepatitis-B surface antigen anti-HBs immune complexes in the lots in 78 percent of cases which they could dissociate and study.

In the period after the introduction of screening, they could find no immune complexes in any of the lots and no hepatitis B surface antigen.

Other studies have shown that lots of immune globulin made before the introduction of screening have very low titers of anti-HBs presumably because of HBsAg that entered because there was no screening whereas lots made afterwards, in the 1970s, have higher titers of anti-HBs.

[Slide.]

So immune globulin in the intramuscular form has not transmitted hepatitis C. Many of the lots, however, have had HCV-RNA detectable--that is, in those lots made before 1994. There are several follow-up studies of individuals with immunodeficiencies who have received intramuscular preparations of immune globulin weekly for extended periods of time. Those follow-up studies have shown no transmission of hepatitis C virus in any those patients.

In addition, studies of the immune globulins made from the same general donor base as the intravenous material that that transmitted hepatitis C virus in the so-called Gammagard outbreak, the intramuscular preparations did not transmit hepatitis C virus.

Today, many of the manufacturers of intramuscular preparations of immune globulin subject the material to inactivation procedures although, in fact, that is not really scientifically necessary. All of the products are tested for HCV-RNA by PCR and are all negative.

The situation with the intravenous immune globulin is a little bit different. In 1993, there was an outbreak associated with one manufacturer's product, an outbreak of hepatitis C virus infection. None of the other manufacturers' products transmitted hepatitis C virus although several products made in Europe by different methods also had transmitted hepatitis C virus.

Despite this, there has been no transmission since 1994 by intravenous preparations and that is because viral inactivation procedures have been instituted by all manufacturers since 1995. The final product has been screened by HCV-PCR since 1994 by FDA and later by the manufacturers.

[Slide.]

In the Gammagard outbreak, as I said, HCV was transmitted by the intravenous immune globulin. In one study of a small group of patients, it was found that 11 percent of recipients were infected. Whether the recipients were infected was dose-dependent and was related to how much HCV they received with the globulin.

In a very elegant group of studies, Dr. Mei-Ying Yu from CBER along with John Finlayson and other FDA employees showed that the reason that Gammagard had transmitted hepatitis C virus was a direct result of introducing more sensitive tests for anti-HCV. And by

introducing the multiantigen screening tests, the more sensitive tests, more of the antibody to hepatitis C virus was removed from the pool and, presumably, this, now, was not available to inactivate the virus that was present in the pool.

As I said, the solution to this problem has been the stabilization of the material to permit heating and all lots made today are both screened for HCV-RNA and subjected to inactivation. There has been no further transmission since 1994.

[Slide.]

Immune-globulin products do not transmit HIV. In the period of time when HIV was already present in the donor population in the early 1980s but before we had anti-HIV screening available, HIV was never transmitted by either the intramuscular forms of immune globulin, intravenous immune globulin or even hepatitis B immune globulin which, in fact, in those days, was preferentially made, at least by some manufacturers from what we would not consider high-risk plasma; that is, homosexual donors.

But none of this material transmitted HIV to recipients. We now know, based on experimental studies, that the fractionation process, itself, when followed all the way down to the fraction II that immune globulin is made from can remove up to 10^{15} infectious doses per ml and, as I

said before, infected plasma never has more than 10^4 infectious doses per ml.

In addition, it is not been possible to culture HIV from lots of immune globulin even those lots that have detectable titers of anti-HIV in them from the era before screening was available.

[Slide.]

Antihemophilic factor and factor IX complex used to be considered high-risk products for the transmission of viruses. But in the 1980s, methods were developed to stabilize these products to permit inactivation of viruses by heating and other processes. As a result, there has been no transmission of hepatitis B virus by any U.S.-licensed AHF or factor IX product since the introduction of screening and inactivation when the inactivation has been done properly. This means, essentially, none since 1987.

[Slide.]

The inactivated AHF has been shown not to transmit hepatitis C virus. This is based on studies in hemophiliacs who have been treated only in the era since the introduction of inactivated products. Lots made after the introduction of testing and inactivation are also shown to be negative for HCV-RNA.

In a surveillance study conducted over a three-year period by the Centers for Disease Control and the

National Hemophilia Foundation under a contract paid for by the Food and Drug Administration, a survey of 71 hemophilia treatment centers showed no transmission of hepatitis C virus in any of those centers during the three years of the study.

This represented half of the hemophilia treatment centers in the United States and a quarter of the hemophiliacs in the United States.

[Slide.]

The very process of screening plasma for anti-HCV reduces the viral burden to such an extent that no HCV-RNA can be detected in antihemophilic factor even when it is made from plasma that happens to contain HCV-RNA-positive material. This was shown in two studies, one by Dr. Yu and others at FDA and another one from the NIBS&C in England.

[Slide.]

AHF has also been shown not to transmit HIV when it is made from screened inactivated plasma and when the inactivation is done properly. Again, in the same CDC surveillance study conducted with the National Hemophilia Foundation, it was shown that there were no seroconversions to HIV during the three years of the study.

[Slide.]

AHF and factor XI manufactured in the United States today is all subjected to more than one validated

process for virus removal. Every manufacturer of these products in the United States today uses more than one validated process for virus removal.

These processes include heating in a liquid form at 60 degrees for ten hours, heating in a lyophilized form at 80 degrees for 72 hours, treating with a solvent or treating with a detergent.

[Slide.]

In fact, some of the manufacturing processes for these products--that is, the processes by which the products are purified during manufacturing--actually have been shown to remove viruses. Most of the manufacturing processes taken as a whole--that is, the purification plus any inactivation procedures--have been shown to remove or inactivate greater than 10^9 infectious doses per ml of HIV.

In addition, the lyophilization of these products has also been shown to remove some HIV infectivity between 10^1 and 10^4 infectious doses per ml in addition to that provided by the manufacturing processes.

[Slide.]

In summary, there has been no transmission of HIV, HBV or HCV since the introduction of screening tests and inactivation procedures in the United States when these procedures have been done properly. This essentially means that there has been no transmission of these viruses by

plasma derivatives in the United States since 1987 except for IGIV and no transmission by IGIV since 1994.

[Slide.]

As I said, there are a number of different types of inadvertent contamination. It is such a broad area and it is such a difficult topic to grapple with, I felt that it is necessary to break it up into different categories. And so, as I said, today we are going to deal with those situations in which a test is positive.

Some of the different types of inadvertent contamination are shown on here. The ones shown in yellow are the ones we are talking about today. These could involve situations where a test is performed incorrectly or recorded incorrectly and that is discovered after the fact, a situation where a donor sample happens to be retested later for some reason or tested at another site.

It could be a situation in which the plasma is shipped somewhere where pool testing is done in a slightly different way or using a different method and a positive test is detected, or it could be a situation where a new assay becomes available and is applied to the plasma.

Finally, I have decided to include here situations in which red cells are transfused into a patient and transmit infection but the recovered plasma has been shipped somewhere else and pooled.

[Slide.]

So what we are talking about here is three viruses. Each of these viruses is a virus for which we have sensitive assays and for which we have documented valid inactivation methods.

[Slide.]

There are a number of issues related to inadvertent contamination that I think you should keep in mind. One is, this type of inadvertent contamination is a result of our technological advances. Before we could test for these viruses, we didn't have this kind of inadvertent contamination. We just didn't know about the viruses being present.

It is also worth keeping in mind that the issue of inadvertent contamination may be reinvented every time a new, more sensitive, test comes along. I certainly hope that will happen because we hope that we will have increasingly sensitive assays. It is also possible that we may have to revisit this issue if we ever decrease the pool size because a lot of the kinetics of inactivation are based on kind of these large pools that we have today.

The impact of viral inactivation and the concept of risk assessment also have to be kept in mind.

[Slide.]

It is possible that better techniques may be

ahead. As I said yesterday, certainly all of the source plasma and a lot of the recovered plasma used in the United States is now tested by nucleic-acid amplification tests under IND. That will certainly change the dynamics of this discussion and it is hoped that eventually we will be able to have cost-effective nucleic-acid testing that can be applied to individual units.

That, too, may change the picture and we may even effectively eliminate inadvertent contamination as an issue.

[Slide.]

I am just going to very briefly summarize the recommendations of BPAC in June of 1997 and September of 1997. In June of 1997, BPAC recommended that, when notified of inadvertent contamination of a fractionation pool with units reactive for HBV, HCV or HIV, FDA should immediately and uniformly quarantine or recall all products as a first step and then determine regulatory action based on an assessment of product risk, meaning based on the impact of virus removal or inactivation.

[Slide.]

BPAC also recommended that, in such circumstances, FDA should not modify its actions on the basis of product shortages. In other words, the amount of product available for patient use should not affect decisions related to the safety of those products in protecting patients from

infection.

[Slide.]

BPAC also recommended that FDA should not make any distinction between in-process and final products. I think what the committee was telling us was that if we think it is a serious situation to quarantine products that are still in the manufacturing plant, then products that are ready to be shipped or have already been shipped should also be quarantined until a decision is made about their safety.

[Slide.]

In September, 1997, BPAC recommended that, in cases of inadvertent contamination of a pool consisting of units negative for HIV, HBV and HCV in which the pool contains a unit from a donor with a subsequently discovered risk factor, FDA should determine the regulatory action based on an assessment of product risk.

[Slide.]

That assessment of product risk should consider the maximum level of contamination possible from that unit and should consider the capability of virus removal and inactivation.

[Slide.]

The committee recommended that quarantine of distributed product cannot be dispensed with even if there has been a record of GMP compliance. What the committee was

telling us was just because a company has a good record of GMP compliance in recent years is not a reason not to quarantine the product until an assessment can be made.

Essentially, it means that the GMP adequacy has to be based on an analysis of the lots in question and probably based on an FDA inspection. The committee also said they believed that negative nucleic-acid test might obviate the need to destroy the product.

One of the reasons I wanted to show you these recommendations was to remind you of them but, also, I would like to sort of transpose the consideration of GMP issues that occurred in the September discussions to the issue of inadvertent contamination involving tests.

[Slide.]

We are talking about positive tests. What we mean by positive tests here are either a repeatedly reactive screening test with a positive supplemental test or a situation in which the supplemental test was not done, in which case one should act as if it were positive.

We are talking about tests for HBsAg, anti-HCV, anti-HIV 1 and 2 and HIV-1 p24 antigen. We are also talking about some investigational tests. We are talking about nucleic-acid tests on pools or minipools, since this is being done today. And we are also talking about situations in which a serologic test for some reason is done on a pool.

It may seem difficult to conceive of how you could have a pool made up of thousands or tens of thousands of plasma units, all of which were negative for an antibody test, and then have the testing on the pool or minipool, would that same antibody test be positive.

Nevertheless, due either to human error or to, perhaps, some obscure immunologic phenomenon, this is, in fact, possible and has, indeed, happened. So that is another type of inadvertent contamination.

[Slide.]

I am not going to show you a draft algorithm. This merely represents our current thinking on this aspect of inadvertent contamination and I would like to get the committee's input on this. As I said before, although we have worked very hard to prepare this, it still represents the view of a small number of people at FDA so this is not something that we have distributed publicly.

But, after we get additional input including input from the committee, we may make this available for public comment.

On this first slide, we are talking about an inadvertent contamination on a unit of recovered plasma from a whole-blood donor. If a positive test is discovered, here is what we would consider ought to be done. Addressing the issue of a situation in which a donor's red cells

transmitted infection, one would go down this arm of the flow chart.

If the red cells had already been transfused and transmitted infection, the recipient would be notified, the donor deferred and, in cases of HCV and HIV, look-back would be undertaken. The consignee of the recovered plasma would be notified and then the second figure would take effect. We will get to that in a minute.

If the unit has not yet been transfused, and, for some reason, a positive test were discovered, the unit would be quarantined and the consignee of the recovered plasma would be notified to quarantine the plasma.

The original sample would be retested using the same manufacturer's assay system and if, in fact, it turned out to be a false positive, the unit could be released. If it were repeatable and confirmed, or if there were an indeterminate supplemental test, the unit would be destroyed and the donor deferred and, in some cases, look-back would occur.

[Slide.]

When a positive test is discovered on a plasma unit or pool, this diagram shows the actions that would be taken. It would be easier for you to grasp it if you look at it in sections. The top section, really, essentially, shows the quarantine process. If the unit has not yet been

pooled, it should be quarantined. If it has been pooled but not yet processed, the pool should be quarantined.

If it has been processed but not yet shipped, the product should be quarantined. If it has been shipped, the consignees should be notified to quarantine the products.

Then an effort should be made to retest the original unit or an aliquot, or if that is not available, to test a later sample from the donor. In retesting the original sample, using the same manufacturer's test, of course if it is negative, the unit can be released because that means the original test was a false positive of some kind.

But if it is a positive or if there is an indeterminate supplemental, it should be considered that the donor was infected. Similarly, if a later sample from the same donor is tested and is positive, or if no later sample is available, it should be considered that the donor was infected.

At that point, we would like to propose that the issue of GMPs would kick in. If an FDA inspection shows that GMPs were adequately followed for these lots in question, and the pool in question, with regard to virus removal and inactivation, then the unit or the pool with the product could be released.

But if the GMPs are not adequate, the unit, pool

or products would be destroyed, the donor deferred. Look-back would occur and recipient notification would be done in some situations.

As I said, we would welcome any suggestions that the committee can offer us. Thank you.

DR. HOLLINGER: Thank you, Ed. Very good summary.

Open Public Hearing

There are some individuals who have asked to speak at the open public hearing which is open now. The first is Dr. Jean-Jacques Morgenthaler from the ZLD Laboratory Blood Transfusion Service in Bern, Switzerland.

Dr. Morgenthaler?

DR. MORGENTHALER: Good morning.

[Slide.]

A case of inadvertent contamination which involved ZLD was described to this committee during its meeting of 19 and 20 June, 1997. The corresponding writeup has been resubmitted for reference but the case will not be discussed again.

Today, we will try to deal with the issue of inadvertent contamination. A confirmed seroconversion of a donor is not identical with inadvertent contamination since it is not yet proven that the infectious donation has been incorporated into a fractionation pool. One of the two following conditions has to be met in order for the incident

to qualify as inadvertent contamination.

Either the recipient of the corresponding component, erythrocytes or platelets, develops a post-infusion infection which is, then, a real window donation or a unit that tested positive was erroneously released.

[Slide.]

Window donations may occur in any plasma pool. However, notification of the plasma fractionate is haphazard rather than systematic. In many cases, these donations are not identified for one of the following reasons. First, cells were not transfused because they were past their shelf life. Second, the recipients of the cellular products died which, unfortunately, happens quite often because of the severity of the underlying disease.

Accident victims, for instance, may receive up to 100 erythrocyte concentrates and the chance of survival is, nevertheless, very poor. Or, third, there are no other components to transfuse; for instance, when source was obtained.

In these cases, window donations would not be recognized as such. The safety of stable plasma products is, however, not jeopardized because it rests on validated virus inactivation steps. The possibility of incorporating a window donation into a fractional pool is the very reason why virus inactivation is an integral part of the

manufacturing process.

[Slide.]

A general recall in case of an inadvertent contamination has no scientific rationale. Such a recall would be tantamount to questioning the safety of stable plasma products in general. Additionally, because of the haphazard nature of notification of such incidents, recalls would give a false sense of safety.

ZLD is in favor of conducting a risk assessment together with the competent authorities in cases of inadvertent contamination. This is in line with CGMP rules. This assessment will bring to light any additional risks this particular batch might have.

This procedure, by the way, is also being advocated by the European Agency for Derivation of Medicinal Products. This assessment has to be carried out before initiation of a recall. If the assessment is done after recall, the products will be destroyed independently of the outcome of the assessments because no manufacturer will want to put products which were temporarily out of its control back on the market.

Thank you for your attention.

DR. HOLLINGER: The second person who has asked to speak is Mr. David Cavanaugh from the Committee of Ten Thousand.

MR. CAVANAUGH: Thank you. The discussion that we had this morning in terms of viral contamination refers to parts of processes that have been put in place for some time. However, recent events have made us focus on other forms of product contamination that we are still following up in several hospitals around the country from some time ago which brings to mind the whole issue of GMP.

I would like to speak to that for a moment. The question of compliance with GMP is of tantamount concern to our organization. The recent release of a GAO report entitled "Plasma Products Risks are Low if Good Manufacturing Practices are Followed" painted a very disturbing picture of the GMP landscape.

It is troubling. Two of the four fractionators are currently under court-ordered consent decrees. In reviewing those decrees, we are struck by the depth of the problems being addressed by the court. We were also concerned about the degree of ongoing oversight being applied by the court in these situations.

Consent decrees can be an effective regulatory tool if the court of record continues to follow compliance closely and is willing to use the tools at its disposal when compliance with that decree does not occur in a timely fashion. Consent decrees do not preclude or replace FDA usage of its power over the licensing of the manufacturers

of plasma-derivative products.

When compliance continues to be a problem with a given regulated entity, FDA must exercise its power to gain compliance with the regulations that are of critical importance to the health and well-being of the end users of plasma-derivative products.

The pressure to improve GMP compliance has resulted in numerous discoveries of threats to product safety both before and after product release. This pressure has been described as a ramp-up or a multiyear process. Do we know how hard FDA is pressing each year? While work with individual companies on regulated products includes the requirement for substantial protections of proprietary data, this committee and the interested public have a right to be kept informed as to the progress of such a lengthy process.

As it is, even members of the committee are not given all the facts. COTT is concerned about the apparent lack of a long-term public plan for this upgrade process. FDA should develop and publicize yearly target standards. This set of goals should be accompanied by release of FDA public policies on coping with any associated risks of shortage and compromises in quality that may be result of this long-needed campaign of pressure for compliance with GMPs.

BPAC should urge CBER to develop such planning

tools more explicitly, to do so in public in much the same manner as FDAMA policy development is occurring and to disseminate to industry, consumers, Congress and the media, the resulting staged quality-improvement goals in safety and supply-monitoring procedures.

If members of the Blood Products Advisory Committee are to effectively advise the FDA regarding issues of GMP compliance, they must be better informed and prepared by access to relevant information such as the CFR, all relevant GAO reports regarding plasma-products FDA and ongoing updates regarding the current GMP landscape as discussed here.

We were surprised to learn that a BPAC member requesting a copy of the current consent decree between FDA and the Alpha Therapeutics Corporation was informed that he would have to file a Freedom of Information Act request. Why is it necessary for a BPAC member to have to undertake a FOIA request in order to view documentation so relevant to the work of this committee?

DR. HOLLINGER: Thank you.

Is there anyone else, in terms of the public hearing today, that wants to speak to this issue on inadvertent contamination?

Yes?

MR. NAGLER: Rick Nagler from the Hemophilia

Federation of America and the Hemophilia Association of the Capitol Area. The process looks good except for that last one on the right, the fourth one. I am worried about the word "quarantine." If a pint of blood has to be labeled "quarantined," how is it going to be quarantined in the blood bank? Should it not be sent back to its source?

Should it be labeled with a big, red label, "Quarantined?" Based on the consent decrees and the violations that we have had in the past, it worries me that a pint of blood that is quarantined would remain in the blood bank without going someplace else and the risk of somebody wanting to use that pint of blood in an emergency situation.

DR. HOLLINGER: Thank you.

Anybody else? If not, then, that will close the open public hearing and we will now open it up for committee discussion on these issues.

Committee Discussion and Recommendations

DR. HOLLINGER: Ed, can you tell us, just to start, initially, just a little bit about how much of a problem this is, give us some feeling over the last several years about how often you have been contacted about a positive unit being erroneously identified later or identified by another--or about the donor history? Can you separate them out and give us some thoughts about--

DR. TABOR: I can't give you actual numbers. It is certainly something that we have had to deal with. There were a number of complicated ones when pooled testing was first introduced because we were having American plasma being shipped overseas where pooled testing first started and we were finding out about situations in a new framework where you had a positive pool with a new, more sensitive test, that is nucleic-acid amplification test, PCR or what have you, and where we had to decide what to do with the pool.

