

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

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Pages 1 thru 187

Rockville, Maryland
December 11, 1998

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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.
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Linda A. Smallwood, Ph.D., Executive Secretary

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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

Welcome and Opening Remarks: Linda A. Smallwood, Ph.D.
Blaine F. Hollinger, M.D.

**IV Inadvertent Contamination of Plasma Pools for
Refractionation (HIV, HBsAg, HCV)**

Edward Tabor, M.D.

Open Public Hearing

Committee Discussion and Recommendations

**V Recombinant B-Domain-Deleted Antihemophilic Factor,
ReFacto, Genetics Institute**

Introduction and Background
Andrew Chang, Ph.D.

Sponsor's Presentation, Genetics Institute

Introduction: Frederick T. Gates, Ph.D.
Background: John L. Ryan, Ph.D., M.D.
Chemistry, Manufacturing and Controls:
Ed Fritsch, Ph.D.
ReFacto Clinical Experience:
Suzanne G. Courter, B.S.N.
Summary: John L. Ryan, Ph.D., M.D.

Review of Orphan Drug Provisions:
John McCormick, M.D.

Open Public Hearing

Committee Discussion and Recommendations

1 P R O C E E D I N G S

2 Welcome and Opening Remarks

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

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

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

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

1 Dr. Chamberland.

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

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

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

22 Thank you.

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

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

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

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

15 Thank you.

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

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

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

4 So, Dr. Tabor?

5 **Inadvertent Contamination of Plasma Pools**

6 **For Fractionation (HIV, HBsAG, HCV)**

7 DR. TABOR: Good morning.

8 [Slide.]

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

11 [Slide.]

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

25 There is a third area of inadvertent contamination

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

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

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

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

24 [Slide.]

25 This flow chart shows an outline of the

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

10 [Slide.]

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

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

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

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

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

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

19 [Slide.]

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

1 [Slide.]

2 The safety of albumin was recognized quite early.
3 For instance, in a study conducted by Paine and Janeway
4 reported in 1952, they studied 237 albumin recipients who
5 received albumin from 92 lots. They expected a very high
6 rate of hepatitis which was defined by the presence of
7 jaundice at that time because testing for the viruses was
8 not available, and they expected to find jaundice in
9 39 percent of recipients because of the high prevalence of
10 icteric plasma in the donor pool and because of the large
11 number of units entering the pool.

12 In fact, of the 33 recipients who received only
13 albumin, there was no jaundice observed at all and, even in
14 204 recipients who received albumin plus other products,
15 only two had jaundice.

16 [Slide.]

17 Volunteer studies were conducted in the '40s and
18 '50s that also showed that albumin and, particularly, heated
19 albumin, was safe with regard to transmitting hepatitis B.
20 Gellis, in 1948, reported studies in which an infectious
21 plasma was put in an albumin preparation and heated at
22 60 degrees for ten hours.

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

1 material developed clinically recognizable hepatitis.

2 [Slide.]

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

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

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

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

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

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

18 [Slide.]

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

25 This, again, underlies the fact that just

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

8 [Slide.]

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

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

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

1 [Slide.]

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

11 [Slide.]

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

19 It is worth noting that the maximum titer found
20 in infectious plasma during HIV infection is 10^4 infectious
21 doses per ml. In fact, it is usually never higher than 10^3
22 infectious doses per ml. Therefore, heating HIV for only
23 one-sixtieth as long as we heat albumin can inactivate one
24 log greater titer of HIV than is ever found in infectious
25 plasma.

1 [Slide.]

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

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

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

22 [Slide.]

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

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

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

12 [Slide.]

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

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

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

6 [Slide.]

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

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

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

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

8 Despite this, there has been no transmission since
9 1994 by intravenous preparations and that is because viral
10 inactivation procedures have been instituted by all
11 manufacturers since 1995. The final product has been
12 screened by HCV-PCR since 1994 by FDA and later by the
13 manufacturers.

14 [Slide.]

15 In the Gammagard outbreak, as I said, HCV was
16 transmitted by the intravenous immune globulin. In one
17 study of a small group of patients, it was found that
18 11 percent of recipients were infected. Whether the
19 recipients were infected was dose-dependent and was related
20 to how much HCV they received with the globulin.

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

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

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

11 [Slide.]

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

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

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

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

7 [Slide.]

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

17 [Slide.]

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

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

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

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

9 [Slide.]

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

16 [Slide.]

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

23 [Slide.]

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

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

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

8 [Slide.]

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

16 In addition, the lyophilization of these products
17 has also been shown to remove some HIV infectivity between
18 10^1 and 10^4 infectious doses per ml in addition to that
19 provided by the manufacturing processes.

20 [Slide.]

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

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

3 [Slide.]

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

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

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

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

1 [Slide.]

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

6 [Slide.]

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

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

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

24 [Slide.]

25 It is possible that better techniques may be

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

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

10 [Slide.]

11 I am just going to very briefly summarize the
12 recommendations of BPAC in June of 1997 and September of
13 1997. In June of 1997, BPAC recommended that, when notified
14 of inadvertent contamination of a fractionation pool with
15 units reactive for HBV, HCV or HIV, FDA should immediately
16 and uniformly quarantine or recall all products as a first
17 step and then determine regulatory action based on an
18 assessment of product risk, meaning based on the impact of
19 virus removal or inactivation.

20 [Slide.]

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

1 infection.

2 [Slide.]

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

10 [Slide.]

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

17 [Slide.]

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

22 [Slide.]

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

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

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

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

14 [Slide.]

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

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

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

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

10 [Slide.]

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

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

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

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

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

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

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

20 [Slide.]

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

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

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

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

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

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

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

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

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

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

7 **Open Public Hearing**

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

12 Dr. Morgenthaler?

13 DR. MORGENTHALER: Good morning.

14 [Slide.]

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

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

1 to qualify as inadvertent contamination.

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

6 [Slide.]

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

15 Accident victims, for instance, may receive up to
16 100 erythrocyte concentrates and the chance of survival is,
17 nevertheless, very poor. Or, third, there are no other
18 components to transfuse; for instance, when source was
19 obtained.

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

1 manufacturing process.

2 [Slide.]

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

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

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

22 Thank you for your attention.

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

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

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

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

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

1 of plasma-derivative products.

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

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

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

25 BPAC should urge CBER to develop such planning

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

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

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

20 DR. HOLLINGER: Thank you.

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

24 Yes?

25 MR. NAGLER: Rick Nagler from the Hemophilia

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

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

14 DR. HOLLINGER: Thank you.

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

18 **Committee Discussion and Recommendations**

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

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

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

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

19 DR. EPSTEIN: Very often.

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

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

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

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

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

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

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

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

1 for the other types of inadvertent contamination.

2 DR. HOLLINGER: Questions?

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

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

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

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

1 something we can modify.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 concern.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 nature.

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

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

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

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

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

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

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

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

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

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

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

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

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

1 episode.

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

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

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

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

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

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

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

16 So that is the way we are going.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 The question does tend to sort itself into two

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

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

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

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

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

24 DR. KOERPER: Okay.

25 DR. EPSTEIN: There was simply antibody and

1 antigen tests.

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

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

5 DR. KOERPER: But that is coming into place.

6 DR. EPSTEIN: Yes.

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

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

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

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

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

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

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

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

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

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

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

1 from this country to other countries. Are the practices the
2 same for European or South American, whatever, manufacturers
3 in other parts of the world as they are in this country?

4 And, if so, does the FDA have any regulatory--

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

20 [Break.]

21 **Recombinant B-Domain-Deleted antihemophilic Factor**

22 **ReFacto, Genetics Institute**

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

1 record.

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

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

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

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

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

1 address today.

2 **Introduction and Background**

3 DR. CHANG: Thank you, Mr. Chairman.

4 [Slide.]

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

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

15 [Slide.]

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

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

25 [Slide.]

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

7 [Slide.]

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

10 [Slide.]

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

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

22 [Slide.]

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

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

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

6 [Slide.]

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

11 [Slide.]