But the issue of inadvertent contamination is one that has been with us for many years. If I had to guess how many times a year, I would say it is certainly less than a dozen times a year that it actually comes to our attention. And I don't know how often, really. I am just pulling that number out of the air.

Does anyone else from FDA have any thoughts on how often we deal with this?

DR. EPSTEIN: Very often.

DR. TABOR: Okay; I stand corrected, then.

DR. EPSTEIN: For HIV, HBV, HCV, it has become rare. I think that what Dr. Tabor stated is correct, that we had a series of such incidents when pools were being tested for HIV antibody and then when minipools were being tested by PCR. We have had, I would say, outside of that,

perhaps only once or twice a year, an incident in which either we had a reported donor seroconversion from the cellular products or an inadvertent release of units with markers.

There was a period of time when we were dealing with what we would call compliance violations where units were being released based on so-called testing into compliance where, for technical reasons, we were regarding these as marker-positive although the actual status of the donor was arguable. But those are behind us. That was a cohort several years ago.

So I think, currently, these incidents are sporadic, no more than one or two a year.

DR. TABOR: But to put it in context, one of the reasons why we began addressing the issue of inadvertent contamination is that FDA's policy on this has been different at different points in time during the past decade or two. There was some interest, particularly by one of the associate commissioners, last year and the year before, to try to tighten it up and develop a consistent policy.

DR. HOLLINGER: And the algorithm is mostly to attempt to formalize more what you would do under the circumstances that it occurred; is that correct?

DR. TABOR: Correct. After we get your input on this algorithm, we can then modify it to develop algorithms

for the other types of inadvertent contamination.

DR. HOLLINGER: Questions?

DR. VERTER: I wonder if you could just let me know your thinking on any--in the first algorithm, you have the word "positive test discovered," in quotes, which suggests initially that you don't believe it is positive. Then, on the right-hand arm, you say if the second test, even if the same test is negative, the assumption is that the original test was false.

DR. TABOR: I think that is an ambiguous use of the word "positive." When I had in quotation marks, what that meant was that you have a report of a positive test, possibly an unconfirmed positive, and the second thing you are referring to is really a retesting to verify whether or not it was positive.

DR. VERTER: What if there was a positive test? But if, somehow, the unit slipped through. There was a positive test that someone overlooked so there was a documentation that the test--it shouldn't be in quotes--that it was positive, and then the second test is negative. What would you do under those circumstances?

DR. TABOR: I think if you had a confirmed positive--say, if you had a confirmed positive HBsAg that was incorrectly--that was overlooked, then it should be treated as a positive without the retesting. That is

something we can modify.

DR. STRONCEK: I have a couple of questions. One is if the plasma hasn't yet been pooled and there was a question about it, and it was found out to be positive, why would you quarantine it? Why would you let it back in the pool? Why wouldn't you throw it out? I think it is one issue when it is pooled and it is a separate issue when it is not pooled.

DR. TABOR: That is a good suggestion. There would be no reason not to throw it out if it is a single unit.

DR. STRONCEK: The algorithm, though, I agree with it in principle. It is very nice work. The only other thing that may need clarification down the line is if you have a test of record that is confirmed positive, why would you go back and repeat the testing and, if you decide that the test of record--somehow, if there is some confusion about the original testing, are you going to let the manufacturer, themselves, repeat the testing and then say it is negative? Then you would have a positive test and a negative test and they would decide, or are you going to set up guidelines or is that going to be kind of a paper audit and, if you agree with the manufacturer, you wouldn't come out and look at their CGMP records?

DR. TABOR: I can't necessarily answer that but

what I can tell you is what happens in practice, when there is a complicated situation such as the ones that Dr. Epstein was describing, usually we do the testing as well. But, of course, the manufacturer also retests. If the tests are being done, they should all agree.

But that is something we can consider. What about the issue of GMP evaluation? Are you satisfied with that as a way of dealing with it?

DR. KOERPER: That, actually, was my question. I am assuming what you mean is that somebody reviews the records and makes sure that, if PCR testing was done, that the pool tested negative for all the markers.

DR. TABOR: That FDA inspectors would visit the facility and examine the records for the production of lots resulting from that pool and make sure that everything was done appropriately, appropriate temperatures were reached, the right time, and appropriate records were kept and so forth.

I think the importance of that is, as some of the public comments pointed out, there have been some problems that some manufacturers have had in the past, and so it certainly seems worth looking at that before making a decision.

DR. CHAMBERLAND: I just wanted to clarify--as I understand it, the current proposed algorithm excludes

issues, situations, where post-donation information becomes available about possible risk factors or risk behaviors for the donor or it is learned that the donor has subsequently seroconverted. Am I correct?

DR. TABOR: This algorithm does not address that but I think the next step is that if the committee and other people at FDA are satisfied with this algorithm for this type of a contamination, it may be that a very minor modification can make this useful for post-donation information.

If you have thoughts about that, even though we were not planning to address it today, I would be glad to hear them now or at any time.

DR. HOLLINGER: Just on this same question, though. If you had the lot and someone found out that they had a history that would have excluded them, made them not suitable as a donor, rather than throw out the whole lot or think about this, you might go back and test the donor with more sensitive assays that we at least have available rather than throw out the--you would use some judgment in that.

DR. TABOR: Just speaking almost off the cuff about this, it is my opinion that the main change that would occur in this algorithm for dealing with donor histories would be to involve the use of as many tests as are available in the scientific community for any viruses of

concern.

In other words, in a situation where you had a donor history that you should have excluded but didn't, you would certainly want to test the donor with every available test before making a decision.

DR. HOLLINGER: I would agree with that but I can certainly see how that creates a little bit of a problem for you as well as the manufacturer because this would have been a unit just on the basis of a history alone that might have excluded that person for not just viruses and other things that you could test for versus ones that are not known.

But, nevertheless, I think it is a reasonable approach.

DR. NELSON: I can see where there could be some real dilemmas here. In particular, as you know, one of the problems with the PCR test, although it is extremely sensitive, it is also susceptible to contamination and, therefore, false positives. I guess we are not routinely doing that now but I guess we will be, and I just wonder how big a problem is that in, let's say, lots or pools or whatever that are sent to Europe or other places where PCR testing is done.

Do you often find that what you are dealing with is a false positive PCR or are we doing to have more problems, not with real inadvertent contamination but

problems in deciding what is going on because, obviously, it can be a false positive but it is also more sensitive so it could be a true positive. The dilemma could be very real.

DR. TABOR: When pool testing, and minipool testing, began, there were a number of situations like those that were brought to FDA's attention. What is happening now in the United States is that minipools are being tested and so positive units are being identified before the actual pooling occurs.

But the inadvertent contamination situation could still develop where, for some reason, a pool was tested later or there was human error involved.

DR. NELSON: I remember that, in Mike Busch's--in the study they did to look at window-period donations, they used this technique--I think it was 50 or 100 in the pool. They found pretty much the same rate that we did by following the recipients. But, as I recall, they had several that they ended up concluding that the initial positive PCR was actually a false positive.

So I can see that in practice this may be kind of a difficult problem.

DR. HOLLINGER: Of course, if the original sample has been contaminated, it will always be positive regardless. Unfortunately, it will always be positive regardless of what happened, not just if the test is

contaminated but the sample, itself, and you just keep testing a contaminated sample. It always creates another dilemma.

DR. BUCHHOLZ: Perhaps I have missed something along the way but, a few moments ago, the comments with respect to this algorithm does not address seroconversion or later identification of being in a risk group.

I am a little confused as to what would need to be different here? I mean, what was stated was we were going to do a whole lot of additional tests in someone who seroconverts or is subsequently identified as a high-risk-factor donor.

Isn't the case in the handout the worst case; that is, a positive that turns out to be a true positive that, in fact, if GMP is adequate, the product or pool is released? I am confused as to why less definitive evidence of positivity would require a different schema. Perhaps I missed something.

DR. TABOR: No; I think that is a very good point. What you are essentially saying is why can't we use this same algorithm for situations in which a positive history is found because a positive history is a screen to try to eliminate people with lower titers of virus--

DR. BUCHHOLZ: This represents, I believe, the worst case, if you have a positive donor and you are going

to say, after you define that it is positive, if the GMP was adequate. So why could that not suffice for any situation?

DR. EPSTEIN: Sometimes it is in reverse in that the expected titer of viral contamination, should seroconversion be real, would be higher pre-seroconversion than post-seroconversion. So the titer in a positive unit, for example in HIV, is, in fact, lower. Similarly, in hepatitis C, the titer of a window-period unit is much, much higher.

So I think we can't just generalize, that there are some differences to take into consideration. But I think that the concept that Dr. Tabor was putting forward is that if you have a potential inadvertent contamination, you want to be able to rule it in or rule it out. The purpose of the additional testing is to figure out what is true in order to decide what is necessary to do with the product.

DR. BUCHHOLZ: If that is the case, I assume, then, that there are established guidelines--not guidelines for us but guidelines that FDA would have or the manufacturers would be provided--that says less than so many infectious-disease transmissible doses per ml is acceptable and, if that is the case, should that information be on here.

Your point is a valid one, but it seems to me that, without some sort of predefined--and I don't know even

if that level of information is available. We were impressed by the efficacy of the various inactivation processes and the manufacturing process that cleans things up. So, given that framework from what was presented earlier this morning, I would wonder if there is some definitive level at which you would say, "Ah; this is a problem," as opposed to, "This is not a problem."

The same question would go to a unit that is confirmed positive in the schema unless this was just not mentioned, would appear to go through the process without benefit of the testing that a seroconverting donor would undergo.

So, perhaps, if there could be some clarification as to that aspect of it, it would be helpful.

DR. TABOR: I think, certainly, for positive units for these three viruses, I feel completely comfortable with the inactivation processes, the capability of the manufacturing and the inactivation processes to remove and inactivate the viruses at the maximum titer that could be present.

What you are suggesting about setting a cutoff for what we would permit in a incubation phase sample in an inadvertent contamination that involved someone from a risk group is something we would have to consider. I am not sure how much more data there is on the acceptable levels for the

inactivation procedures to deal than what I have already presented, but it may be that what you suggest is something we should incorporate.

DR. BUCHHOLZ: I would just like to clarify the record. I think it was Dr. Epstein that was suggesting that and I am trying to find out if, in fact, that information is available but, in fact, it would seem to me that the likelihood of that situation happening is probably low, but a real one and to be as prepared as possible to try and identify all the ramifications of this type of schema, which I applaud. I think this is very helpful.

But that would seem to be an area that, perhaps, should be better defined.

DR. HOLLINGER: Also, along that same line, Don, I think the issue is somewhat different for the recipient versus the plasma, the derivative or the components that might be applied. If you accept, Ed, what you said, and I tend to agree with you that the products are pretty well inactivated.

If the procedures are done properly, and so on, at least the ones we know about, then the safety, I think--you could say you don't even really have to do any of this, basically, if you want to establish that there haven't been any problems at the manufacturer's end in terms of GMP and so on.

The recipient is a little bit different, obviously, in that case because that person might receive product which is infectious and, therefore, needs to be, as you said, notified or any of them that have received platelets or fresh-frozen plasma, of something of that nature, to be notified and certainly with a look-back procedure, too.

So there are some differences. It is a lot simpler, I think, right now, I would feel, with the derivatives.

DR. EPSTEIN: I would like to come back to the point made by Dr. Buchholz. I agree that the scientific concept underlying the approach to inadvertent contamination or, indeed, the approach to product safety in general is to keep the contaminating burden--in this case, the viral burden--below a level at which we have high assurance that the manufacturing process could clear contamination at that level.

That is the reason that we have a concept of combining screening with process clearance and deliberate inactivation. The problem is gaps in our knowledge. I think that Dr. Tabor very nicely illustrated today how that concept worked for hepatitis B and albumin, that there was, in fact, a limit above which even the ten-hour heating could not render a product virally safe for hepatitis B.

So we do agree that, in the end, what we are trying to do here is keep the burden in the fractionation pool below a level at which we believe that the processes render the product to be safe.

What is happening is that we are inching toward that endpoint. What we are doing is we are saying, "Well, can't we look at prior experience with positive units?" What happens today is that, for example, say, a foreign regulatory authority performs an antibody test on end products or on samples of a pool and, say, finds HIV antibody--and this did occur a couple of years ago--it implies that a positive unit got pooled.

Now, one could take two approaches. One could say, "Well, let's find the unit and see if it was a true positive." What happened in this instance is that we had tens of thousands of units tested and never found the positive. But we couldn't test them all because we couldn't locate them all and the donors all couldn't be located.

So then what do you do? You say, "Was GMP followed?" We sent inspectors in and we checked every batch record and we reviewed all the inactivation validations, and we didn't find a deviation. But we didn't stop there. We did hundreds of tests on pools and end products, but antibody tests and PCR tests to ask the question was there any evidence of a virus residual in the products.

Now, mind you, finding positive PCR wouldn't have proved that there was any live virus left because you could have nucleic acid and dead virus. But, nonetheless, as a level of reassurance, we did all that testing and found no PCR positives and decided that products were safe to release.

What is being asked here is can't we stop at the GMP level based on what we know about positive units just for HIV, HBV, HCV and taking into account the available epidemiological data spanning, in some cases, many decades and, in other cases, a shorter period of time.

That is really the question that we are putting to you. In the case where the information is uncertain, we are saying, well, we just to have all our tools. But, in the case where we know what we are dealing with, we are saying, doesn't GMP settle the matter.

If we found that there were breaches of GMP, I think we would immediately be back into the realm of trying to figure out what the risk was based on risk assessment. But what we are saying here is that we know these--we have a lot of data on clearance, a lot of data on inactivation, a lot of data on the titer in a positive unit and the lot of history in dealing with product safety, even some history that goes back years where there was experimental contamination of the product, and also experiments of

nature.

So what we are trying to say is can't we reach closure based on the GMP investigation. Do we really need to bring out the full armamentarium of testing to the nth degree in any such incident. I think that is the core of the question at hand.

It gets more complicated for other agents. When you asked before how often does this happen, if you look at the entire spectrum, post-donation history, CJD, hepatitis A, seroconversion to parvo, funny test results, it is not uncommon. But actual reports of pooling an HIV, HBV, HCV reactive unit, those have become rare.

DR. BUCHHOLZ: If I could just follow up, Jay. I think your point is well taken with respect to the difference between possible infectious infectivity in terms of infectious dose concentrations, if you will, or units per ml in the seroconverting donor.

But, as you point out, from the historical record, surely in the historical record the incidence of donors with an undisclosed risk history or seroconversion that was not appreciated historically before we had as good testing as we have today, would imply to me that that experiment has already been done and is part of the database that was presented this morning that supports the safety of this approach and this algorithm.

I guess I would again go back to not understanding why a seroconverting or a high-risk donor would be treated differently today based on the fact this has to have happened and is really integral to the safety database that was reported.

DR. EPSTEIN: I agree. I think that the safety record based on epidemiology tells us that, despite the fact that there is no question that window-period units have entered these products as long as we have been making them, the products have been safe.

I would tend to agree with that argument. I think that the issue gets framed differently when we have information versus when we don't have information. But I would tend to agree that the underlying science is that it has happened, whether we could prove it retrospectively or not, and that the manufacturing processes for all the products, at least since 1987 with the sole exception of the Gammagard incident, have assured us of safety and that we really don't need to continue wringing our hands over HBV, HCV, HIV when the products are manufactured properly.

So I tend to agree with that point but I think that what Dr. Tabor was trying to do here is crawl before we walk before we run. Now, we are going to come back to the discussion of window periods and risk histories. We just weren't trying to put that on the table today.

You have leaped ahead and I think you have made a sound argument. I don't dispute. I tend to be of that mindset.

DR. TABOR: I am very pleased to hear those arguments because, between now and either the next BPAC or very-soon BPAC meeting, we will have to create an algorithm probably for those cases and your comments will be very helpful.

DR. NELSON: Perhaps this is maybe a ridiculous analogy or question, but I keep remembering the outbreaks of infectious diseases like the salmonella outbreak that occurred from a pasteurized milk and that, in fact, did follow proper pasteurization. But it was contaminated afterwards.

There are many in the foodborne epidemiology, many instances of this where there were really good inactivation processes that were followed. But the problem was after that occurred. I don't know if this is possible or has ever happened with a blood product but it would not surprise me that this might be possible.

So, therefore, I would like to say, and I am sure the FDA would do a careful investigation to make sure that was not a problem or possible, but I am concerned about just somebody looking at records and saying, well, this is okay. It is conceivable that we could get burned by such an

episode.

DR. HOLLINGER: Jay, would you like to respond.

DR. EPSTEIN: Most of the concern in the direction that you are pointing to has to do with bacterial contamination. We do know of the critical importance of maintaining sterile materials and intact containers and closures, and we do worry about all of the downstream things that happen after inactivation procedures.

Those issues have tended not to come to the fore over viral contamination because it would require de novo contact with the virally contaminated material. One can conceive of such scenarios; for example, if you had a contamination and then you didn't adequately disinfect containers.

But I think that there have been no such incidents and that that set of concerns is very real for bacterial contaminations and really sort of hasn't been apparent for viral contaminations.

I would like to make one more remark about the issue of keeping the viral burden low beneath a defined limit which was part of your earlier comment, Dr. Buchholz. I think that we are evolving in that direction with the standards of PCR negativity on pools. We have evolved toward that standard partly because of the thinking in Europe.

It has been adopted voluntarily by the fractionation industry. In order to achieve a PCR-negative pool, minipool testing is now being done, as Dr. Tabor said, to prevent pooling of the PCR-positive unit. But the result of doing the PCR on a pool at a defined sensitivity of PCR is to set an upper limit to the viral burden in the pool for things you can test for.

This is becoming the practice for HIV and HCV. Some fractionators have already introduced it for hepatitis A although that is more difficult because it can't be kept out of all the pools. There is no effective donor screening. But I would just like to plant the seed that, as we introduce a standard of direct viral testing on the pool, we are, in fact, putting an upper limit on the viral burden of pools for things for which we can test.

So that is the way we are going.

DR. BUCHHOLZ: If that is the case, then, if you have in your plasma schema the original unit which comes back and you retest the original sample using the same manufacturer's test and it passes this time, it is negative, you would go ahead and use it. Why would you not implement the additional testing on that unit at that time?

In other words, what I am concerned about is the discrepancy between a unit that is treated as a positive or a false positive and a different apparent standard for those

that are seroconverters or subsequently found to be high-risk donors.

I wonder if you wouldn't want to treat, however you treat them, and I don't know the answer to that, but however you treat them that they might be treated together. In other words, instead of simply doing the original test and, if it passed this time, if it was negative, nothing to worry about, that you would not address the very issues that you raise relative to the viral burden.

DR. STRONCEK: I am favor of this algorithm. I am not quite following what Don and Dr. Epstein are saying but I have a concern that we are giving the implication that we are saying it is okay to have a certain amount of HIV virus in a sample. I don't want to give anyone that impression.

I don't think this committee should either. I think if it is inadvertent, you may want to set levels down the line, but it sounds like the discussions are leading into we are saying it is okay to have a certain level of virus before inactivation.

I would not want to be in favor of that and I wish maybe the committee could table this discussion and, if there are specifics down the line on this issue, we could come back.