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

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

25 [Slide.]

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

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

15 [Slide.]

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

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

25 The committee is being asked to comment on how the

1 discrepancy in assay results may affect dosing
2 recommendations.

3 Thank you.

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

9 **Sponsor's Presentation**

10 **Introduction**

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

13 [Slide.]

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

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

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

5 [Slide.]

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

10 **Background**

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

17 [Slide.]

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

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

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

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

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

15 [Slide.]

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

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

1 [Slide.]

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

6 [Slide.]

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

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

21 **Chemistry, Manufacturing and Controls**

22 DR. FRITSCH: Thank you John.

23 [Slide.]

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

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

13 [Slide.]

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

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

1 domain may be removed.

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

8 [Slide.]

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

15 [Slide.]

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

19 [Slide.]

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

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

5 [Slide.]

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

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

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

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

1 molecules.

2 [Slide.]

3 The ReFacto drug product is formulated with all
4 simple, pharmaceutically acceptable excipients, is stable at
5 2 to 8 degrees following lyophilization, has a small
6 reconstitution volume and, most importantly, contains no
7 human serum albumin in the formulation.

8 [Slide.]

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

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

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

1 however, shows that this heterogeneity has no functional
2 consequence.

3 [Slide.]

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

11 [Slide.]

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

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

25 Finally, I will close with a discussion of the

1 assay variability in the field.

2 [Slide.]

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

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

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

17 [Slide.]

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

1 substrate resulting in an optical density change.

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

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

13 [Slide.]

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

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

23 [Slide.]

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

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

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

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

14 [Slide.]

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

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

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

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

10 [Slide.]

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

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

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

1 [Slide.]

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

6 [Slide.]

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

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

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

22 [Slide.]

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

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

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

9 [Slide.]

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

20 [Slide.]

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

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

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

6 [Slide.]

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

14 [Slide.]

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

19 [Slide.]

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

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

5 [Slide.]

6 Shown in the left is the same data I just showed
7 you in which both assays were conducted in the central
8 laboratory. On the right, analysis of more than 190 plasma
9 samples from the PTP study are shown. These derive from
10 62 patients and from 23 separate treatment centers.

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

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

20 [Slide.]

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

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

3 [Slide.]

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

9 102 patients have been enrolled in the PUP trial
10 with 97 of these patients having received ReFacto to date.
11 The median exposure in PUPs is 19 days with a range from 1
12 to 447 days. Of the 28 surgical procedures performed, four
13 patients participated in the surgery study alone and there
14 was a total of 279 exposure days.

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

17 [Slide.]

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

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

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

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

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

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

18 [Slide.]

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

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

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

5 [Slide.]

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

15 93 percent of responses were rated as excellent or
16 good. In the safety data for the 112 patients, one of the
17 112 patients developed an inhibitor after 93 exposure days
18 which is an incidence of a little less than 1 percent and is
19 consistent with what is reported in the literature for other
20 recombinant factor-VIII products and plasma-derived
21 products.

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

1 [Slide.]

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

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

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

20 93 percent of the responses were also rated as
21 excellent or good. The primary focus of the PUP trial, of
22 course, is to assess the natural occurrence of inhibitor
23 development. 26 of the 97 patients, or 27 percent, have
24 developed inhibitor, which is consistent with the literature
25 from factor-VIII products, particularly at this point of

1 data maturity where we have reached the median exposure of
2 19 days.

3 15, or, again, the rate of 0.2 percent, other
4 adverse events were reported and, again, were similar to
5 adverse events reported with other factor-VIII products.

6 [Slide.]

7 Twenty-five patients underwent a total of
8 28 procedures in the surgical assessment. Both major and
9 minor procedures were performed including 17 orthopedic
10 procedures which are representative surgeries in this
11 population.

12 Estimated blood loss was as expected and two
13 procedures required transfusions of packed cells.
14 100 percent of the responses were rated as excellent or good
15 by the surgeon or investigator and adverse events were rare.

16 [Slide.]

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

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

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

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

11 [Slide.]

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

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

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

1 stage assay.

2 [Slide.]