DR. HOLLINGER: Go ahead, Jay. I didn't quite hear that. One thing that I did hear was that these pools

have contained, for some period of time, blood in it that had HIV or HBV or HCV and have remained roughly stable. That doesn't mean that if there is a manufacturer's problem in the preparation that that creates a real potential risk in there, but it does give some reassurance, I think, to all of us particularly with HCV which does, have--as Jay has said, probably the highest concentrations of virus do seem to occur in the window period which is different from B in which the highest concentrations occur later on during the chronic phase, and HIV, also.

But, Jay, you wanted to respond to that, please.

DR. EPSTEIN: I think that Dr. Stroncek is getting very close to the heart of the issue. The ideal model is there is no virus in the pool because we have done all the screening. The reality is different. The reality is that some window-period units will enter the pool even despite look-back efforts and that there will sometimes be instances in which you know that you pooled a positive unit.

For example, we had a case where the donor gave plasma which went into recovered plasma and into pooling red cells and platelets. The red-cell and platelet recipients got HIV. So we know that that unit if plasma was HIV-contaminated. There is no question about it.

So that is what we are saying. We are saying what should we do if we know we pooled a contaminating unit. I

think that, although the science may not be different when you have statistical certainty of pooled a seroconverting unit, the practical reality from a policy point of view presents itself as different when you have the actual knowledge that you have pooled a contaminating unit.

If we were to take the point of view that any known contamination means the products are unacceptable, then we will be taking these products out of production. What we are trying to argue is that, given the state of scientific knowledge, given the assurance level or the validation of the processes, that we can get past that point in these incidents.

That is the very issue that we are putting in front of you because what has happened in the past is, I would say we have been inconsistent. There have been points in time over the last decade where products affected in this way have been allowed out and there have been points in time in the last decade when products affected in this way have been held in quarantine forever.

We are trying to come to closure and say, what is the right thing to do? Can we not trust the scientific data and the real-world experience monitored through epidemiology and decide, in the face of contamination, it is still an okay product.

The question does tend to sort itself into two

phases. One is figuring out that it really happened and the other is figuring out what would we do about it if it did happen. I think some of the confusion lies at that level. We are sort of getting mixed up the question of what do you have to do to figure out if it is real from the question of what do you do if it is real.

But the issue of what do you do if it is real speaks directly to Dr. Stroncek's point. Yes; in the ideal world, there would be no contamination. But, in the real world, contaminations occur. So what should we do with these products?

DR. KOERPER: In the example you have cited, the finding that the donor was infectious occurred because the recipients received untreated, unvirally attenuated products, not because a hemophiliac received a factor concentrate and seroconverted.

So the hope is that all these viral attenuation products--first of all, the units should have tested negative, the plasma unit, either in a minipool as it was incorporated, meaning the viral load was low enough to be below--

DR. EPSTEIN: There was no minipool testing at the time.

DR. KOERPER: Okay.

DR. EPSTEIN: There was simply antibody and

antigen tests.

DR. KOERPER: But now we do have minipool testing; right?

DR. EPSTEIN: No; not the entire system. No.

DR. KOERPER: But that is coming into place.

DR. EPSTEIN: Yes.

DR. KOERPER: So that the testing will be even more sensitive than was done in that instance. So the unit has to pass that minipool testing before it is incorporated and then it is going to have all the viral attenuation processes applied as well.

So I see there is enough of a safety net there that the product is probably safe. I think the situation is different if a hemophiliac is documented to seroconvert from a product. You approach the algorithm totally differently.

DR. EPSTEIN: I think if we have a demonstrated transmission from an end product, there would be no debate for recalling that product.

DR. ELLISON: Isn't minipool testing done routinely? Isn't the part of GMP?

DR. ELLISON: Minipool testing is being developed under investigation. At this point in time, we believe that all plasma for fractionation in the source-plasma side of the industry is undergoing minipool testing under one or another investigational study.

However, not all recovered plasma is yet under that same system, let alone screening of components of transfusion. However, that is starting to take place now. In the early part of 1999, we will see that go into place.

DR. HOLLINGER: Any other comments from any of the committee members? Ed, what do you want from the committee?

DR. TABOR: The discussion so far has been very helpful. I think that is really what we were looking for and we will try to finalize this in a form where it can be put out for public comment. We will try to come back to you with either a modification for the other types of inadvertent contamination or if, after going after your comments, we feel it requires no modification, we will bring that back to you.

I think the real challenge is going to be coming back to you some day with the inadvertent contaminations due to the viruses we cannot test for which and for which inactivation does not work. We will do that.

DR. HOLLINGER: Since we know there are some that are not being tested for right now--I mean, there are tests for it but they are not being tested for right now because they may not cause the disease like TT virus and HGV and so on.

DR. NELSON: Some products that are used in this country are imported from other areas as well as exported

from this country to other countries. Are the practices the same for European or South American, whatever, manufacturers in other parts of the world as they are in this country? And, if so, does the FDA have any regulatory--

DR. TABOR: I would be happy to answer that but there are people who know more about the import process than I do here so maybe I would ask one of them to answer.

DR. EPSTEIN: To import a regulated product requires that it be licensed in the U.S. so it has to meet our standards. Short of license, it would have to have an investigational exemption. Before we would exempt such a product, we would do an assessment of good manufacturer practice, at least to reach some basic level of safety assurance.

And then, of course, there would be warnings to the participants of research about the safety concerns should any exist. The only other case in which products are imported under the 1996 revised Export Act, there is a provision for the import of unlicensed products solely for the purpose of processing for export, so-called "import for export."

In the area of blood products, that legislation was written so that the blood product must either meet U.S. standards or receive a specific exemption for import by the Secretary of HHS. So the fact is that we have very, very

tight control over the quality of blood products that might be imported.

The bottom line is they have to meet the same standard. They have to meet the U.S. standard.

DR. HOLLINGER: Do you have the authority, the FDA, to go into other countries and do GMP evaluations and so on in the product is being imported in this country?

DR. EPSTEIN: We request it but if we are denied the opportunity to either obtain the information or physically inspect, it is simply within our power to deny entry of the product or to seize it at the border. And we do this.

DR. HOLLINGER: Can I ask just one other question. Are blood banks required to save a sample on donors? I know many of them do, but is that a requirement for a period of time or just--

DR. EPSTEIN: No; it is not a requirement.

DR. HOLLINGER: Do you have any idea how many of the blood banks, particular the American Red Cross, the larger organizations save a sample?

DR. EPSTEIN: Perhaps there are members of the industry that could comment. I have no figure. It is not an uncommon practice but it is certainly not a requirement or a standard practice.

DR. NELSON: I have worked with several blood--I

don't think many of them do. I think some that have an active research program do, but I would--

DR. HOLLINGER: So, to go back to the original, unless it is in a plasma unit that they have not pooled or something or have a product, a fresh-frozen-plasma product, there is not anything that is available here.

DR. STRONCEK: I think it is very rare for that to happen. If a new test is being implemented and you want to go back and test your fresh-frozen plasma you have stored you might save aliquots for a period of several months so you can go back and test. But, logistically, it is difficult and expensive to save aliquots.

DR. HOLLINGER: I want to thank the committee, again, for the comments and Ed for your presentation, too. I appreciate that.

We are going to take a break now until 10:30 at which time we will reconvene for the next session which will be on the recombinant b-domain-deleted antihemophilic factor.

[Break.]

Recombinant B-Domain-Deleted antihemophilic Factor

ReFacto, Genetics Institute

DR. SMALLWOOD: Again, Dr. Hoots, one of our guests has reported an association with the Genetics Institute, Baxter and Bayer. This is to be read into the

record.

DR. HOLLINGER: Thank you, Linda. I have taken this opportunity to invite our expert guests to sit with the committee here today since they will be helping us in our discussions and deliberations later on. These are Keith Hoots, Craig Kessler and Margaret Rick. We are delighted that you are here to help us with this.

What we are going to do on this topic, recombinant b-domain-deleted antihemophilic factor, ReFacto, from Genetics Institute. What we are going to do is start out and have an introduction and background by Dr. Chang from the Division of Hematology at the FDA. This will be followed by the sponsor's presentation.

Then there will be a discussion on the review of the orphan-drug provisions. We will then have an open public hearing. Three groups have asked to speak to this issue. Then we will break for lunch and then come back with an open committee discussion.

I mention that to you because if you have questions, specific questions, and so on from any of these speakers, you will probably need to just make some notes and so on so we can come back to these issues at the time rather than doing it right when they present.

So we will ask Dr. Chang to please give us an introduction and background to the issues that we need to

address today.

Introduction and Background

DR. CHANG: Thank you, Mr. Chairman.

[Slide.]

Actually, this is just a brief introduction of topics that we are going to cover in this session that the Chairman just pointed out. I will give a brief introduction and background for the committee discussion. Followed by me, the sponsors will present. The sponsor is Genetics Institute.

After GI's presentation, Dr. John McCormick will give a review of the orphan-drug provisions. The open public hearing after lunch and Dr. Ross Pierce will present a question for the committee.

[Slide.]

FDA is currently reviewing a biological license application for ReFacto. ReFacto is an antihemophilic-factor recombinant. This BLA application is sponsored by Genetics Institute.

The product is labeled by the sponsor for use in control and presentation of hemorrhagic episodes and for routine and surgical prophylaxis in patients with hemophilia A, congenital factor-VIII deficiency or classical hemophilia.

[Slide.]

The BLA is currently under active review by FDA. I want to emphasize, though, here that the BLA application is still under active review. At the current time, we will present the question in the afternoon for which we feel we need discussion by the committee. More questions may come up during the review.

[Slide.]

The action by the agency, approval or complete response letter, is due on February 3, 1999.

[Slide.]

ReFacto has a number of properties that distinguish it from other antihemophilic-factor products. Unlike the two licensed antihemophilic-factor recombinant products, Recombinate and Kongenate, ReFacto was designed with a genetic construct locking the b-domain of the protein. The molecular structure of ReFacto will be presented by GI. The detailed structure will be presented by GI so I am not going to present that here.

In addition, the measured potency of ReFacto is more highly dependent on the type of assay used to test the protein than that of other factor-VIII products.

[Slide.]

There are several potency assays for the factor-VIII activity in vitro. One assay is called the one-stage clotting assay, on the two-stage clotting assay and a third

the chromogenic substrate assay. One one-stage clotting assay is used by the FDA for the lot release purpose.

Most U.S. manufacturers and most clinicians to assess factor VIII potency also use the one-stage clotting assay.

[Slide.]

ReFacto is labeled with factor-VIII activity determined by a chromogenic assay. All doses throughout the clinical trials were calculated on the basis of the labeling potency.

[Slide.]

Here is a figure which I copied from the paper published by Dr. Mikaelsson's laboratory. Here are the ReFacto and the two other recombinant antihemophilic factor VIII available in the market. This is one of the plasma-derived factor VIII products called Octonative M. This is a percentage of chromogenic substrate activity over here compared to the one-stage clotting assay by using the APPT reagent available on the market.

The ratio between the one-stage clotting assay and the chromogenic assay for ReFacto is close to 50 percent which is significantly lower than the two other recombinant products. When you compare this with the plasma-derived product, the ratio between two assays is close to 1.

[Slide.]

FDA is obligated to provide guidance to the physicians about product potency and appropriate dosage. Potency is defined as the specific ability or capacity of the product as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through administration of the product in the manner intended to effect a given result.

The requirements for the dosage information are that labeling shall state that recommended the usual dose, the usual dose range--doses shall be stated for each indication when appropriate. This section of the label shall also state the intervals recommended between doses, the optimal method of titration dosage, the usual duration of the treatment.

[Slide.]

The labeling potency and the potency during clinical trials of this product, which is ReFacto, were determined using a chromogenic assay that is not standard in the U.S. which gives results that are different from those of the standard clotting assay.

Physicians dosing on the basis of the proposed labeled chromogenic potency will find factor-VIII recovery in vivo using the one-stage assay than they would with plasma-derived and other recombinant factor-VIII products.

The committee is being asked to comment on how the

discrepancy in assay results may affect dosing recommendations.

Thank you.

DR. HOLLINGER: We are now going to have the sponsor's presentation. I am call on Dr. Derek Gates who is the Director of Regulatory Affairs at Genetics Institute who will then introduce the other speakers for this part of the presentation.

Sponsor's Presentation

Introduction

DR. GATES: Thank you, Dr. Hollinger. Good morning members of the committee.

[Slide.]

I would like to thank the FDA for allowing us to present to the Blood Products Advisory Committee on ReFacto, a b-domain-deleted form of recombinant factor VIII. Please note that copies have been distributed to all members of the committee of our slides so that you can make notes during the presentations and you can more easily follow along.

Today Genetics Institute will present a series of talks designed to introduce ReFacto to you including how potency of ReFacto is measured using the chromogenic assay. Then, in order to form a basis for your further consideration of the issues and the FDA question, we will briefly describe the clinical trials which demonstrated the

safety and efficacy of ReFacto when it was labeled in units determined using the chromogenic assay, dosed using traditional dosing criteria and monitored using the assay available in local laboratories.

[Slide.]

Our first speaker will be Dr. John Ryan, Senior Vice President of Clinical Research and Development at GI who will provide you with a brief background on hemophilia and the development of ReFacto.

Background

DR. RYAN: Thank you very much. Thank you Mr. Chairman, members, for the opportunity to speak today. I will provide a brief overview of Genetics Institute's ReFacto presentation and, in particular, and of the greatest interest today, to focus the discussion on the assays used for analysis.

[Slide.]

Hemophilia A occurs in approximately 17,000 people in the United States and represents a significant medical problem. Replacement therapy with both plasma-derived and recombinant factor VIII has provided an improved quality of life for the hemophilia population.

However, viral contamination of plasma-provided products, something you discussed earlier today, has severely impacted this patient population in the past and

has emphasized the value of recombinant therapy. However, in spite of the development of recombinant products, an adequate supply of factor-VIII concentrate remains a continuing problem for the hemophilia population.

Genetics Institute has a corporate commitment to the worldwide hemophilia population. We have developed and manufactured the first approved recombinant AHF concentrate which is used by Baxter for the product Recombinate. We have also developed and are marketing BeneFix for hemophilia B.

Recently, we acquired ReFacto from Pharmacia & Upjohn. Genetics Institute is currently completing the clinical development and worldwide regulatory filings for ReFacto.

[Slide.]

ReFacto is the clinical formulation of recombinant factor-VIII SQ and is a b-domain-deleted form of factor VIII. It is the first serum albumin-free formulation of a recombinant factor VIII. Clinical trials began in 1993 by Pharmacia & Upjohn and, most recently, the pharmacokinetic trials, the previously treated patients, previously untreated patients and surgery patients have been analyzed.

In fact, the BLA, as was mentioned, was submitted in February of this year. Suzie Courter will discuss these trials later in our discussion.

[Slide.]

The indications sought are that ReFacto is safe and efficacious in the treatment and presentation of bleeding episodes as well as for routine and surgical prophylaxis in patients with hemophilia A.

[Slide.]

In our presentation today, we will discuss the use of both the chromogenic and the one-stage clotting assays for monitoring therapy with ReFacto. In this context, the structure and activity of ReFacto will be reviewed in some detail. In addition, as requested by FDA, we will demonstrate that appropriate dosing of ReFacto is supported by the clinical trials which have been carried out.

This trials have used ReFacto labeled with the chromogenic assay. However, therapy has been monitored using either the chromogenic assay or one-stage clotting assays very successfully. The Clinical Development Program will be reviewed to demonstrate these points and I would now like to introduce Ed Fritsch who will discuss the structure and activity of ReFacto.

Chemistry, Manufacturing and Controls

DR. FRITSCH: Thank you John.

[Slide.]

I will be discussing various aspects of the product and analysis of ReFacto or R-VIII-SQ. The key

themes that will be emphasized are that ReFacto, a b-domain-deleted form of factor VIII, is structurally and functionally similar to full-length factor VIII except, of course, for the absence of the b-domain; that the production process for ReFacto was designed to achieve a high level of viral safety; that consistent with the recommendation of MASAC, the Medical and Scientific Advisory Committee of the National Hemophilia Foundation, ReFacto is formulated without human serum albumin or any other protein stabilizer and will be the first factor-VIII product formulated without albumin; and, finally, that the chromogenic substrate assay is the most appropriate method to quantify ReFacto activity.

[Slide.]

Factor VIII is a 2332 amino-acid protein that consists of three major domain; the N-terminal 90 kilodalton domain, the C-terminal 80 kilodalton domain, and a large central region known as the b-domain. There are three N-linked carbohydrate additions sites, indicated by vertical lines, in each of the 90 and 80 kd domains and multiple sites in the b-domain.

Intracellularly, the primary translation product is processed at the N-terminus of the 80-kd domain to produce a metal-bonded heterodimeric molecule. The b-domain is highly sensitive to proteolytic degradation resulting in a variety of degraded forms in which part or all of the b-

domain may be removed.

The molecule contains a small region at the N-terminus of the 80-kd chain which is involved in vWF binding and three thrombin cleavage sites indicated by arrows which are important in activation. Following activation by thrombin, the vWF binding region and the b-domain are released and the active cofactor is produced.

[Slide.]

ReFacto, or R-VIII-SQ, is a b-domain deletion in which 894 amino acids of the b-domain were deleted by fusion of the sequence SQN which is found in the amino-terminal-five amino acids of the b-domain with the same sequence SQN found in the carboxyl-terminal-twelve amino acids, hence the name SQ.

[Slide.]

The molecule contains the full 90 kilodalton domain and 80 kilodalton domain but contains only fourteen amino acids of the residual b-domain.

[Slide.]

Intracellularly, ReFacto is processed again into a metal-bonded heterodimeric molecule which if you compare with the full-length factor-VIII process molecule, they are very similar except the full-length has this large b-domain which adds a lot of heterogeneity due to the carbohydrate processing as well as the proteolytic degradation.

The vWF binding domain and the thrombin cleavage sites are retained in the ReFacto molecule. Following activity by thrombin, the same activated cofactor is produced as from full-length factor VIII.

[Slide.]

A critical aspect of the production and safety of ReFacto is the design of the cell-culture system. The host system, the Chinese hamster ovary or CHO cells, have been used extensively in the biotech industry and have a long and safe history for multiple products including chronic-use products such as erythropoietin, factor IX and full-length factor VIII.

The cells are grown in medium that is devoid of any human or animal-derived protein except for pharmaceutical-grade human serum albumin. The cells have been extensively tested and shown to be free of infectious virus.

The purification process for ReFacto contains a high-affinity anti-factor-VIII monoclonal-antibody step as well as four conventional chromatographic steps. In addition, a solvent-detergent step has been introduced into the process in order to inactive lipid-enveloped viruses.

The purification process has been extensively validated for the removal of viruses, DNA, host-cell protein, human serum albumin, monoclonal antibody and small

molecules.

[Slide.]

The ReFacto drug product is formulated with all simple, pharmaceutically acceptable excipients, is stable at 2 to 8 degrees following lyophilization, has a small reconstitution volume and, most importantly, contains no human serum albumin in the formulation.

[Slide.]

A number of studies have shown that ReFacto is structurally very comparable to the 90/80 kilodalton form of plasma-derived factor VIII that can be isolated in small quantities from factor-VIII concentrate. This comparability evaluation included amino-acid sequence information, post-translational modifications and higher order structure.

The only structural difference noted was at the C-terminus of the 90 kilodalton in which ReFacto exhibits some heterogeneity. Some of the molecules contain the residual amino acids of the b-domain as expected. However, some also show proteolytic processing in which approximately 20 amino acids at the C-terminus of the 90 kd chain have been removed.

The small quantities of the 90/80 kilodalton material plasma-derived factor VIII have precluded similar analysis for the plasma-derived product. All functional testing, like that which I will show in the next slide,

however, shows that this heterogeneity has no functional consequence.

[Slide.]

Extensive functional tests have demonstrated that ReFacto is comparable to full-length factor VIII in interactions with a number of coagulation factors such as von Willibrand factor, factor Xa, thrombin and activated protein C in its neutralization with a number of antihuman factor-VIII-inhibitor antibodies and in elimination pattern, half life and hemostatic effect in hemophilic dogs.

[Slide.]

The only significant difference between the molecules, as Dr. Chang just pointed out, is in the measurement of potency by the chromogenic substrate and the one-stage clotting assays. For ReFacto, different values are obtained in these two assays whereas, for full-length factor VIII, more comparable values are obtained, especially for plasma-derived.

I will focus the rest of this discussion on this assay difference describing some of the key features of the assays and going over the data demonstrating the discrepancy as well as the data indicating that the discrepancy is an artifact of the phospholipid reagents that are used in the typical one-stage clotting reactions.

Finally, I will close with a discussion of the

assay variability in the field.

[Slide.]

The traditional one-stage clotting assay it most commonly used method for monitoring factor VIII activity level in patient samples. The assay attempts to recreate the entire intrinsic clotting cascade in a test tube. Factor-VIII-deficient plasma is supply all the necessary factors shown in boxes except for factor VIII.

In the presence of an activator or this pathway, usually a negatively charged molecule such as ellagic acid, calcium and phospholipid which I will talk about more, the amount of factor VIII added determines the overall rate of the reaction.

This reaction is easy to perform and relatively inexpensive but variable due to the obvious complexity of the reactions that need to occur.

[Slide.]

The chromogenic substrate assay focusses on the central portion of this cascade. Activated factor VIII, factor X and thrombin, which quantitatively converts the added factor VIII to the active cofactor, are added in excess. The presence of calcium and phospholipid, again, the amount of factor VIII added determines the rate of the reaction resulting in the conversion of factor X to factor Xa. Now factor Xa is measured by cleavage of chromogenic

substrate resulting in an optical density change.

This assay is more precise and rugged and amenable to automation but also more expensive, especially for acute use. In 1993, the Scientific and Standardization Committee of the International Society of Thrombosis and Hemostasis recommended that the chromogenic assay for quantifying factor VIII was most appropriate due to its higher precision and accuracy.

For both types of assays, an international plasma standard is typically used as a standard for assessing clinical samples and an international concentrate standard for testing drug product.

[Slide.]

This is the data. I am going to run through some of the data that Andrew just showed you. When a plasma-derived sample was tested in this assay using a plasma standard, and shown here is a monoclonal purified Octonative-M product, the measured potency by the one-stage clotting and the chromogenic substrate assay were approximately the same.

This is, of course, expected using the like-versus-like principle for standard and sample.

[Slide.]

However, when either of the two recombinant full-length products or ReFacto were tested in the same assaying

using the plasma-derived standard, we find lower values than seen for the plasma-derived product. The one-stage clotting activity of the full-length recombinant products is approximately 80 percent that of the chromogenic substrate activity and, for ReFacto, it is about 50 percent of the chromogenic activity.

This finding for ReFacto is consistent across all batches of ReFacto that have been manufactured over multiple years including through several process changes.

Again, the International Plasma Standard was used as the standard in all these assays and so the like-versus-like principle is not strictly retained for the recombinant products.

[Slide.]

To begin to understand the basis for this discrepancy, we have investigated a number of features of the product and the assay. Various aspects of ReFacto structure and function were considered in comparison to full-length factor VIII including post-translational modifications, the presence of activated factor VIII, interactions with other coagulation components, stability of working dilutions, interference by solvent-detergent reagents.

However, none of these provided any clues as to the cause for the discrepancy. Of course, the major

difference is the absence of the b-domain. In one preliminary set of experiments, we have prepared a completely independent b-domain-deleted mutant, or variant, and expressed and purified it in a process different from that used for ReFacto.

For this deletion, the one-stage clotting activity was also lower than the chromogenic substrate activity suggesting, but certainly not proving, that the absence b-domain leads to the discrepancy.

[Slide.]

Whatever structural feature on ReFacto is important, there must also be a component in the assay that interacts differently with ReFacto than with full-length factor VIII. We have examined a number of aspects of the assay including the contact activators, the influence of vWF, the contaminants in the reagents, activation kinetics, incubation time and phospholipid.

Again, none of these showed any effects except for phospholipid.

In the one-stage assay, the phospholipid reagent typically comes from animal brain extracts because these are readily available in bulk and because they result in more rapid clotting times. However, the assay was originally developed using platelet-rich plasma from hemophilic patients as the source for phospholipid.

[Slide.]

So the same samples, shown previously, were, therefore, tested in an assay in which platelet-rich plasma was used as a of phospholipid. As you can see how, the values are all much more normalized, approximately 1 to 1.

[Slide.]

In an attempt to take this one step further, synthetic lipid vesicles were prepared in which the total phospholipid content was maintained the same but which different ratios of phosphatidylserine, a charged phospholipid, and phosphatidylcholine, and uncharged phospholipid, were included.

Platelet factor III, the important phospholipid component in activated platelets, contains less than 10 percent phosphatidylserine whereas animal-brain extract typically contains 20 to 30 percent.

As you can see, the percent phosphatidylserine in the mixture does have an impact on the assay for ReFacto delivering normal values when the percent phosphatidylserine is low, like that in platelet factor III, and depressed results at higher values.

[Slide.]

So these results point to an effect of the b-domain and the nonphysiologic phospholipids used in the traditional one-stage reagents. This conclusion is not

unexpected considering the complexities of the reaction that have to occur between factor VIII, factor IXa, factor X and phospholipid in the so-called "tenase" complex which ultimately results in the conversion of factor X to Xa.

It is easy to imagine within this complex both stearic effects due to the polypeptide structure of the b-domain as well as phospholipid charge effects having an impact on the assay.

[Slide.]

The analysis presented so far as focused on testing of factor VIII concentrate; i.e., drug product in vials. I would like to focus the remainder of this discussion on the analysis of samples from patients treated with ReFacto showing that the same assay discrepancy is observed, that analysis of antigen levels in these patients show that the antigen levels correlate with the chromogenic substrate values and, finally, close with a discussion about the variability in the field with the one-stage clotting activities.

[Slide.]

Cmax patient plasma samples from 18 patients from the pharmacokinetics that Ms. Courter will show shortly were tested for both one-stage clotting activity and chromogenic substrate activity.

As you can see, for plasma-derived factor VIII,

comparable values are obtained in both activities whereas, for ReFacto, again, lower values are observed for the one-stage clotting relative to the chromogenic substrate consistent with the results we have seen in analysis of vialed product.

[Slide.]

These same samples were also tested using an ELISA based on antibodies against the 90 kilodalton chain. The results showed that the amount of factor VIII detected by the ELISA for both products correlates very closely with that seen by the chromogenic substrate assay. However, again, for ReFacto, the amount detected by ELISA does not correspond to that seen in the one-stage clotting assay.

[Slide.]

The last point I would like to address is assay variability comparing results from a central, well-controlled laboratory with those from local coagulation laboratories at the various treatment centers.

[Slide.]

The pharmacokinetic assay data that I just described were generated in a well-controlled central laboratory and, not unexpectedly, show a very tight correlation. Shown plotted here are the chromogenic substrate values and the one-stage clotting values for more than 200 samples from that study.

The data is very tight with a mean of about 0.56 and a CV of only 18 percent. However, data collected from a large number of other laboratories presents a different picture.

[Slide.]

Shown in the left is the same data I just showed you in which both assays were conducted in the central laboratory. On the right, analysis of more than 190 plasma samples from the PTP study are shown. These derive from 62 patients and from 23 separate treatment centers.

Here, samples were tested by the one-stage clotting assay at the local laboratory and by the chromogenic substrate assay at the central laboratory. The results show significantly more variability, the CV of this dataset being about 49 percent and the ratio about 0.65.

This variation in the one-stage clotting activity presumably reflects the use of different reagents, standards, as well as assay methodology at the different centers.

[Slide.]

So, in conclusion, ReFacto is well characterized and functionally comparable to full-length factor VIII in almost all respects. The production and formulation of ReFacto were designed to achieve a high level of viral safety and the assay discrepancy appears to be an artifact

of the reagents used in the typical one-stage clotting assay.

Additionally, the clotting assay exhibits large variability in results among treatment centers. Together, this information supports the use of the chromogenic substrate assay as the most appropriate method for assigning potency.

So I would like to turn the program over now to Ms. Suzanne Courter who will discuss the clinical data that support the safety and efficacy of ReFacto labeled with the chromogenic substrate assay potency and monitored and dose-titrated using either one-stage or chromogenic substrate assays.

ReFacto Clinical Experience

MS. COURTER: Thank you, Ed, and good morning.

[Slide.]

The objectives of the global clinical plan for ReFacto were to assess efficacy and safety of ReFacto in the treatment and prevention of bleeding episodes as well as for routine and surgical prophylaxis. Most of the patients administered ReFacto in the home-care setting where they could treat bleeding episodes expeditiously.

They were instructed to treat themselves at the same dose that they used with their prior plasma-derived or recombinant factor-VIII concentrate. All vials provided to

patients during home therapy were labeled with a potency determined by the chromogenic assay.

[Slide.]

To date, the use of ReFacto has been evaluated in more than 213 patients. The previously treated patient population for which safety data is available are comprised of 112 patients. There have been a total of 22,605 exposure days with a median exposure of 155 days.

102 patients have been enrolled in the PUP trial with 97 of these patients having received ReFacto to date. The median exposure in PUPs is 19 days with a range from 1 to 447 days. Of the 28 surgical procedures performed, four patients participated in the surgery study alone and there was a total of 279 exposure days.

So, overall, the data comprises more than 29,000 exposure days during the last five years.

[Slide.]

I will review the clinical data that was presented in the BLA submission which was submitted to the FDA in February of this year concentrating on four evaluations that were performed.

The first was a crossover pharmacokinetic evaluation comparing ReFacto to a commercially available plasma-derived product. Secondly, a previously treated patient evaluation was performed which incorporated on-

demand therapy for the treatment of hemorrhage and routine prophylaxis exclusively with ReFacto.

Once we gained adequate experience with ReFacto in the previously treated patient population to ensure lack of a new immunogen, we began a previously untreated patient study. Treatment is this study is still ongoing although accrual is complete and the data are quite mature.

We also performed an evaluation of ReFacto in the surgical setting which is the most objective efficacy assessment because response can be visually assessed. This was performed with patients who were participating in the previously treated or untreated protocols or patients requiring replacement therapy specifically for an elective major procedure.

What I plan to present is a brief review of these data followed by a more detailed efficacy profile and assay data review.

[Slide.]

We performed a crossover PK evaluation in which we compared ReFacto to one plasma-derived factor VIII that is commercially available here in the United States. These data I am showing you are based on chromogenic-assay-derived plasma factor-VIII activity samples.

Upon unmasking, the data showed that ReFacto is comparable in all pk parameters to plasma-derived factor

VIII. The elimination half life and recovery represented in both IU per deciliter per IU per kilogram given and actual percent rise were equivalent between plasma-derived factor VIII and ReFacto.

[Slide.]

We have assessed efficacy in 2,380 bleeding episodes from the previously treated patient population which comprises over 4,000 infusions. 88 percent of hemorrhages resolved within two infusions. The average dose used the in treatment of hemorrhage is resolved within two infusions. The average dose used in the treatment of 29 IUs per kilogram and for routine prophylaxis is 26 IUs per kilogram. I will be showing you some comparative data shortly.

93 percent of responses were rated as excellent or good. In the safety data for the 112 patients, one of the 112 patients developed an inhibitor after 93 exposure days which is an incidence of a little less than 1 percent and is consistent with what is reported in the literature for other recombinant factor-VIII products and plasma-derived products.

There were 53, or a rate of 0.2 percent, other adverse events reported and the nature of these events was also similar to those reported for other factor-VIII products.

[Slide.]

For the previously untreated patients, we have assessed 433 hemorrhages in 808 infusions. One has to be very cautious when determining the efficacy profile in PUP as the dose will be equivalent to the potency of the vial used and the weight of the patient since whole vials are always used except for pharmacokinetic evaluations.

They also tend to be treated more often with repeat infusions due to their inability to articulate their response and due to the nature of the episodes as they begin to walk and bump their heads.

Nonetheless, we still assessed the efficacy profile and 84 percent of hemorrhages resolved within two infusions. The predicted average dose in this population would be 54 IUs per kilogram since, in the trial, we predominantly used 500 IU potency vials. As you see, that is exactly what we saw with the average dose for hemorrhage being 53 IUs per kilo and the average dose for prophylaxis being 55 IUs per kilo.

93 percent of the responses were also rated as excellent or good. The primary focus of the PUP trial, of course, is to assess the natural occurrence of inhibitor development. 26 of the 97 patients, or 27 percent, have developed inhibitor, which is consistent with the literature from factor-VIII products, particularly at this point of

data maturity where we have reached the median exposure of 19 days.

15, or, again, the rate of 0.2 percent, other adverse events were reported and, again, were similar to adverse events reported with other factor-VIII products.

[Slide.]

Twenty-five patients underwent a total of 28 procedures in the surgical assessment. Both major and minor procedures were performed including 17 orthopedic procedures which are representative surgeries in this population.

Estimated blood loss was as expected and two procedures required transfusions of packed cells. 100 percent of the responses were rated as excellent or good by the surgeon or investigator and adverse events were rare.

[Slide.]

Now I would like to concentrate on the efficacy profile observed with the ReFacto data. As I mentioned, the ReFacto potency on all vials is determined by the chromogenic assay. However, most clinical coagulation laboratories use the one-stage assay, as you have heard in the previous two talks, to determine the plasma factor-VIII activity.

Therefore, the assay discrepancy that Dr. Fritsch described is apparent in local institutions throughout the

world. As you know, these assays are used for diagnosis in monitoring factor-VIII activity as well as dose titration. Since factor-VIII replacement therapy is performed predominantly at home by patients or parents, the actual clinical situations where plasma factor-VIII activity is monitored is limited.

But, of course, monitoring and dose titration to achieve targeted circulating levels of factor VIII is critical for life-threatening bleeds and for surgery which occurs approximately 10 percent of the time.

[Slide.]

I would like to go through these data to show you how the assay relates to the efficacy profile observed and, as I mentioned, all vials of ReFacto were labeled in international units determined by the chromogenic assay and all doses throughout the clinical trials were calculated using the labeled potency.

The efficacy profile for ReFacto--or, in other words, the patient- and physician-rated clinical response, the number of infusions and dose used for bleed resolution and the average dose for prophylaxis--are all comparable to other factor-VIII products.

Finally, we observed that ReFacto is safe and efficacious when plasma factor-VIII activity was monitored and the dose titrated by using both the chromogenic or one-

stage assay.

[Slide.]

Where the data are most compelling is in the previously treated patient trial where the factor-VIII activity is not usually monitored since, again, patients are treating themselves at home. Therefore, these data are not biased by dose titration based on the surrogate endpoint of efficacy but, rather, by the clinical response experienced by the patient and the number of infusions and dose used.

In terms of response rating, 93 percent of the infusions were rated as excellent or good for ReFacto compared to 92 percent observed with the full-length recombinant factor VIII.

[Slide.]

With ReFacto, 71 percent of bleeding episodes resolved within a single infusion and 88 percent resolved within two. These results are comparable to the second commercially available full-length recombinant factor VIII that have these efficacy profiles reported in the literature.

The average dose used in the ReFacto clinical trials was 29 IUs per kilo and that compares favorably to both recombinant products where 27 to 28 IUs per kilo were the average doses used in their previously treated patient trials. These labels were based on the one-stage assay.

There was no difference in the range of all doses used for these bleeding episodes although the range was somewhat wider with one of the full-length recombinant factor-VIII products. As expected, all bleeding episodes resolved with the exclusive use of ReFacto.

In terms of the average dose used for routine prophylaxis, it is very comparable at 26 IUs per kilogram in the ReFacto study compared to 25 IUs per kilogram reported often in the literature.

[Slide.]

As I mentioned, the circumstances where plasma factor-VIII activity is monitored is in the case of surgery or major hemorrhage where patients are actually hospitalized and appropriate replacement therapy is critical. So we have analyzed the surgical data in a way to show the average dose used separating those patients whose plasma factor-VIII activities were monitored by a one-stage assay versus the chromogenic assay.

I do want to emphasize that all doses were determined by the labeled potency in both of these patient groups which, again, was determined by the chromogenic assay.

This slide represents the data observed in the previously treated patients. Nineteen of the procedures performed in the previously treated patients were monitored

by the one-stage assay and three by the chromogenic assay. The average preoperative dose was comparable in both datasets at 59 and 57 IUs per kilogram, respectively.

However, in no case, was a second preoperative dose given prior to surgery and estimated blood loss was always as expected intraoperatively.

If we look at the doses given on the first day of surgery, an average of 49.5 IUs per kilogram when monitored by the one-stage assay was higher than the average of 36.3 IUs per kilogram given when monitored by the chromogenic assay. This reflects where the assay discrepancy has an effect.

Since both major and minor procedures were performed, the targeted factor-VIII activity levels vary in the individual procedures. However, the first day of surgery is when all replacement therapy would be aggressive. When we examined the average dose used in the first post-operative week, the average dose was 549 IUs per kilogram per week in the one-stage-monitored group and 678 IUs per kilogram per week in the chromogenic-assay-monitored group.

This is reflective of the three surgeries that were performed with monitoring by the chromogenic assays which were major procedures, two knee replacements and a hip replacement, whereas the 19 procedures monitored by one-stage include some minor procedures where doses would be

decreased or even stopped in the first post-operative week.

In all cases, ReFacto was safe and efficacious irrespective of which assay was used to monitor the factor-VIII activity levels.

[Slide.]

What we have proposed in the package insert for ReFacto, which is in appendix 4 of your briefing book, our standard guidelines for factor-VIII replacement therapy to target plasma activity and are similar to many package inserts for currently available factor-VIII products.

The standard factor-VIII replacement therapy currently in clinical practice for minor uncomplicated hemarthroses is to correct the circulating factor plasma activity to a level of approximately 20 to 30 percent with some variance up to 40 percent in some treatment centers.

For moderate hemorrhages, the target level is a little higher and ranges from 30 to 60 percent circulating activity. Then, of course, finally, for the major bleeds such as retroperitoneal or CNS hemorrhages or surgical coverage, it is recommended that you target circulating factor-VIII levels 60 to 100 percent.

In the surgical setting, factor-VIII levels may be targeted to or near the trough level expected. Ranges are traditionally given in many package inserts to reflect the subtle and not-so-subtle differences amongst different

treatment centers.

These target factor-VIII activity levels are based on the general rule of thumb that one unit of factor-VIII concentrate would increase the circulating factor-VIII activity by 2 percent which is what several current inserts state as well as our proposed package insert.

The equation to calculate the required dose is then provided as the required units equal the body weight in kilograms times the desired factor-VIII percent rise times 0.5 IUs per kilogram.

[Slide.]

In conclusion, labeled potency determined by the chromogenic assay was used in all the clinical trials to calculate doses and efficacy profiles are comparable to other factor VIII products in the treatment of bleeding episodes as well as in routine and surgical prophylaxis. ReFacto is safe and efficacious when plasma factor-VIII activity is actually monitored and dose titrated by one-stage or chromogenic assay.

[Slide.]

In terms of how to address the assay discrepancy between the chromogenic assay and the one-stage assay that will be prevalent in clinics, we have proposed language in the package insert under dosing which is, again, in your briefing book, which we think will address this discrepancy.

First, we state that the product is labeled on the basis of chromogenic assay and recommend monitoring of plasma factor-VIII activity for surgical intervention and when clinically indicated. Monitoring of the factor-VIII activity should be performed on the chromogenic assay. However, a one-stage assay can be used if the chromogenic assay is not available.