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

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

14 [Slide.]

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

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

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

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

10 [Slide.]

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

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

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

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

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

7 If we look at the doses given on the first day of
8 surgery, an average of 49.5 IUs per kilogram when monitored
9 by the one-stage assay was higher than the average of
10 36.3 IUs per kilogram given when monitored by the
11 chromogenic assay. This reflects where the assay
12 discrepancy has an effect.

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

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

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

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

5 [Slide.]

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

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

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

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

1 treatment centers.

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

7 The equation to calculate the required dose is
8 then provided as the required units equal the body weight in
9 kilograms times the desired factor-VIII percent rise times
10 0.5 IUs per kilogram.

11 [Slide.]

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

20 [Slide.]

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

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

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

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

17 [Slide.]

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

20 **Summary**

21 DR. RYAN: Thank you.

22 [Slide.]

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

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

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

8 [Slide.]

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

14 [Slide.]

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

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

1 [Slide.]

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

9 Thank you very much.

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

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

16 **Review of the Orphan Drug Provisions**

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

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

1 hemophilia.

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

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

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

25 Now, for the last criterion, a demonstration that

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

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

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

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

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

4 I would be happy to take any questions.

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

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

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

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

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

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

1 DR. McCORMICK: The Baxter product, and Bayer, are
2 on the market because of an agreement between the two
3 companies. I believe that is public knowledge.

4 DR. HOLLINGER: We can't very well act on this
5 without that information, actually. I mean, it is a
6 critical piece of information. There is an issue right.

7 DR. McCORMICK: There is an exclusivity right.

8 DR. HOLLINGER: And yet there is another product
9 out there that does not have that right; is that correct?
10 And it is because of some licensing agreement or approval by
11 the company.

12 DR. McCORMICK: That's correct.

13 DR. HOLLINGER: Which they have a right to do.

14 DR. McCORMICK: That's right. They have a right
15 to share the exclusivity or to sell it. The exclusivity is
16 owned by the manufacturer and they can do what they want
17 with it.

18 DR. HOLLINGER: Can you explain orphan drugs. How
19 does a recombinant product--my concept of an orphan drug was
20 a little bit different. I thought it was something the was--
21 -maybe you would just explain to me what orphan drugs are,
22 then.

23 DR. McCORMICK: An orphan drug is a drug that is
24 intended to treat a population of less than 200,000
25 patients. That is what the law defines an orphan drug as.

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

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

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

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

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

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

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

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

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

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

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

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

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

7 DR. McCORMICK: No.

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

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

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

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

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

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

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

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

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

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

25 DR. McCORMICK: Perhaps you could ask the industry

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

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

9 DR. McCORMICK: Talking strictly off the cuff--

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

13 DR. KESSLER: Oh; I'm sorry.

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

17 DR. HOOTS: Just to follow up that, though, just
18 in terms of the scientific onus and irrelevant, I think, to
19 these two products but, because it is probably going to come
20 up again in this context, we are talking about, by
21 definition, an orphan drug where a population is less than
22 200,000. In this case, it is a log lower than that. It is
23 20,000.

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

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

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

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

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

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

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

25 If, in fact, they have plans of bringing

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

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

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

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

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

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

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

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

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

13 That is the question for this committee.

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

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

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

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

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

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

17 Open Public Hearing

18 DR. RAMIES: Good morning.

19 [Slide.]

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

1 [Slide.]

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

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

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

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

22 [Slide.]

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

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

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

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

11 [Slide.]

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

20 [Slide.]

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

24 [Slide.]

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

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

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

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

17 Thank you very much.

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

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

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

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

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

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

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

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

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

23 DR. HOLLINGER: If you based it on chromogenic.

24 DR. RAMIES: So it is a relative--

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

1 Ramies to comment on the shortage of the product?

2 DR. HOLLINGER: Sure.

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

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

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

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

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

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

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

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

16 DR. RAMIES: No.

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

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

1 And, again, basically for ethical reasons.

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

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

9 DR. BUCHHOLZ: Okay.

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

14 Thank you very much.

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

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

20 [Slide.]