The language also notes that the one-stage clotting assay yields results lower than the chromogenic assay. We have simply referred to the discrepancy's existence since the real-world situation across several local laboratories revealed variable results, as Dr. Fritsch showed you.

This is intended to alert patients and physicians to the assay discrepancy but to leave the standard of care, in regard to dosing, in the hands of the treating physician.

[Slide.]

Now I would like to pass the podium to Dr. John Ryan who will summarize the presentation.

Summary

DR. RYAN: Thank you.

[Slide.]

In summary, we have just been shown that ReFacto has undergone extensive clinical development and has a mature database. Both safety and efficacy have been

demonstrated in PTPs, PUPs and in the surgical setting and, as been emphasized, the chromogenic assay most accurately measures the amount of factor VIII in the vial.

Indeed, in our clinical trials, dosing based on this labeled potency was comparable to what has been shown in the literature for other factor-VIII products in all the clinical settings.

[Slide.]

The question that was posed by the FDA for this committee is reiterated here. It is, "Is the information supplied in the dosage and administration section of the proposed product label sufficient to dose and monitor this product appropriately?"

[Slide.]

In response to this important question, dosing in clinical trials again was based on the labeled potency measured by the chromogenic assay. However, monitoring of factor-VIII activity can be done by either the chromogenic assay or the one-stage assay, clotting assay. This has been successful in all of our clinical trials including the surgery setting.

Thus, we believe we have answered the FDA's question in the affirmative and this translates to a dosing recommendation which we have proposed, shown on my final slide.

[Slide.]

The product is labeled on the basis of the chromogenic assay and, when clinically indicated, factor-VIII blood levels should be determined using the chromogenic assay. The one-stage clotting assay may be used if the chromogenic assay is not available. However, it must be noted that the one-stage assay yields results which are lower than the values obtained with the chromogenic assay.

Thank you very much.

DR. HOLLINGER: Thank you, Dr. Ryan, for that succinct presentation from the sponsor and the slides that we could look at while you were presenting it.

The final discussant here is Dr. John McCormick who is going to review the Orphan Drug Provisions since there is an issue related to that.

Review of the Orphan Drug Provisions

DR. McCORMICK: I guess what I would like to do is just very, very briefly discuss the issues that are involved with the approval of this product and then answer any questions that the advisory panel may have.

Basically, Kogenate, the Bayer product, was approved in February of 1993. At the time, it was given seven years of marketing exclusivity. The marketing exclusivity was for the product which is recombinant factor VIII for the indication which was the treatment of

hemophilia.

That exclusivity prevents another product which is deemed the same product for the same indication from coming on the market during the period of exclusivity. As we have just heard, ReFacto is a very similar product to Kogenate and, under the regulations which deal with macromolecules and proteins, would probably be deemed the same product.

That means that if ReFacto were to come on the market, it would have to demonstrate one of three things. One, it is either a safer product or it is a more efficacious product, or it must demonstrate that the manufacturer of the product with exclusivity cannot meet the demand of the market.

In order to demonstrate that it is a more efficacious product, it is almost required that this be done in head-to-head clinical trials. To demonstrate that it is a safer product, it is usually required that this be demonstrated in clinical trials. However, certain exceptions have been made where either data from separate trials were compared or if a product is what I would like to determine intuitively obvious--for instance, HIV would be present in one product and could be excluded in another product--it would not be necessary to demonstrate that in a clinical trial.

Now, for the last criterion, a demonstration that

there is, in fact, a shortage, there is presenting no experience in the agency for using this as a vehicle for allowing a product on the market. However, our interpretation of what the regulations and the law requires is that, one, we must notify the manufacturer that the FDA believes that a shortage exists.

Two, we will ask the manufacturer who holds the exclusivity to demonstrate, to the FDA's satisfaction, that either a shortage does not exist or two, they can provide the FDA with a credible plan that will alleviate the shortage.

If the manufacturer holding exclusivity fails to do either of those, then exclusivity for the product will be removed and any manufacturer will be allowed to enter the market. In order for the manufacturer to satisfy the shortage, they may do this either by increasing their own production within a reasonable period of time or allowing another manufacturer to enter the market either through a licensing agreement or simply waiving their exclusivity for the other manufacturer.

The issue has been raised that, at present, there is not an adequate supply of recombinant factor VIII. The Office of Orphan Product Development has instituted what we perceive as our obligations under the law. Depending on what information we accrue, we will make a determination

whether or not, one, a shortage exists and two, if a shortage does exist, whether the present holder can satisfy the demand.

I would be happy to take any questions.

DR. HOLLINGER: I am going to allow some questions at this particular time on this particular issue.

DR. KOERPER: I am a little confused. Could you explain how Kogenate could get an exclusivity when it was licensed after Recombinate which is also a recombinant factor-VIII product that was licensed prior to Kogenate?

DR. McCORMICK: The exclusivity for a product is determined by whether or not somebody applies for an orphan designation. Recombinate did not apply or did not pursue the exclusivity. Therefore, Kogenate was the only product which was designated and approved and, therefore, the only product which received the exclusivity.

DR. KOERPER: Recombinate was already on the market when Kogenate applied for exclusivity.

DR. McCORMICK: Kogenate applied for exclusivity in I believe it was 1988 or 1989. It was done early in the process prior to approval.

DR. KOERPER: So they applied for it before their product was licensed? But then Baxter was able to get their product licensed even though Bayer had the exclusivity? I'm sorry; this process just confuses me.

There is a certain amount of confusion because, originally, the law was written to cover drugs for which it could not be reasonably expected that they would make a profit within seven years.

However, because of the very low level of enthusiasm from the industry, it was felt that some other determination of what really was an orphan needed to be made. Approximately one year after the original law was passed, the definition of an orphan was changed from a drug which will not make a profit within seven years to a drug which is intended to treat a disease with a prevalence of less than 200,000.

DR. HOLLINGER: I always had the misperception that it was sometimes a drug that was out on the market but had not had any protection and was, therefore, a company was allowed to use it. But, again, it has to be under that rule of less than 200,000.

DR. McCORMICK: Less than 200,000. The original rule, that it will not make a profit within seven years, is still within the law so that there are actually two avenues of demonstrating that you can be an orphan. One is that it will not make a profit. The other is that it will be used to treat a population of less than 200,000.

DR. HOOTS: Since you stated that there is no precedent for this to be called into play at this particular

time, would it be appropriate for the FDA to consider, in this discussion, publicly presented data with regard to a national shortage that is already on the public record and was presented to the Blood Safety and Availability Committee in August with an extraordinary amount of detail about impact of the shortage, presented multifactorially from consumers, from providers and from industry as indication that a shortage now exists.

DR. McCORMICK: Yes; I think it would be appropriate for the FDA to consider that.

DR. HOLLINGER: Before we get too far on this orphan-drug think, Dr. Smallwood has just advised me that it is important for us to understand the orphan drug, for all of us, but, apparently, the issue that is germane to this committee here is the labeling, primarily.

My understand is, and correct me from the FDA if we are wrong about this, the only thing that we are really wanting to deal with today is the labeling, particularly. It is the only consideration here, not exclusivity and things like this.

Am I correct in that? I want to be sure that that is correct.

DR. VERTER: Are we really limited? Can we not discuss the studies that were presented if they are not germane to exactly labeling? Is that what you are saying?

DR. HOLLINGER: We want to limit here mostly primarily to the Orphan Drug Provisions, primarily.

DR. VERTER: No; I mean later on. I did have a question about that part and that is is that saying that if there is a demonstrated shortage which is unquestionable then issues of safety and efficacy are almost irrelevant?

DR. McCORMICK: No.

DR. VERTER: The way you presented it is--

DR. McCORMICK: What it says is that if there is a shortage, then another approved product which has demonstrated safety and efficacy can come on the market. The demonstration that a drug is different can only be accomplished--in order for a drug to come on the market when there is exclusivity involved requires that a drug demonstrate that it is different.

It must be different either by showing that it is safer or that it is more efficacious. That is what determines difference in proteins, essentially, that are very similar.

DR. VERTER: The reason I asked that is because when you started out you had an A or a B or a C.

DR. McCORMICK: Right. I apologize for the confusion.

DR. KESSLER: I would like to ask you about perceived or real differences in viral safety between the

currently available recombinant factor VIII and the proposed VIII-SQ, particularly trying to get your impression of the incremental benefit of albumin-free formulations. Do you believe that there is an incremental benefit viral-safetywise to having an albumin-free formulation and, if you don't, can you tell me why so many manufacturers are now trying to make such albumin-free formulations?

DR. McCORMICK: I started off the morning by listening, as you did, to a discussion on the transmission of viruses, known viruses, in albumin. I think that the consensus of this group, as well as the people that presented, was that the possibility of transmission of at least known viruses through albumin is relatively low.

I think that you are right. It is a question of incremental. The question is it intuitively obvious that albumin-free is better than having albumin in the product. I would say that that is a debatable question and that if, in fact, there were a significant problem, then it could be demonstrated in a clinical trial.

DR. KESSLER: Just as a follow up, if you don't believe that the incremental safety is better, then why are so many manufacturers now trying to improve their currently available recombinant factor VIII concentrates by making them albumin-free?

DR. McCORMICK: Perhaps you could ask the industry

that question or, perhaps, you could survey the panel here.

DR. KESSLER: You all are also making an incrementally safer recombinant factor VIII also without albumin; is that correct? So you must have perceived that there is a safety benefit or not? I am just curious as to whether or not, if you are talking about incremental safety advantages, is there a perceived, proven or theoretical improved safety feature with albumin-free formulations?

DR. McCORMICK: Talking strictly off the cuff--

DR. HOLLINGER: Craig, maybe there is a misinformation. Dr. McCormick is with the FDA, not with the company.

DR. KESSLER: Oh; I'm sorry.

DR. HOLLINGER: I think the question is important but I think we sort of jumped into another person. I'm sorry about that.

DR. HOOTS: Just to follow up that, though, just in terms of the scientific onus and irrelevant, I think, to these two products but, because it is probably going to come up again in this context, we are talking about, by definition, an orphan drug where a population is less than 200,000. In this case, it is a log lower than that. It is 20,000.

The statistical power required to show the difference in safety for something like albumin is so

inordinately greater than the capacity of the population to provide the numbers to do such a trial is that it would never be done.

So it seems like at some point, there has to be consideration on the safety side of theoretical arguments rather than side-to-side comparisons.

DR. McCORMICK: I would argue that the reason that the number of patients would need to be so large is because the risk is so small.

DR. HOOTS: Oh; clearly. But that doesn't mean it is negative, or zero.

DR. BUCHHOLZ: Could I just get some clarification with respect to the shortage. You inferred a time period of several months ago. My understanding is that one of the manufacturers has just had a facility that has come under approval for manufacturer of recombinant factor VIII. Was that added capacity to the system taken into account in determining the shortage? How is that projected to, in fact, affect things?

DR. McCORMICK: The regulations require that one, our office query the manufacturer who holds exclusivity on whether or not they can meet the demand within a reasonable period of time. The reasonable period of time is to be determined.

If, in fact, they have plans of bringing

significant new capacity into play, then that will satisfy any demand from us.

DR. BUCHHOLZ: Okay. I must admit I am a little confused about the exclusivity issue with respect to the two manufacturers but, in this particular case, it is my understanding that the added capacity is not with the manufacturer who holds the orphan-drug status; i.e., it is with Baxter.

I am confused about whether shortage was shortage determined prior to the time that Baxter's new facility was licensed or whether that is a very recent determination because my understanding is the capacity is fairly significant with this new facility.

DR. McCORMICK: I would believe that the determination of shortage means not just what one manufacturer can supply to the market but what is available in the market and whether or not the demand is being met. It would be at the time the issue was raised.

DR. HOLLINGER: Dr. McCormick, you will be here this afternoon, too?

DR. McCORMICK: I wasn't planning on it but if there is a reason to be here, I will be happy to stay.

DR. HOLLINGER: I was just thinking if there are any other questions, it may be worthwhile. Are there any questions specifically?

DR. OHENE-FREMPONG: I would just like to have a restatement of the question for the committee. I have a feeling that this last discussion seemed to take us off a little from it.

DR. HOLLINGER: The question, if this is a correct question for the committee, is on C55. So you can read it from that one. It is, "Is the information supplied--" but you all have it in your handout so you can read it there anyway. It is, "Is the information supplied in the dosage and administration section of the proposed product label," and there is an attachment, "sufficient to dose and monitor this product appropriately?"

That is the question for this committee.

DR. McCURDY: It seems to me that there may be two aspects to this. One of them is the use of the assays for the product and for clinical care. I would think we might depend heavily upon or consultants and maybe several members of the committee who may have a lot of experience in that.

It would particularly be important that clinicians using the material not be confused if they shift from one product to another so that patients would get an overdose which would be expensive and contribute to a shortage, if it is necessary, or an underdose that would not be effective.

The other issue which occurred to me, as I read one of the slides here and remember the presentation, these

CHO cells are grown in a medium that contains pharmaceutical-grade human serum albumin. I wonder if there is any purification process that can ensure that the end result is albumin-free. It might be very low and negligible and, perhaps, of no clinical or infectious-disease importance, but I am not sure that it be labeled as albumin-free.

DR. HOLLINGER: Those are both good questions, Paul, and just keep those because we should discuss those. Those are important issues. But I will tell you what I would like to do right now. We have three other speakers in the open public hearing here which I would like to have give their presentations.

The first one would be from Bayer Corporation, Dr. David Ramies. There is a handout for the committee for this.

Open Public Hearing

DR. RAMIES: Good morning.

[Slide.]

As already mentioned, my name is David Ramies. I am with Bayer Corporation. I am the Project Director for Kogenate, our current recombinant factor VIII. Actually, we were asked to present our clinical experience with Kogenate with regard to the one-stage assay and the chromogenic assay within the context of this discussion today.

[Slide.]

One thing I think that is very important to point out here, and it was already touched on by our colleagues from Genetics Institute, in contrast to the ReFacto product, Kogenate is a full-length factor VIII from recombinant DNA source. Bayer assigns final contained potency by the one-stage coagulation assay.

Our clinical experience with Kogenate is based on dosing with the one-stage assay. Results of our pharmacokinetics and recovery studies, again, also based on the use of the one-stage assay.

Finally, we have used in clinical evaluation of our second-generation Kogenate which is comparable in the product profile to the ReFacto product in that, although we use a human albumin form in cell culture, we have a purification process in formulation without albumin.

Traditionally, as has already been highlighted to the committee, the one-stage assay is commonly used by clinicians to assess recovery and, as such, it is used to traditionally or historically monitor and adjust patient dosing of factor VIII in treatment of hemophilia A.

[Slide.]

We were asked to present clinical experience comparing one-stage to chromogenic. What we have available are results from testing of plasma samples from our recent

crossover study comparing Kogenate to recombinant factor VIII. SF is the designation "sucrose-formulated."

We have data from 20 patients. Patients were dosed based one the one-stage assay on the order of 50 units per kilogram. As a consequence of this study, we did establish bioequivalence between these two forms of our product.

What we have is a summary of 363 data points comparing results of the one-stage assay to the chromogenic assay.

[Slide.]

This is simply a typical profile for one of the patients in the study. It simply demonstrates--the lower plot here indicates results from the one-stage assay and the higher plot shows the chromogenic assay. This line indicates the ratio of the one-stage to chromogenic which is on the order of 0.67 or, more simply, for every two units assayed by the one-stage, there are three units of activity by the chromogenic.

[Slide.]

This is a higher level summary slide simply indicating that the mean ratio for all the test points in the PK study again was roughly 0.67, or roughly 0.7.

[Slide.]

This is the final slide. As a result, from these

data, the chromogenic results were higher relative to the one-stage assay, again the mean ratio being 0.67 for both Kogenate and our second-generation product. We saw this consistently on a patient-to-patient basis. This relative difference was always one stage lower relative to the chromogenic result and it was also seen consistently regardless of the sample point.

As I mentioned, the previous slide showed ten-minute recoveries out to 48 hours.

The final bullet point. If we were to convert to the use of chromogenic method for assay of final biopotency, again, we have the issue that has already been commented on. We have to consider that the one-stage is commonly used to assess recoveries in the clinical setting. Recoveries would be lower than expected and this may require an adjustment in factor VIII dosing.

Thank you very much.

DR. HOLLINGER: I would like to allow a couple of questions here, if anyone has any questions regarding this particular aspect here from Kogenate, from Bayer. Does anybody have any questions?

DR. McCURDY: I am wondering if there is a consistent ratio of 0.67 between the two, I am not sure that I understand why it would require a change in dosing. It would suggest to me that you are treating the laboratory

result rather than the patient. If it is adequate to use the one-stage assay at 1.0, then maybe it ought to be adequate--no; the other way around, but anyhow.

And I am not entirely clear at this point what the relationship is between the clinical effect in hemostasis and the two assays.

DR. HOLLINGER: Between the biological response and so on. Do people who use Kogenate use it using this two equals three?

DR. RAMIES: No. Actually, again, we assign biopotency by the one-stage so the lower value. Again, this is for our full-length native factor VIII by recombinant source and this was pointed out by GI. Obviously, there is a difference in the construct.

So we are simply presenting our data and this is the relationship we see with these data.

DR. HOLLINGER: But, in essence, then, you would say, at least with Kogenate, based on the ratio of 2:3 that actually patients are probably getting more than what they--more or less?

DR. RAMIES: Actually, they would be getting less if we dosed based on the chromogenic.

DR. HOLLINGER: If you based it on chromogenic.

DR. RAMIES: So it is a relative--

DR. ELLIS: Would it be appropriate to ask Dr.

Ramies to comment on the shortage of the product?

DR. HOLLINGER: Sure.

DR. RAMIES: Actually, my capacity here today was really in tune with presenting the scientific data. But I can tell you that Bayer obviously takes the supply-shortage situation very seriously. As Dr. McCormick pointed out earlier, we have received correspondence from the FDA and we are in the process of responding to it in a manner that takes into account the interests of the most important population here, namely the patients, Bayer, and certainly addressing the FDA's concerns.

Overall, Bayer has a lifelong commitment to the patients. We have, over the past five years since Kogenate's approval, improved our capacity fourfold and continue to do so with ongoing development such as our second-generation Kogenate.

DR. RICK: Could you tell us how you determined the recommendations for the package insert?

DR. RAMIES: Actually, again, our basis for the second-generation product, as with the first-generation or currently licensed Kogenate, was all based on the one-stage assay which is currently in use.

DR. RICK: No. I realize it is the one-stage assay. Is this the clinical information that was generated in the 1960's?

DR. RAMIES: Actually, this information is from our more recent PK crossover study. As I mentioned, we used the one-stage to show bioequivalence. We provided samples to a local coagulation laboratory in order to assess one-stage versus chromogenic because, although one-stage is traditionally used by clinicians and it is also in use by FDA, we also have a consideration for Europe because, obviously, the chromogenic assay is the compendial assay.

As such, right now, we don't envision any change to our dosage recommendations for the new product over the currently licensed Kogenate.

DR. RICK: My questions, really, are more directed toward the biological endpoint, I guess, and I would need to know if any studies were done to assess or titrate lower doses and look for a biological endpoint.

DR. RAMIES: No.

DR. RICK: I think that is going to be one of the problems that we face with all of these labels and that is that I am not sure that the one-stage assay was ever--or, perhaps, it can't be ethically--titrated much. But I am not sure that we know what the most efficacious dose is in all circumstances.

DR. RAMIES: Right. To answer your question, we haven't taken patients down to a breakthrough level, if you will, to titrate a dose for efficacy. We haven't done that.

And, again, basically for ethical reasons.

DR. BUCHHOLZ: I wonder, as a point of information, if those who are on the committee might provide us with some information with respect to monitoring of post-infusion dosage levels. My assumption would be that if patients are on home care, that--

DR. HOLLINGER: Don, I want to keep this for later, if you don't mind.

DR. BUCHHOLZ: Okay.

DR. HOLLINGER: It is a critical question but I want to just sort of see if there are any other questions about the Kogenate, particularly, anything that you wanted to ask about Bayer.

Thank you very much.

The next speaker is Dr. Edward Gomperts who is going to be speaking for Baxter Hyland Immuno.

DR. GOMPERTS: Good morning to the committee. Thank you for the opportunity to present to you this morning.

[Slide.]

My name is Edward Gomperts. I am Vice President of Medical Affairs and Clinical Development for the Baxter Hyland Immuno Division.

[Slide.]

I have some general observations and then some

specific information. Factor VIII clotting activity in the diagnostic laboratory which is the laboratory which is used at the hemophilia treatment centers to monitor patients undergoing surgery or potential inhibitor therapy or serious hemorrhages. At this laboratory, the assay results that come out of it interpret into what happens to the patient from the point of view of treatment and whether hemorrhage continues or does not.

The standard measurement of clotting activity is the one-stage aPPT-based assay, both in the clinical diagnostic laboratory, virtually throughout the United States. There might be one laboratory that use the chromogenic-substrate assay. So, by and large, the one-stage assay is the assay system that is used in diagnostic laboratories.

But also it is the assay system used in the quality-assurance laboratory of most factor-VIII concentrate manufacturers--not all, but most. As we have heard this morning, the one-stage aPPT assay does not interpret equivalently to the two-stage assay which has not been discussed to any great extent at this point and also the chromogenic-substrate assay on both potency designation and clinical-lab assay. And I will talk to the specific point subsequently.

[Slide.]

Pharmacodynamics have been established through extensive clinical research and use post-licensure. In other words, the potency designation on the product, whether they are the very early first-generation non-viral inactivated products where breakthrough bleeding and dosage was evaluated back in the late '70's to the much more recent and fairly extensive studies that were carried out with Recombinate and also post-licensure.

As already mentioned, it is generally accepted that one unit per kilogram body weight, either plasma or the currently licensed recombinant factor VIII products, Recombinate and Kogenate, interpret into a 2 percent increase in plasma level.

Therefore, to control a relatively minor hemorrhage, although potentially very painful and potentially constructive--to control that knee bleed, 20 units per kilo will result in an increment of an approximately 40 percent level. This is the usual standard dose to control such a hemorrhage.

Intracranial hemorrhage which is, of course, a very different issue, a dosage of 50 units per kilo is sufficient to convert the clotting factor VIII level to that level which is established across a normal population; in other words, 100 percent.

[Slide.]

It is also important to recognize that as far as a recombinant and Hemofil M are concerned that in our quality-assurance laboratory, one unit of factor VIII in the product is equivalent to one unit of factor-VIII standard. And the currently used standards, or the Mega standard which is based on a plasma-derived factor VIII and currently and very recently, the World Health Organization No. 6 standard has very recently been established and this is a recombinant factor-VIII standard.

Essentially, they are equivalent. This has been established.

[Slide.]

In a number of studies that we have carried out, a pharmacokinetic crossover study, in this particular study a Hemofil M study was carried out in a number of patients. In this particular study, there were two lots of Hemofil M that were evaluated, potency designated by our quality-assurance lab but, in addition, by a standardization laboratory, the National Institutes of Biologic Standards just outside of London.

These two lots evaluated in the two separate labs, both on one-stage aPPT assay and chromogenic substrated, and it is clear that one-stage assayed these particular lots differently to that of chromogenic substrated and the product is potency designated on a one-stage assay in the

United States.

[Slide.]

In a similar type study where recombinant with our Thousand Oaks licensure pharmacokinetic-equivalence study, a very similar series of observations were made both by our quality-assurance lab and the National Institutes of Biologic Standards again evaluating these two lots of Recombinate by one-stage assay and chromogenic substrate, again there were differences.

But, in this situation, it was a little different. The chromogenic substrate assay is a little higher with Recombinate than with Hemofil M. But, again, in the United States, the potency designation is on a one-stage assay.

[Slide.]

So, in summary, the one-stage system is the standard procedure for both potency designation and clinical efficacy. Recombinate and Hemofil M vary usually 10 to 15 percent, maybe a little greater in the occasional lots, between one-stage and chromogenic. It is important that comprehensive clinical research is required to document that dosing based on chromogenic substrate assay interprets into clinical efficacy.

Clearly, the label for both Hemofil M and Recombinate provides information so that a clinician will be able to appropriate treat their patient on the potency-

designated product based on the one-stage assay in that particular patient.

Thank you.

DR. HOLLINGER: Thank you, Ed.

Are there any questions to Dr. Gomperts as it relates to the product from Baxter, the Recombinate.

DR. PIERCE: Dr. Pierce from FDA. In view of your last bullet point, would Baxter be comfortable with the clinicians monitoring therapy using the chromogenic assay. That could be expected to result in less product being used compared if the one-stage clotting assay were being used.

DR. GOMPERTS: We would be uncomfortable with that unless there is specific clinical information as to dosage in relationship to that particular assay. There would need to be data to support the management of a patient under those circumstances.

DR. PIERCE: If you were going to design a clinical trial or a clinical experience to validate the use of following patients, monitoring patients, for example, with the chromogenic assay, would you give an estimate as to the size of clinical experience that you would like to see before your company might be wanting to put that into the labeling as an alternative for monitoring patients, using the chromogenic assay?

DR. GOMPERTS: Clearly, I have thought through

this particular issue on a number of occasions as to how the study might be structured. As to the numbers of patients at each particular dosage level, I haven't personally tested that through our statisticians. But, certainly, it would need to be constructed over a dosage range with sufficient power to demonstrate efficacy or lack thereof.

DR. HOOTS: Ed, obviously, you are having to face this in the EU as well, particularly in Scandinavia where they are pretty much exclusively dosing and monitoring with the chromogenic. What has been the feeling among the people, the investigators and the treating physicians, that you supply there.

Have they still been dosing pretty much on the one-stage even though they are monitoring with the two-stage? How have they approached it? Or do they just continue to use a one-stage even though they prefer having a chromogenic?

DR. GOMPERTS: I have not had that discussion with them. I am under the impression that the one-stage assay is used pretty broadly in Europe as well as the United States.

DR. HOLLINGER: I just want to ask one more question, just for my own clarification. When I get at PTT, it is in seconds. How does that translate over into IUs per ml and at what level is it considered a level that you are trying to reach?

DR. GOMPERTS: The PTT, Blaine, that you receive back from the laboratory is the PTT assay. It is a simple test. That principle is applied to the clotting factor in a--it is the same activator, phospholipid, is used. But then it is set up in different dilutions and compared against a standard or control.

So this is essentially a rate assay, how quickly the endpoint is reached. And the endpoint in the PTT system is the generation of fibrin, whether it is the actual fibrin breaking a current or fibrin forming a clot and, therefore, triggering a light path. So there are a number of ways that the endpoint can be reached but there are dilutions taken of whatever it is that you want to measure.

And then those dilutions will produce a clotting time put on a curve, and that curve is established by the control. In that way, the assay is established. Now, in the quality-assurance lab, the controls will be the standard whether it is a Mega standard, WHO standard and, ultimately, does interpret into that. That is the rock against which we compare everything.

DR. HOLLINGER: The final speaker that has asked to talk to the group today is from Centeon, Dr. Fred Feldman.

DR. FELDMAN: Mr. Chairman, ladies and gentlemen. Centeon 2 was asked to provide comments and data that could

help decide which way to go when there are uncertainties about assay discrepancies and concentrate use.

[Slide.]

My name is Fred Feldman. I am Vice President of R&D at Centeon and I will address and show you some data on one-stage, two-stage and chromogenic assays, particularly as regards to product labeling and use of coagulation factor VIII.

[Slide.]

I have provided you with a copy of my presentation but have deleted the material that has already been presented this morning, not to be redundant. Some of you may know that in the 1970s and 1980s, the routine assay that was used for evaluating factor VIII labeling by the National Institute of Biological Standards and Controls was the two-stage assay, the thromboplastin generation test.

In fact, during this time period, the two-stage assay was also typically used by the then Bureau of Biologics of the FDA in the United States. Until recently, the European Pharmacopeia mandated a two-stage assay for factor VIII and, as was referred to earlier this morning, that has been changed to a recommendation to use the chromogenic assay.

But that recommendation was based on equivalence in testing between all assays that were available, one-

stage, two-stage and chromogenic. Neither the Scientific Standardization Committee nor the European Pharmacopeia has yet concluded how to deal with differences in assay discrepancies in labeling. They still have to go through that deliberation.

As commented by the prior speakers, the one-stage assay, the activated partial-thromboplastin time, is the predominant test that is used in clinics and hospitals to measure response to factor-VIII infusion, factor-VIII infusion based on adherence to the labeled potency that is on the vial.

Typically, historically, native factor VIII in plasma has shown identical potencies, when measured by the different assays, whether one-stage, two-stage or chromogenic, the numbers were the same.

[Slide.]

That leads to the dilemma that we have today. The early concentrates that were developed also showed equivalence in testing independent of which assay method was used. Later, as concentrates evolved through heat treatment or solvent-detergent treatment and came to higher purity levels, some assay discrepancies started to be seen.

Dr. Gomperts showed you some right before me but, generally, those assay discrepancies were small. They were less than 20 to 30 percent. When they were seen, generally

the one-stage assay showed a higher number than the two-stage. So what we have before us today is significantly different.

The first-generation recombinant factor-VIII concentrate, you just saw data on that so, if you can give me the next slide.

[Slide.]

These are test results. I will show a couple of slides on those. I am showing you exactly what we see when we test our own product that at Centeon. This is a plasma-derived factor VIII. It is very high purity and it is pasteurized. This incorporates all the changes that have come into processing since the early experience.

In those, if you test according to different assays, which is what this chart is, this is for this lot, the one-stage potency, the assay by two-stage and the assay by chromogenic. The second column here is the percentage of one-stage label. This column is the percentage of the one-stage label and the chromogenic assay.

What you can see, generally, for products like this there is not a discrepancy, that independent of whether the label is applied by a one-stage assay, a two-stage or a chromogenic by the quality-control lab, that it generally doesn't make any difference, that there is equivalence in labeling independent of the manufacturer and the QC test.

So what this slide generally shows is that it is possible to prepare a very high-purity factor VIII with no differences in labeling no matter which assay you use.

[Slide.]

The next slide basically shows you ten lots. It shows that it is consistent that the ratio of a chromogenic assay to a two-stage is constant in products like this.

[Slide.]

The next question, then, is what happens when products like this are put into a clinical study. This is data that was reported by Kasper and colleagues on looking at different assay methods, whether a one-stage in two different locations or a two-stage test with regard to specific recovery in a series of patients.

What you see is with the one-stage assay, there was general consistency. The two-stage assay showed a little bit lower results but, overall, these results were pretty much equivalent and independent of the label that was applied by the manufacturer or the method that was used in testing. The clinician could know exactly where they were in the treatment of the patient.

[Slide.]

I will show you next slides that show in vivo recovery comparing one-stage and chromogenic assays in two other products. These are products that our company

manufacturers in Germany and distributes in Europe. The only difference between the two is one has no albumin added as stabilizer and one does. And it doesn't seem to make any difference with regard to the fidelity of the assays.

So what you have here are the different patients in three different centers, to take center bias out of it. On the ordinate, what you have is the ratio of recovery if one looks at the one-stage assay compared to the chromogenic assay. What you can see generally is that, in different patients, the recovery is generally around 100 percent. There is some variation, plus or minus 20 percent. Sporadically, in a couple of patients, the recovery is even higher.

In none of these is the recovery by a one-stage assay less than a chromogenic. Patient-to-patient, and we have also seen batch-to-batch, the assay can be reliably depended upon and a clinician can know where they are, no matter which assay they use.

[Slide.]

The next slide shows you more data of the same type. With a second product, it shows the same thing, 100 percent recovery. It doesn't matter whether it is the one-stage or two-stage. One patient shows a higher recovery based on the chromogenic but this could be variance based--dependent on that particular day with that patient. But the

product shows consistency.

[Slide.]

I have tried to summarize what the dilemma is as I see it. The dilemma seems to me to be a dilemma that the manufacturer is involved in, first of all, of how to put a label on the product that can be depended upon and that can be used to dose treatments and that the clinic can then know where the patient is in that course.

In testing and labeling a product, if the manufacturer, in his quality-control lab, obtains highly discrepant values according to different assays, that is a different condition from what has existed before. The dilemma it leaves the manufacturer in is then what should he put on the label, which assay.

So, for example, if, for the one-stage assay, the potency were to be 500 units per vial and by a two-stage or chromogenic assay, the potency would be 1,000 units per vial, which potency do you put on the label? Do you put a 500 or do you put 1,000? It makes a big difference in how the clinician decides what he going to dose with after that, especially if, when the clinician uses the product and if the potency has been applied with 1,000 per vial label but the clinician sees, in a study of 50 percent recovered by a one-stage assay and 100 percent by a chromogenic, what does he think?

Which one is okay? Is it okay to disregard the 50 percent recovery number on the average patient under treatment in the clinic on that day and how does he follow and how does he know whether he is in a treatment range that he has come to expect before.

[Slide.]

In our thinking of it, we have come to think of it in the following way and maybe have some suggestions that might help with this. First of all, you have only heard a little bit of the detail of coagulation. Believe me, it gets much more complicated as you get into reagents and test methods, and you can spend days on any of this.

Our first thinking is maybe it would benefit by convening an expert working group to deal with assay calibration and standardization. The working group could be chaired by the FDA, the IBS&S, the Scientific Standardization of the International Society of Thrombosis and Hemostasis. Maybe they could come up with recommendations that would be useful here.

The second comment partly follows off a comment that has already been made this morning by the panel and that is the determination of the correct label may not be ascertainable by stopping bleeding alone. The reason for that is that many treatments use excess dose.

Until today, there is no agreement yet on a

minimal effective dose. So what that means is that with a dosage that is treated in excess, if there is a discrepancy that brings it down into a lower range, you may not see that by bleeding studies alone. The impact of short-fall dosages, then, might only be seen with prophylaxis and long-term joint outcomes or low-dose treatments.

I believe that comment follows off the kind of discussion that Dr. Rick started.

It is our thinking that potentially the most responsible way for a manufacturer to deal with this would be that if a product has highly discrepant labels, to assign a potency to the batch that uses the more conservative value to insure that the patient doesn't get into bleeding consequences or long-term treatment consequences over the course of his lifetime.

Thank you.

DR. HOLLINGER: Thank you, Dr. Feldman.

Any questions to Dr. Feldman regarding Centeon's product, the plasma-derived monoclate as it relates to the assay or anything of that nature?

Is there anyone else in the audience who would like to speak to these issues? If so, please do so at this time. Otherwise, this will end the public hearing.

MS. HAMILTON: I am Jan Hamilton, Executive Director of Hemophilia Federation of America. I just have a

question that probably should be addressed by maybe all of those, or somebody maybe can answer it. I am really not clear as to the purpose for introducing this other form of assay, the cryogenic assay, at this time.

Do they feel that it is a better assay than the one-stage and that maybe others should look at that, or is it just their preference?

DR. FRITSCH: We feel that, for the product, ReFacto, the chromogenic substrate assay provides the most appropriate and accurate labeling of the factor-VIII product. Certainly, the data that Ms. Courter showed you, all the clinical studies were based on the label as determined by the chromogenic assay.

Also, we are not necessarily recommending that worldwide treaters switch immediately to the use of that for monitoring their product. The data we have says that the product can be safely and effectively used wither it is monitored by either the one-stage or the chromogenic assay.

MR. NAGLER: My question is just as a matter of agenda. I was wondering if--we have received a lot of information over the last two days and I was wondering if there would be three minutes after lunch in which I could have a moment to address the committee regarding all of the information over the last two days.

DR. HOLLINGER: I think we would like to do it now

because this is the public hearing portion of it. I would like to close it and then open it up later on. We will have some opportunity, probably, to have some comments at that point, if that's okay. That would be okay with me.

MR. NAGLER: I would like to reword some stuff. It is only three minutes.

DR. HOLLINGER: We will give it to you.

MR. NAGLER: Thanks.

DR. ARONSON: I would like to reiterate a statement. My name is Aronson. I am representing myself, and my wife, too. In regard to patient testing, it has always confused me a little bit, but Duncan Thomas, in 1982 in regard to a similar discussion on assay variation, that we don't understand why the hematologists like to always measure things. In fact, there is a new book that says it is because of commercialization.

But, in fact, the clinician, if they want accurate results, should consider the shift to the chromogenic assay. It is very well established that one of the biggest variations in your clinical result is the quality of the sample. That, to some extent, is going to be damped out by the chromogenic assay because of its insensitivity to the products.

The assay has served us well for many years, the one-stage. But we can move on and probably should. And the

clinicians would if the price was right.

DR. HOLLINGER: Thank you for that comment.

MR. CAVANAUGH: Dave Cavanaugh, Committee of Ten Thousand. I don't know if you are going to reopen this after lunch, and it is a question, perhaps, for Dr. McCormick, is to any degree the question about supply as a basis for exclusivity waiver waiting on the decision of this group regarding assay labeling?

DR. HOLLINGER: Could you answer that, at all, Dr. McCormick? It is a little different. It is not dealing just with exclusivity but whether the labeling--I presume you are saying that the labeling is going to make a difference in whether the product is available and if there is a problem with product availability. And that might make a difference.

DR. McCORMICK: Actually, I am probably not the best person to deal with this because it ought to be dealt with by my colleagues in blood products. But the review of this product and its appropriateness for approval and its time to decision is totally and completely controlled by the PDUFA deadlines, the Prescription Drugs User Fee deadlines.

I am not sure exactly what they are specifically for this drug but that is what will determine at what point the drug gets an action of some type, either an approval which means it can go on the market, or a tentative approval

which means that there is some exclusivity issue barring it from going on the market.

But the decision on whether or not it is a safe and efficacious product and adequate labeling is determined--falls within the standard PDUFA deadlines.

MR. CAVANAUGH: Can I just say that I interpret that that the answer is "maybe?"

DR. McCORMICK: The determination on whether or not this drug will go on the market will be made based on the shortage question because I don't think the company is trying to demonstrate that it is a safer product or that it is a more efficacious product. Certainly, the question of shortage has been raised.

The determination on whether or not the product is approvable will be made under the PDUFA deadlines.

DR. PIERCE: I just wanted to ask a question of Genetics Institute. You indicated that the information about the comparative precision of the local one-stage clotting assay in your previously treated patient trial with the central-lab chromogenic assay and you showed that there was, indeed, more scatter with the local versus the central laboratory.

But could you describe for us what the variability was for the--there were three subjects in the surgery trial that you indicated had local laboratory determinations by

the chromogenic assay and, of course, there would be a larger number of samples there.

What was the coefficient of variation for the local chromogenic assay, the ratio of the local chromogenic assay to the central chromogenic so that we could put the greater variability of the one-stage clotting assay, when done locally, into context against the local chromogenic where the limited data are available.

DR. HOLLINGER: I am going to ask you to hold that until we come back, though. That is a question we will deal with right when we get back.

I am going to close the open public hearing for right now. We are going to take a lunch break until 1:30 and we will reconvene here at that time for the committee deliberations.

[Whereupon, at 12:30 p.m., the proceedings were recessed to be resumed at 1:30 p.m.]

AFTERNOON PROCEEDINGS

[1:35 p.m.]