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

24 [Slide.]

25 I have some general observations and then some

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

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

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

25 [Slide.]

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

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

14 Therefore, to control a relatively minor
15 hemorrhage, although potentially very painful and
16 potentially constructive--to control that knee bleed,
17 20 units per kilo will result in an increment of an
18 approximately 40 percent level. This is the usual standard
19 dose to control such a hemorrhage.

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

25 [Slide.]

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

10 Essentially, they are equivalent. This has been
11 established.

12 [Slide.]

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

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

1 United States.

2 [Slide.]

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

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

14 [Slide.]

15 So, in summary, the one-stage system is the
16 standard procedure for both potency designation and clinical
17 efficacy. Recombinate and Hemofil M vary usually 10 to
18 15 percent, maybe a little greater in the occasional lots,
19 between one-stage and chromogenic. It is important that
20 comprehensive clinical research is required to document that
21 dosing based on chromogenic substrate assay interprets into
22 clinical efficacy.

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

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

3 Thank you.

4 DR. HOLLINGER: Thank you, Ed.

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

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

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

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

25 DR. GOMPERTS: Clearly, I have thought through

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

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

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

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

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

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

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

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

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

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

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

3 [Slide.]

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

9 [Slide.]

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

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

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

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

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

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

16 [Slide.]

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

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

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

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

7 [Slide.]

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

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

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

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

4 [Slide.]

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

8 [Slide.]

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

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

22 [Slide.]

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

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

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

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

19 [Slide.]

20 The next slide shows you more data of the same
21 type. With a second product, it shows the same thing,
22 100 percent recovery. It doesn't matter whether it is the
23 one-stage or two-stage. One patient shows a higher recovery
24 based on the chromogenic but this could be variance based--
25 dependent on that particular day with that patient. But the

1 product shows consistency.

2 [Slide.]

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

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

15 So, for example, if, for the one-stage assay, the
16 potency were to be 500 units per vial and by a two-stage or
17 chromogenic assay, the potency would be 1,000 units per
18 vial, which potency do you put on the label? Do you put a
19 500 or do you put 1,000? It makes a big difference in how
20 the clinician decides what he going to dose with after that,
21 especially if, when the clinician uses the product and if
22 the potency has been applied with 1,000 per vial label but
23 the clinician sees, in a study of 50 percent recovered by a
24 one-stage assay and 100 percent by a chromogenic, what does
25 he think?

1 Which one is okay? Is it okay to disregard the
2 50 percent recovery number on the average patient under
3 treatment in the clinic on that day and how does he follow
4 and how does he know whether he is in a treatment range that
5 he has come to expect before.

6 [Slide.]

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

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

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

25 Until today, there is no agreement yet on a

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

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

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

16 Thank you.

17 DR. HOLLINGER: Thank you, Dr. Feldman.

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

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

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

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

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

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

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

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

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

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

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

7 DR. HOLLINGER: We will give it to you.

8 MR. NAGLER: Thanks.

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

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

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

1 clinicians would if the price was right.

2 DR. HOLLINGER: Thank you for that comment.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2 [1:35 p.m.]

3 **Committee Discussion**

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

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

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

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

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

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

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

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

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

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

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

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

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

25 It becomes important, particularly--I think the

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

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

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

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

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

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

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

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

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

18 MS. COURTER: Correct.

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

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

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

25 DR. McCURDY: Actually, I am concerned about the

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

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

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

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

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

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

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

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

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

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

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

12 [Slide.]

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

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

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

1 second preoperative dose to achieve the targeted level
2 because they were treated to near 100 percent. I assume
3 that, in most of the cases, it was close enough within the
4 20 percent variability you often see.

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

9 Does that address it?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6 But when we have patients who are in the hospital
7 with major bleeding episodes such as intracranial or post-
8 operatively, that is when we are measuring these levels at
9 least on a daily basis. Those of us who have seen all this
10 information and understand that if I give a dose of 50 units
11 per kilo, I expect my peak to be 100 percent and it is only
12 50 percent, but it is because it has been done by a one-
13 stage, I may know to multiply it by 2 but someone who is
14 covering for me, even, while I am out of town at this
15 meeting, may not realize that and may redose.

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

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

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

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

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

14 Craig alluded to the fact that medical-legally, if
15 I have trough levels that, instead of 50 percent or 25 or
16 30 percent, and someone comes in and reviews this chart who
17 doesn't know that I know what I'm doing, they don't know
18 about this ratio factor, they then see that I was only
19 letting the trough levels come to 25 to 30 percent.

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

25 But it is proving it in the laboratory and in the

1 chart that becomes and issue for us right now.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 If those need to be retrained or they have to be

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

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

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

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

1 measure it.

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

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

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

1 absolutely and impeccable truth.

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

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

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

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

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

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

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

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

1 DR. KOERPER: There is a major nationwide study
2 trying to answer that question. We don't know. About
3 25 percent of newly treated patients develop inhibitors
4 after their first ten to twenty exposures to the product.
5 Some of those are high-titer, long-lasting inhibitors which
6 are major problems for treatment.

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

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

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

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

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

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

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

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

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

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

12 So I think that there is going to have to be some
13 mechanism on both the mentality of reimbursers as well as
14 the mentality of physicians and patients when they get a
15 factor VIII, a recombinant factor VIII, that this is
16 different from the other two that are on the market.

17 There is another point that I wanted to ask.
18 Perhaps the GI group can answer this. On the proposed
19 package insert, there is a comment that states that if the
20 inhibitor is present at levels of less than 10 Bethesda
21 units per ml, administration of additional antihemophilic
22 factor may neutralize the inhibitor.

23 That is a little higher than most of us usually
24 consider to be a neutralizable inhibitor level. I am
25 wondering whether or not the Bethesda assays were done using

1 the chromogenic assay or whether the inhibitor levels were
2 done using a plasma-based one-stage assay and whether you
3 have any in vitro or in vivo data that you can overcome
4 inhibitors at 10 Bethesda units.

5 DR. MIKAELOSSON: I am Marianne Mikaelsson. The
6 Bethesda assay is performed with the chromogenic substrate
7 assay. But we have validated the assay in collaborative
8 studies with Chapel Hill running a Bethesda with the one-
9 stage assay. So the results agree very well.

10 In the Bethesda, we also run samples with normal
11 plasma as a test base and also samples where ReFacto is
12 diluted into severe hemophilia A plasma as test base.

13 DR. KOERPER: Why did you choose the number 10?

14 MS. COURTER: Again, that was standard of care.
15 That is what has been in package inserts for several years.
16 I think the challenge is what do you do between 5 and 10. I
17 agree.

18 DR. HOLLINGER: I notice in your proposed
19 labeling, at the bottom, where you are talking about the
20 values are lower, and this was brought up a little earlier
21 here by one of the other discussants, it says the one-stage
22 clotting assay yields results which are lower than the
23 values obtained with the chromogenic assay. It says; see
24 clinical pharmacology.

25 I don't see anything. Maybe I missed it. I don't

1 see anything in the clinical pharmacology that discusses the
2 one-stage or the chromogenic assays and the issues related
3 to that. Maybe I don't have a more up-to-date one but it is
4 the one that was sent to us.

5 MS. COURTER: I think that is exactly what you are
6 missing is what we have done. The one that was sent out
7 originally to you was the original language where we still
8 had the 50 percent wording under the dosing section. Again,
9 we wanted to move that our of there to not temp people to
10 use the factor of 2 and find out that their laboratory was
11 not, in fact, that factor.

12 So we moved it to the clinical pharmacology where
13 we showed, in the PK study, in a well-controlled central
14 lab, a level of approximately 50 percent.

15 It is appendix 4 in your black briefing book that
16 you got. What you would do is you would count five gold
17 pages, I think. You kind of go toward the back of the
18 briefing book, count four gold pages in and the section
19 starts saying "Advisories." Page 18. Second paragraph,
20 where we describe the pharmacokinetic study.