Committee Discussion

DR. HOLLINGER: The meeting will now reopen. We are in the committee deliberations at this point. The question is fairly straightforward for the product. The question for the committee is seen on C55 of their presentation. You have also a separate piece of information on it. "Is the information supplied in the dosage and administration section of the proposed product label sufficient to dose and monitor this product appropriately?"

We can deal with whether tests are appropriately available and things like this at any length, but I would like to open this up now for discussion. If there are questions you have of Genetics Institute, that is appropriate. Otherwise, we will start with Dr. Linden.

DR. LINDEN: I have a question for Dr. Ryan or someone from Genetics Institute. The original submission for the package insert proposed specifying that the difference between one-stage assay and the chromogenic assay was about 0.5. That was later changed to delete that so it gives a lot less information. It just says it is lower.

What was the reasoning for that and how, if at all, do you intend to provide people the information on the comparison between these two assays?

DR. RYAN: I will be happy to answer that question because that was a change in what we had put in the package circular. The data was actually shown by Dr. Fritsch because of the massive amount of variability from center to center in the one-stage assays, we did not feel it prudent to put in any specific factor. It is as simple as that.

I would like to take this opportunity to just mention one thing. We got into a lot of discussions from the end of our presentation until the time we get to discuss the presentation, so I would like to reiterate for the committee that the clinical study reported by Suzie Courter is, in fact, the largest clinical study that has ever been done for a recombinant factor VIII.

We have a significant amount of data demonstrating that both safety and efficacy have been demonstrated using the product labeled by the chromogenic assay. So, in fact, a study has been done, the study that we reported done, using product labeled by the chromogenic assay. And safety and efficacy have been demonstrated even in the surgical setting.

So we very strongly feel that the chromogenic assay for ReFacto most accurately measures the amount of factor VIII in the vial and that dosing, based on the labeled potency, as was shown in our clinical trials, is comparable to other factor-VIII products.

Monitoring, however, can be done either using the chromogenic assay or the one-stage clotting assay as was done in our clinical trials.

DR. KOERPER: Can you tell me what percentage of the patients were monitored in a laboratory that used one-stage in the clinical trials and what percentage were monitored in a laboratory that used the chromogenic, especially in the surgical?

MS. COURTER: For the actual monitoring by chromogenic versus one-stage, it was 99 percent were monitored by one-stage. 1 percent was monitored by chromogenic.

DR. HOOTS: A question in the large tome that we received about the surgical trial, in particular, on page 248 which is page 62 under the GI number, there is a table which compares the means of the patients on the surgical trial by chromogenic and one-stage or chromogenic.

The problem with that comparison, I think, is that as you stated before, it is not clear what percent of each is in the second asterisk; that is, the one-stage method or chromogenic. It gives a feeling that there is not too much difference but then, when you look individual by individual, the differences are greater between the chromogenic and the one-stage.

It becomes important, particularly--I think the

best basis of comparison besides the initial dosing is the week-1 dosage because, obviously, when you are managing the patient post-operatively, you are worried about the nadir level.

Presumably, one of the questions I wanted to ask is do these clearly reflect nadir levels on both the chromogenic and the one-stage and then, in the individual ones that precede this that this reflects the total aggregate of, are those one-stages performed centrally, therefore the variation is low, or are those one-stages that you report for each individual patient done locally compared to the central chromogenic?

The reason I am asking that is because, in most cases, particularly the orthopedics which I looked through there which is really the critical acid test for hemophilia, most cases, even the one-stage, if it was a nadir, was 0.5, just slightly above 0.5.

But, in a few cases, it was down to the 0.3 or 0.2 range. It is really important, I think, to know if that one-stage was something that would be likely to appear out in the real world or if that was a well-controlled one-stage with a well-controlled phosphatidylserine, phosphatidylcholine, ratio.

DR. CHAMBERLAND: From now on I am going to stand up here because I heard about half of what you said because

of the projector. But are you referring to a surgical report, the surgical experience?

DR. HOOTS: Yes; the surgical experience. I don't know if you have the same thing I do but where you delineate each patient and you measure their chromogenic pre-, post-op and one week during surgery--

MS. COURTER: And then the second week post-operatively. Yes. All of the one-stage results were local laboratories so that is absolutely reflective of the real-world situation. You are right, the range we did see of ratio goes all the way down to 0.2 and up to 2.3. It goes the other way, too. And there is variation of the one-stage around the world.

DR. HOOTS: When I looked at the clinical responses, in each case, there was no breakthrough bleeding at those points or at any points you were monitoring or any other points, for that matter; is that correct?

MS. COURTER: Correct.

DR. HOLLINGER: Don, you had had some questions. Do you want to come back to the questions you had had.

DR. BUCHHOLZ: I think the question has been answered.

DR. HOLLINGER: Paul, you had some questions earlier.

DR. McCURDY: Actually, I am concerned about the

potential of products labeled with different potencies being used out in the real world. I am not concerned particularly with the consultants to the committee because they are going to be managing enough patients and have enough experience so they are not the ones that are going to have problems.

What I am concerned about are the patients that are being managed in smaller towns. They may or may not get into hemophilia treatment centers for periodic evaluation and consultation. For them, I am concerned that a transition from one product to another may wind up with mistakes in dosing.

I think we should make every effort to make mistakes difficult rather than easy to make.

DR. HOLLINGER: In some respects, the initial proposal which said it is 50 percent or 60 percent at least gave you a number to work with. The proposed one just says "lower." What is lower? If I see a one-stage and chromogenic is not available, what do I make of that? Or is it saying it doesn't matter? You treat it and you watch and see what they are and you just don't know.

But I don't think that is what is done in the real world in following patients, at least in surgery. Perhaps one of our colleagues, the people here who treat patients, tell us a little bit about what the potential problems are here so we can have a feeling for this if you would.

DR. KESSLER: I think this is the crux of the discussion, obviously. One of the things that bears on this issue is not only the actual care of the patient but also some of the medical-legal implications of dosing on the basis of chromogenic numbers and following the patient on one-stage assays.

For instance, one of the things that is somewhat concerning is the guideline table which is proposed in the package insert in which you discuss type of hemorrhage into minor, major and moderate bleeding.

You give guidelines for factor VIII level required. There should be some modification in this table to indicate that the percentage of factor VIII is either going to be measured by one system or the other because, if you need to reach 100 percent for major GI and intracranial bleeding and you give chromogenic substrate units and only get half of what you expect on a one-stage assay and the patient is still bleeding, that is not only bad for the patient but, obviously, there are medical-legal implications as well.

So I think there has to be some clarification in this situation even though, I have to state, that having used this product in some of the clinical trials, I agree with the idea that all these patients who did go to surgery seemed to do quite well, although sometimes patients, I

think, and maybe you could comment on this, Suzie--how many patients in the surgical trial being monitored with one-stage assays based on the chromogenic substrate administration doses required repeat dosing in order to get to the theoretical optimal level for surgery and whether or not that was triggered by the one-stage assay and whether similar observations and repeat dosing had to be done in the three centers that were basing their administration only on chromogenic assays.

MS. COURTER: I would like to address the surgical. I actually show the data in a summary sense.

[Slide.]

In the surgical trial, everyone was dosed on the label so everyone, to adopt your terminology, got chromogenic substrate units. All doses were done--and not adjusted for what the one-stage meant.

When they were monitored by the one-stage assay, the determined factor-VIII activity for that sample was what they titrated the dose on. So, in other words, with the one-stage assay, you actually saw an increase in dose. On the first day of surgery, in the post-operative doses, you see a higher use of ReFacto when it is being monitored by the one-stage.

Again, these are in the 10 percent of situations where you are monitoring the activity. No patient needed a

second preoperative dose to achieve the targeted level because they were treated to near 100 percent. I assume that, in most of the cases, it was close enough within the 20 percent variability you often see.

But, within that day, they repeat infusions every eight hours to twelve hours to maintain the level. In no case was there breakthrough bleeds or were there any other problems, complications, of the surgery.

Does that address it?

But, now, to go back into the table on how to address the actual targeted correction, with the variability that we observed in patient plasma, we actually don't think we should change the percent target but say, "treat according to the assay that you have."

We just think that you are giving the proper amount of protein on a chromogenic-labeled product like ReFacto.

DR. HOLLINGER: But, in reality, in your summary case, and I just assume your numbers, you would be giving twice as much if you use the one-stage. You would be giving twice as much product as you would need. I am just assuming that it is 50 percent or maybe 60 percent or something like this, but assuming 50 percent, you would be using twice as much product as you ordinarily would need if you used a chromogenic assay.

MS. COURTER: If you used a one-stage assay.

DR. HOLLINGER: If you used a one-stage assay.

MS. COURTER: That is absolutely a possible scenario. It is also possible it is 1 to 1. It is also possible it is a little less. It really is that variable. But yes, in general, you would see a higher use during the times that you were monitoring by one-stage assay.

DR. HOOTS: I just want to get back to Paul's question. Like Craig, we have been thinking a lot about this. I think you have to separate--the first and foremost for us is making sure you have adequate hemostasis. You do that before you ever put on your cost efficacy hat.

I think the good news is, from my perspective, that at least the data that is provided, and I think it is extensive, suggests that what is delivered according to the chromogenic labeled package notation is actually biologically viable hemostatic protein.

It is confirmed to be by looking at both the functional assay, the factor-VIII coagulant assay which measure the protein equivalent. All those things suggest the we are giving what is supposed to be given.

In the worst-case scenario that you were talking about, if you have no experience with taking care of a person with hemophilia and they show up in your emergency room or at your doorstep and you have to treat them as a

physician, if you believe what I just said, then as long as you dose according to the recommended dose, the person should stop bleeding based on all clinical parameters we have.

Generally, that is what happens out in places that don't take care of hemophilia because, by the time subsequent dosing and monitoring comes along, they usually get transferred, fortunately, to hemophilia centers because they feel like they are over their head in the management of that.

At that point in time, at least you do have the luxury of having people available informationally to know that this disparity exists and say, "Do yo want to send the patient here," of, "If you are going to monitor by one-stage, here is what you can expect."

At the very least, if you get 30 percent and you wanted 50 percent, you are erring on the conservative side because your one-stage is going to, most likely, underestimate, not overestimate the reality. Therefore, you have got a little extra window.

The good news, I think, in this particular scenario is for clinical management, the error is in the right direction. If I put on my cost-efficacy hat as a hemophilia treatment center or as a member of blood safety and am worried about usages and availability of product and

how many total units are being used in the United States, then it shifts.

But I think you clearly have to separate those two issues out and I think the committee needs to separate those two issues out. But that is not to say, and I really do believe it is very important, that at some point down the road, we get a better clarification of this so that we can answer both the clinical efficacy and the cost efficacy issue on this product simultaneously.

DR. McCURDY: Keith, what about the group that is between those two extremes, the hemophilia treatment center on the one hand and the no experience on the other? What about the medium-sized town where they see hemophiliacs and they treat them but they don't have your experience and your background.

DR. HOOTS: I think, in that case, they are going to clearly, unequivocally, at least in 1999, they are going to be using a one-stage assay because almost no one has chromogenic available outside of the most sophisticated research hemophilia centers.

Therefore, if they dose according to the package insert as proposed, a patient comes in with a massive intracranial hemorrhage, they are going to 50 units per kilogram. They are going to get 100 percent, approximately, but, because of the recovery, they may actually only get,

when they measure it, 70 percent. It comes back 70 percent at the peak and then, certainly, if they wait twelve hours, which is the half life to give the next dose, by that time, they may get a scary level back.

It may be 30 percent. And that is what I was saying. The good news is that, if it were measured another way, it would actually be higher and the patient is actually at less risk than they were perceived. But since they perceive that there is a risk, they are going to redose at a higher dose then they would otherwise do, which, again, from a clinical standpoint is good because the patient is, therefore, likely to be, instead of 30 percent if they were truly 50 percent.

And then they dose again to make up for that increment, they are going to end up well over 100 percent after the second dose. So each time, the error is always in favor of the patient, I think. It would be far worse, it seems to me, if the coefficient of variation were bidirectional.

As long as it is in one direction, at least it is easier to protect the patient which is, I think, what our number-one priority here is.

DR. KOERPER: The issue is exactly as Keith said. The issue is with monitoring patients when they are in the hospital. When we have patients who are on home therapy, we

have calculated a dose. They give their dose every other day or when they have a bleed. If they are on prophylaxis, and they don't have breakthrough bleeding between their two doses, we assume we have given enough. We are not having them come in frequently to check their trough levels.

But when we have patients who are in the hospital with major bleeding episodes such as intracranial or post-operatively, that is when we are measuring these levels at least on a daily basis. Those of us who have seen all this information and understand that if I give a dose of 50 units per kilo, I expect my peak to be 100 percent and it is only 50 percent, but it is because it has been done by a one-stage, I may know to multiply it by 2 but someone who is covering for me, even, while I am out of town at this meeting, may not realize that and may redose.

But the other problem is I don't know what that multiplication factor is for my laboratory as opposed to some other laboratory. Someone suggested this is like having an INR. In other words, you have a fudge factor and, as long as you multiply what result your lab gives you by that fudge factor, that ratio factor or whatever you want to call it and you end up with the number that you wanted to have, then you look like you are fine.

But I don't know what that fudge factor or that ratio is for my lab unless I can get my lab to set up the

chromogenic assay and, on a single specimen, assay it both ways and tell me what the factor is.

If they are going to go to the trouble to set it up for that, then they might as well do all the assays by the chromogenic. So this is the real issue, I think, right, that in each individual laboratory, we don't know what that ratio or that factor is.

Now, five or ten years from now, it may be that most large hemophilia centers, large medical centers, will have switched to the chromogenic assay. At that point, this may become a moot point. But, between then and now, I am not quite sure what I can do, how I can adequately monitor my patient.

Craig alluded to the fact that medical-legally, if I have trough levels that, instead of 50 percent or 25 or 30 percent, and someone comes in and reviews this chart who doesn't know that I know what I'm doing, they don't know about this ratio factor, they then see that I was only letting the trough levels come to 25 to 30 percent.

It becomes awkward. I think that is the dilemma that most of us clinicians are facing right now. I believe that the product works. I believe if I use the dosage on the bottle or the box and do my calculations, I am going to get an adequate dose.

But it is proving it in the laboratory and in the

chart that becomes and issue for us right now.

DR. RICK: I think we are back to the original question which is how much we need, really, replacement, what percentage we need to reach for or different bleeding problems we see in the patients. Clearly, it is going to be different for different types of bleeding in different areas of the body.

That really hasn't been determined strictly. I don't think that we should be asking one particular company to do that. Those are not the implications of what I am saying at all. In fact, they have shown that there is good efficacy in the dosing that they have used.

However, as you are pointing out, there are a lot of ancillary problems that go with this because the recommendations for the last 40 years have indicated that levels of 25 or 50 or 75 percent should be attained to insure adequate hemostasis.

I guess one question that comes to my mind, and I have no idea of the answer at this point, is in terms of our one-stage assays that are being utilized in this country, how many different types of phospholipid and other reagents are we actually using and is there any way to determine the likelihood of a ratio between the chromogenics and the one-stage assays with these reagents, chromogenic versus a one-stage with certain reagents versus other reagents.

That may be too much to be asking but that is really the only way we can sort of solve this problem in the interim until we all get chromogenics which, I think, clearly are the way of the future and will be a better assay.

DR. HOOTS: To follow up what Margaret was talking about, I'm sure we all have anecdotes but I am absolutely sure that the variability on the phospholipid is quite extensive across the United States. Working in two institutions, it is variable between just two institutions and the PTT normal range is probably--you can't necessarily infer from that that it is all because of the phospholipid.

But, certainly, they are all kind of calibrated into their own little specific range. Most of us have had experiences where the lab changed a reagent without telling you. And suddenly you start overreacting or underreacting to certain things. So it is problematic.

DR. STRONCEK: I guess I agree with what most everyone is saying, that this looks like a good product and it sounds like eventually it may end up licensed if they can get around the orphan-drug issue.

I think the way the product insert is written is honest based on the data but it sounds like, because of the problem with the lack of availability of the chromogenic assay that there needs to be a little more information in

the product insert concerning that the data was obtained for the drug using the chromogenic assay and it is very difficult to correlate the results of the one-stage and the chromogenic.

It sounds like, until we get to the point where more labs have the chromogenic assay, it would be worthwhile for the clinicians to have more detailed information.

DR. MITCHELL: I agree with that. I think that, instead of putting a single figure, though, it might be better to put a range, to say that when you use a one-stage testing, it may give results from 50 percent to 75 percent of the chromogenic result.

I guess I have a question as to how much physicians know about what the laboratory is using to test for PTT and whether they know whether one-stage is a PTT or what. Again, I am not in clinical medicine right now but when I was there, we just ordered a PTT and we didn't say whether we wanted a one-stage or a two-stage or a chromogenic.

So I think that that also is going to have to be defined in the package insert if there are people like me who--not that I would treat a hemophiliac--but who might happen to come upon a hemophiliac and there may be no other options.

DR. HOLLINGER: Along those same lines, do we,

then, potentially assume too much, that people who are taking care of patients who need clotting-factor concentrate of some sort that they are just going to know this, that almost all these people are going to know it?

That is sort of what our assumption is that they are all going to be taken care of people like you or hematologists that certainly know what is going on. But I presume there are times, obviously, like you just mentioned, that that might not be the case.

DR. ELLIS: I would like to say that there really is sort of precedence, I think, for using products, replacement clotting-factor products that may not fall within the conventional idea of dosing. For instance, recombinant factor IX has variability from individual to individual as far as its recovery is concerned--that is, the incremental increase in factor IX activity after giving a calculated dose.

Yet, in that particular product, there is a fudge factor given of sorts to try to overcome some of that uncertainty. In the real world, what most physicians have done, however, is, prior to administering recombinant factor IX concentrate, most patients are tested during a basal healthy state to see what their actual response would be to a particular dose so that, for all future usage, then they would know what their particular use was as well.

I am wondering whether a similar type of approach is going to be, I think, adopted by most clinicians who use this product as well to be able to make sure that the assays that they are using in their hospital will somehow have some relationship to the dosing that the physician is going to prescribe for that patient in any particular clinical situation.

DR. OHENE-FREMPONG: As I remember, in most cases, patients are treated with replacement factor, there is no monitoring of the results in terms of factor level. The only times when they are monitored is when a patient is going to receive it repeatedly or in preparation for surgery to determine how much to give.

The patient and the family can be educated to know how much to use for any type of bleeding. The treatment center, hemophilia center, knows very well how to reassess any new product and recalculate with the patient needs. It is the clinical situation in between these two, the emergency departments that see a patient who has a knee bleed and they just need to give one treatment.

They don't monitor that treatment but they have been taught, the physicians have been taught, that you calculate a 30 percent correction by multiplying this factor by what you need and that's it.

If those need to be retrained or they have to be

trained to read an insert on any new brand in order to administer the product, that is where I see the problem. But, in terms of what the family knows that this child will receive or this patient received, or what the treatment center that is going to direct the surgery, most often it is not the surgeons who are monitoring the results of replacement factor.

It is the hematologists who do it most of the time. But it is the one-time physician who may have learned, and thinks that all factor-VIII products or all factor-IX products are similar and you calculate using this set formula.

Those are the times when I think patients may end up being either undertreated or overtreated based on the new formula called for by the new product.

DR. HOOTS: I think, just to reiterate what I said before, most of the time, they are going to overtreat not undertreat if they do that. But one of the things that I think, without getting--and I am not the person to do it anyway, but without getting too far into arcane pharmacokinetics with this stuff, looking at what was supplied to us in terms of the pharmacokinetic data and areas under the curves and maximum areas under the curve, et cetera, it suggests that--one thing is clear is that the half life is equivalent between the products either way you

measure it.

That really becomes important for the complex management of surgery and severe life-threatening bleeds. Those of us who do that can be reassured with that because we can adjust the baseline accordingly regardless of which absolute recovery we are measuring, chromogenic versus a one-stage aPPT.

So I think one of the things, and it is not, probably, part of what was proposed today, but one of the things, as we think about what could be done to help this situation would be that, perhaps, if this biologic is licensed and put on the market, is for some phase IV studies, particularly, to look at things like continuous infusion because we would predict, if everything that has been said today is true, that if we adjust the recovery upward and then just maintain the same units per kilogram for twenty-four hours, we should be able to maintain an adequate level once we have adjusted the baseline and then total usage really is not dramatically affected over a two-week surgery post-op, or that sort of thing.

So I think those are the kinds of things that it would be nice to absolutely demonstrate. I know they are not asking for an indication for continuous infusion, but those kinds of pharmacokinetics would be really helpful in helping us to make sure that what we think is true is

absolutely and impeccable truth.

DR. VERTER: I don't think it is possible, from the data I have seen here today, to add to the label a factor. There is too much variation between local, central, who is doing it, who is not doing it.

My question to someone is what is the effect on the patient of getting between 20 percent more than he or she needs or doubling. Is there any potential side effect of that?

DR. HOLLINGER: In terms also of inhibitors or things like that.

DR. KOERPER: There is not adverse effect to the patient. If their factor level happens to be 150 percent instead of 100 percent, they will be fine. It is not going to increase the rate of inhibitor formation.

The issue is the cost. This product is going to be fairly expensive. So the insurance company will be paying more money. And the other issue is supply, and it will be used up quicker.

DR. VERTER: But there is not a problem of overdosing toxicities?

DR. KOERPER: No; they are not going to go into DIC or something like that from overdosing.

DR. HOLLINGER: Marion, maybe you can tell me, then, why patients develop inhibitors.

DR. KOERPER: There is a major nationwide study trying to answer that question. We don't know. About 25 percent of newly treated patients develop inhibitors after their first ten to twenty exposures to the product. Some of those are high-titer, long-lasting inhibitors which are major problems for treatment.

Others are low-titer or transient inhibitors that will go away. But the vast majority will appear by ten to twenty treatment dosages. So, once you get beyond that, for a severe hemophiliac, that is easily achieved within the first year or two of life. If they haven't developed it, then the number who are going to develop it beyond that is very, very small.

DR. CHAMBERLAND: Just to follow up on an earlier comment, I was wondering about the comment that you might have to start changing people's behavior if they have been using a product for a long time or they use it infrequently and they assume that all products are created equal with respect to the issues that are being raised.

I wonder if any consideration had been given to committees being asked to address the label, whether the package-insert labeling is sufficient. Is there any way envisioned to try and draw attention--people who using this product to draw their attention to the fact that something is different or something has changed.

Most physicians, especially if they think they know the product they are using, will not read a package insert. So it seems to me that you have to rely on some sort of a visual cue on the bottle, on the package, something that could clue you in that you might need to pay attention that something has changed.

I wonder if there was any thought or consideration about that.

DR. RICK: I don't think there has been anything with regard to factor VIII. But, certainly, we have another example in the use of the INR here in the states which wasn't used for many years and then was finally adapted. I believe that was done most widely through, of course, some publications, but within each hospital, by committees and educational committees, that simply got physicians together and taught them.

When we change assays in the lab, that has to be done and it has been done and can successfully be done, not without some difficulty but it can be done.

DR. CHAMBERLAND: I was going to ask that, so I am glad to hear there is some precedent, but it seems to me that INR is more of the universally used test with the PT, PTT, kind of thing. Physicians across many specialties might be ordering that test whereas this might be more of a focused group of users.

The point is, it could be easier. But I guess the comments about physicians in smaller hospitals that are not seeing large volumes of patients, that was just one thought; is there any way to sort of visually cue people more than just what might be in a package insert.

DR. KESSLER: I think that is a very important point because right now much of our ordering is in a generic form. When you order from a home-care company or order from a pharmaceutical, you order recombinant factor VIII. Now we have a recombinant factor VIII which is not like other recombinant factor VIIIs.

So I think that there is going to have to be some mechanism on both the mentality of reimbursers as well as the mentality of physicians and patients when they get a factor VIII, a recombinant factor VIII, that this is different from the other two that are on the market.

There is another point that I wanted to ask. Perhaps the GI group can answer this. On the proposed package insert, there is a comment that states that if the inhibitor is present at levels of less than 10 Bethesda units per ml, administration of additional antihemophilic factor may neutralize the inhibitor.

That is a little higher than most of us usually consider to be a neutralizable inhibitor level. I am wondering whether or not the Bethesda assays were done using

the chromogenic assay or whether the inhibitor levels were done using a plasma-based one-stage assay and whether you have any in vitro or in vivo data that you can overcome inhibitors at 10 Bethesda units.

DR. MIKAELSSON: I am Marianne Mikaelsson. The Bethesda assay is performed with the chromogenic substrate assay. But we have validated the assay in collaborative studies with Chapel Hill running a Bethesda with the one-stage assay. So the results agree very well.

In the Bethesda, we also run samples with normal plasma as a test base and also samples where ReFacto is diluted into severe hemophilia A plasma as test base.

DR. KOERPER: Why did you choose the number 10?

MS. COURTER: Again, that was standard of care. That is what has been in package inserts for several years. I think the challenge is what do you do between 5 and 10. I agree.

DR. HOLLINGER: I notice in your proposed labeling, at the bottom, where you are talking about the values are lower, and this was brought up a little earlier here by one of the other discussants, it says the one-stage clotting assay yields results which are lower than the values obtained with the chromogenic assay. It says; see clinical pharmacology.

I don't see anything. Maybe I missed it. I don't

see anything in the clinical pharmacology that discusses the one-stage or the chromogenic assays and the issues related to that. Maybe I don't have a more up-to-date one but it is the one that was sent to us.

MS. COURTER: I think that is exactly what you are missing is what we have done. The one that was sent out originally to you was the original language where we still had the 50 percent wording under the dosing section. Again, we wanted to move that our of there to not temp people to use the factor of 2 and find out that their laboratory was not, in fact, that factor.

So we moved it to the clinical pharmacology where we showed, in the PK study, in a well-controlled central lab, a level of approximately 50 percent.

It is appendix 4 in your black briefing book that you got. What you would do is you would count five gold pages, I think. You kind of go toward the back of the briefing book, count four gold pages in and the section starts saying "Advisories." Page 18. Second paragraph, where we describe the pharmacokinetic study.

And then we have, in bold, highlighted that we see an assay--

DR. HOLLINGER: I didn't see that. I looked at this other one that we received.

DR. OHENE-FREMPONG: A question on the inhibitors.

In general, in managing inhibitor patients, the advice is not to just increase the dose. You said something about 27 percent of your patients, the previously untreated patients, developed inhibitors.

Can you characterize the types of inhibitors? Would this be low-titer, high-titer inhibitors and whether the advice to increase the dose would apply to even the high-titer ones?

MS. COURTER: Sure. Could I have slide B6. They are broken out by high and low titer.

[Slide.]

Can you see that? Just to reiterate the pieces of information I had already given you is that, out of the 97 patients, 27 patients did develop inhibitor. The maturity of the dataset was at a median of 19 exposure days and the median exposure date to inhibitor development was 12 days with a range from 5 to 50.

Of the 26 programs that developed inhibitor, 9 percent developed a high-titer inhibitor as defined as greater than 5 Bethesda units. And 17, a low titer, or 18 percent, a low-titer inhibitor.

Ten of those patients, to address treating particularly the high titer, they did not try to override the inhibitor for acute episodes. In fact, they would use bypassing agents. But many of the patients did go on to an

immune-tolerance regimen where they tried to eradicate the inhibitor.

We had ten patients that were on that kind of therapy and six of the high titers received that in the intolerance. And three went to negative. One turned the low titer. And the other went off the intolerant.

The low-titer inhibitors were also treated with immune tolerance.

DR. RICK: Moving away from the inhibitor question back to the question about the label, I would like to support what Dr. Stroncek mentioned. I think that, to say in a label that one-stage assays are "lower" than the chromogenic would add very little information for the physician. I think that, for medical-legal reasons, people would be very reluctant to allow that to be their dosing. I think they would go to their one-stage assay and overtreat most of these patients.

I think the variability question that was brought up and the concerns about trying to chose a range is very real. I think, however, that some of that one-stage variation with the chromogenics would also be found in different one-stage to one-stage assays in different laboratories.

So some of the variability, I think, comes simply from the laboratories using similar methodology, perhaps

different reagents.

I do think that maybe some effort could be made to at least get some range with different factor-VIII assay reagents in the one-stage assays to be able to give some information about a range of one-stage assays versus the chromogenic by which this is labeled and that that would assure physicians some information and, perhaps, defense in medical-legal problems should they occur.

DR. KAGAN: I was wondering, in the national hemophilia centers, what is the availability of the chromogenic test? Is it really only for a research basis? Is it frequently available, infrequently available?

DR. KESSLER: Infrequently available except for research purposes and the practicalities are as follows. The cost of a chromogenic factor-VIII assay is approximately two-and-a-half times more than a one-stage factor-VIII assay.

In this era of cost containment and an era in which laboratories are marginally staffed, the amount that is necessary to institute this test has been considered exorbitant. I think that, in the ideal world, it would be very nice to have chromogenic substrates. I agree with Dr. Rick that, for any coagulation-factor assay, that that is probably a much more accurate assay than all the vagaries that are involved with the one-stage assay.

But, unfortunately, that is not the reality of the situation right now.

DR. McCURDY: I have a couple of more comments. One of them is we have spent a fair amount of time, including myself, talking about physician errors. I guess, as has been brought up, a fair proportion of patients with hemophilia treat themselves at home. Going in one direction for one product to another, they might overdose which is only dangerous to your pocketbook, I guess.

But going in the opposite direction, they could underdose. It might be of some import to provide some type of an alert to the patients or maybe you would have to educate them. I seem to recall--I don't know much about it recently, but there have been diabetics who have gotten into trouble by changing the doses, the concentration of insulin that they use, and using the same volume of double concentrate and getting into difficulty.

I think that most of them are now trained or maybe the doses are all the same now. I don't know. That's one thing. Then the other thing that occurred to me--Dr. Feldman, I think, from Centeon raised the possibility of some type of a conference that might look at the pros and cons of the chromogenic assay versus a clotting-based assay.

If the chromogenic assay were likely to become pretty universal, then the price would likely come down. At

least that has been something that has happened in the past. I think if there were some interest in that at the level of the FDA or other portions, the NHLBI, at least would be willing to discuss the possibility of such a conference that might come up with some recommendations that could be published.

MS. COURTER: If I could address your first issue about the patient treating at home. I actually don't think the patient treating at home would treat differently. It is only in the monitoring situation that this assay artifact appears.

At home, what the previously treated patient data showed you is that the same dose as was used with products labeled on one-stage was used with this product labeled on chromogenic. We saw a similar efficacy profile. So it is not confusing to the patient in the home setting.

It would be when you have that plasma factor-VIII activity in front of you after you gave a dose as to how that would relate one-stage to chromogenic.

DR. FRITSCH: Also, to maybe comment on the second part of the question, certainly the appropriate assay to use has been an ongoing discussion for a number of years and primarily climaxed, I think, at the SSC a number of years ago. But they did recommend the chromogenic assay.

But, since then, of course, there is still the

issue of what is the right standard to use and it has been an ongoing debate. So I think this is still progressing. I think I agree with Dr. Kessler, the biggest problem is cost and then just the inertia of overcoming the fact that everybody is currently using the one-stage assay.

But, ultimately, we believe that the chromogenic will be the most appropriate assay to use.

DR. HOLLINGER: Some of it is very similar to what I view as sort of heparin or low-molecular-weight heparin. In heparin, you would use a PTT to see what is going on. In low-molecular-weight heparin, I understand, you are using factor Xa. You have an assay sort of for that or something else, but physicians still have to know that.

To them, many of them, they are using heparin. They might say, "Well, I can monitor this with a PTT," when they use the low-molecular-weight heparin. So it is a matter of physician education that has to be done here.

Somewhere or other, the question is on the labeling for this stuff, does this have to be--how many of the physicians would look at the insert if it was in the insert versus whether it ought to be on the box and say there are some differences here.

Fortunately, I think what Dr. Hoots has mentioned, and others here, is the fact that it does seem to me that the error is in the right direction. That is probably a

critical issue here more than anything else.

DR. HOOTS: In terms of how would you address your concern outside of the major life-threatening and surgical-- I think it may have Dr. Feldman or Dr. Gomperts, I can't remember who, but somebody suggested this morning a very good way to assess it which is since now children, by and large, are on prophylaxis, a very good way would be to do a random crossover study between full-length factor VIII and b-domainless factor VIII and look for breakthrough bleedings over a year or two or three.

You would expect, if everything we have heard today is accurate, that there would be zero difference if you dosed according to the chromogenic for this product and the one-stage label for the other product.

DR. KOERPER: To answer your question about the physician reading the package insert, most of the time, at least in this setting we are talking about with the patient on the ward or in the operating room, the physician is not even the person who is mixing up and administering the factor. It is the nurse who is doing that. The physician writes the order and then walks away.

The physician may not even realize whether the patient is getting ReFacto versus Recombinate or Kogenate unless they have taken the time to call the pharmacy and say, "Which product are you presently stocking in the

pharmacy?"

So physicians, I would say 90 percent of the time, are not even the ones who are handling the box and doing the reconstitution.

DR. CHAMBERLAND: Actually, I was thinking the very same thing after I made my earlier comment that you have to know what is on formulary in your institution and then you have to know specifically what that particular patient you are ordering is getting. I don't even think this is possible, but it is almost when the results come back of these tests that you need to have in parenthesis what the normal range is and it would vary depending on the product that is being used.

DR. KOERPER: But then the laboratory has to be told what the patient is using. We even have trouble with the laboratory understanding whether the patient is on heparin or not, whether they need to add HepAbsorb to the specimen because the patient is on heparin.

So, trying to get the lab to be clued in on what product the patient is on is going to be very difficult. And what product the patient is getting might vary from one day to the next depending on what the pharmacy chooses to send up, depending on what dose was ordered for that day.

DR. RICK: I think that is true. I think, however, that with the computer age, most of us are finding

that we are putting our orders into a computer. That page can be modified very easily to not accept your order unless you put in the information.

But you are right. If the pharmacy has several different items they are using, then it is a problem. However, I think you could probably get around the practical issue.

DR. KOERPER: It is not a problem for those of us sitting at this table. The issue is for the people who are not as intimately involved in hemophilia care as those of us sitting at this table.

DR. RICK: Right. But I think most hospitals do have a computer system now and I think that part we could probably, with some manipulation, work out. It maybe would make people aware more of what is going on as well, part of the education process.

DR. KOERPER: Exactly.

DR. RICK: And the results, again, in those pages that are returned would have to indicate what level, perhaps, if you are using a one-stage, ReFacto versus others. It should be on the insert that way as well.

DR. HOLLINGER: I am going to call for the question to be voted on here. Actually, the FDA has heard many of the comments here. I think one of them, most importantly, Craig brought up very nicely, has to do with

that table which might be confusing in terms of the percent that you are shooting for particularly with this product.

But the question is fairly straightforward. I would like to see at least us vote on it and then decide if there is anything else that needs to be done or add to it. You all have the question in C55 which is, "Is the information supplied in the dosage and administration section of the proposed product label (attachment 2) sufficient to dose and monitor this product appropriately?"

But then they used a proposed labeling difference that they would like because attachment 2 talks about 50 percent of the values.

Now, the paragraph which they have on C57, I think is what they expect to be and what would have been attachment 2--correct me if I am wrong--which is that they take out the 50 percent. The rest of it is essentially the same with a few minor derivations. But, basically, it says that the one-stage clotting assay yields results which are lower than the values obtained with the chromogenic assay rather than consistently yields results which are approximately 50 percent of the values obtained with the chromogenic assay.

MS. COURTER: May I just add one clarifier. We moved the 50 percent into the clinical pharmacology section and bolded it.

DR. HOLLINGER: Which we looked at just a few minutes ago.

So with that change in mind, I would like to see if the committee would vote on this. I would like to ask if those who agree, are going to vote yes on, is the information supplied sufficient to dose and monitor this product appropriately as found in this proposed labeling which is in C57, to raise your hand.

[Show of hands.]

DR. HOLLINGER: Those who disagree with the statement.

[Show of hands.]

DR. HOLLINGER: Those abstaining?

[One hand raised.]

DR. HOLLINGER: I will ask Dr. Smallwood to read the results of the voting.

DR. SMALLWOOD: There are eleven members here that eligible to vote. The voting is as follows. There were seven "yes" votes, three "no" votes, one abstention. The consumer and the industry reps voted in favor if they could have voted.

DR. VERTER: I would like to ask the indulgence of the committee for two minutes to make a statement to the FDA. If this were down on the Hill, and I hate to use that analogy, anything that the witnesses brought forward, even

though it wasn't in the prime question, we would be allowed to cross examine, so to speak.

I feel particularly frustrated but I didn't bring up the comments during the regular discussion because the question was very specific. It said, "In the dosage and administration section of the proposed product." My comments couldn't, in any way, shape or form, be bent into those sections.

However, I would like to give the FDA some advice which they probably already had from their own people, but there were a number of things in the proposed label, the entire label, which I would take some issue with.

There are statement in there which suggest comparisons. There were no comparisons presented here today with other products. There were a couple and, in fact, the one or two that you could look at, you could actually make an argument that the other product may be better that, for instance, the percent needing only one dose to resolve bleeding.

There was one slide which clearly suggested to me a highly significant difference between this product and the other product. The presentation of some of the safety data, I think, while complete, was not quite the way I would like to see it. I always like to see it on a per-patient rather than over 23,000 days of dosing although I understand why

that is done and I am hopeful the FDA will take a look at some of that.

It is just the continuing frustration that I have expressed before in this committee that the standard of evidence for what is called clinical trials in this committee I think is quite different from the standard of evidence that is used by other FDA committees in phase-III clinical trials.

I understand that this is an orphan-drug situation, that there are, at most, 15,000 to 20,000 patients who may be eligible instead of a half a million a year who have MIs or 450,000 who have CABGs or coronary bypasses, but I still think that, within the confines--you guys are up to bat today but, clearly, there were two others who got products on the market that I didn't get a chance to critique so please try not to take it personally, but I think there is a real need in the blood-products area to design better studies.

I think there is an opportunity to do trials with better comparisons. You may have to go to something which are called the historical comparisons which are very difficult to do and much harder than a truly randomized trial. But I think, even within the fields that you are dealing with, there is an opportunity to design and carry out better phase-III randomized trials which would better

serve the public.

Thank you.

DR. HOLLINGER: Thank you, Joel.

DR. OHENE-FREMPONG: Joel, just a little comment on that. I am not sure whether there was any comparison between this product and another recombinant.

DR. VERTER: Yes; there was.

DR. OHENE-FREMPONG: I thought it was mostly plasma-derived.

DR. VERTER: No. It is on C41, I think. Look in the booklet. There was a comparison between some sort of--one bleeding episode or two bleeding episodes. There is also another comparison further on. There are two or three of them. They weren't stated that way, by the way, with significance tests. I did the tests.

DR. HOLLINGER: Does anyone else wish to make a comment before we adjourn this meeting? I want to remind the committee members that the next planned meeting for the Blood Products Advisory Committee is on March 25 to 26 of 1999, a tentative date. Dr. Smallwood will be getting back with you again.

If there is nothing else, then this meeting is adjourned.

[Whereupon, at 2:40 p.m, the meeting was adjourned.]

CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

Alice Toigo

ALICE TOIGO