21 And then we have, in bold, highlighted that we see
22 an assay--

23 DR. HOLLINGER: I didn't see that. I looked at
24 this other one that we received.

25 DR. OHENE-FREMPONG: A question on the inhibitors.

1 In general, in managing inhibitor patients, the advice is
2 not to just increase the dose. You said something about 27
3 percent of your patients, the previously untreated patients,
4 developed inhibitors.

5 Can you characterize the types of inhibitors?
6 Would this be low-titer, high-titer inhibitors and whether
7 the advice to increase the dose would apply to even the
8 high-titer ones?

9 MS. COURTER: Sure. Could I have slide B6. They
10 are broken out by high and low titer.

11 [Slide.]

12 Can you see that? Just to reiterate the pieces of
13 information I had already given you is that, out of the
14 97 patients, 27 patients did develop inhibitor. The
15 maturity of the dataset was at a median of 19 exposure days
16 and the median exposure date to inhibitor development was 12
17 days with a range from 5 to 50.

18 Of the 26 programs that developed inhibitor, 9
19 percent developed a high-titer inhibitor as defined as
20 greater than 5 Bethesda units. And 17, a low titer, or
21 18 percent, a low-titer inhibitor.

22 Ten of those patients, to address treating
23 particularly the high titer, they did not try to override
24 the inhibitor for acute episodes. In fact, they would use
25 bypassing agents. But many of the patients did go on to an

1 immune-tolerance regimen where they tried to eradicate the
2 inhibitor.

3 We had ten patients that were on that kind of
4 therapy and six of the high titers received that in the
5 intolerance. And three went to negative. One turned the
6 low titer. And the other went off the intolerant.

7 The low-titer inhibitors were also treated with
8 immune tolerance.

9 DR. RICK: Moving away from the inhibitor question
10 back to the question about the label, I would like to
11 support what Dr. Stroncek mentioned. I think that, to say
12 in a label that one-stage assays are "lower" than the
13 chromogenic would add very little information for the
14 physician. I think that, for medical-legal reasons, people
15 would be very reluctant to allow that to be their dosing.
16 I think they would go to their one-stage assay and overtreat
17 most of these patients.

18 I think the variability question that was brought
19 up and the concerns about trying to chose a range is very
20 real. I think, however, that some of that one-stage
21 variation with the chromogenics would also be found in
22 different one-stage to one-stage assays in different
23 laboratories.

24 So some of the variability, I think, comes simply
25 from the laboratories using similar methodology, perhaps

1 different reagents.

2 I do think that maybe some effort could be made to
3 at least get some range with different factor-VIII assay
4 reagents in the one-stage assays to be able to give some
5 information about a range of one-stage assays versus the
6 chromogenic by which this is labeled and that that would
7 assure physicians some information and, perhaps, defense in
8 medical-legal problems should they occur.

9 DR. KAGAN: I was wondering, in the national
10 hemophilia centers, what is the availability of the
11 chromogenic test? Is it really only for a research basis?
12 Is it frequently available, infrequently available?

13 DR. KESSLER: Infrequently available except for
14 research purposes and the practicalities are as follows.
15 The cost of a chromogenic factor-VIII assay is approximately
16 two-and-a-half times more than a one-stage factor-VIII
17 assay.

18 In this era of cost containment and an era in
19 which laboratories are marginally staffed, the amount that
20 is necessary to institute this test has been considered
21 exorbitant. I think that, in the ideal world, it would be
22 very nice to have chromogenic substrates. I agree with Dr.
23 Rick that, for any coagulation-factor assay, that that is
24 probably a much more accurate assay than all the vagaries
25 that are involved with the one-stage assay.

1 But, unfortunately, that is not the reality of the
2 situation right now.

3 DR. McCURDY: I have a couple of more comments.
4 One of them is we have spent a fair amount of time,
5 including myself, talking about physician errors. I guess,
6 as has been brought up, a fair proportion of patients with
7 hemophilia treat themselves at home. Going in one direction
8 for one product to another, they might overdose which is
9 only dangerous to your pocketbook, I guess.

10 But going in the opposite direction, they could
11 underdose. It might be of some import to provide some type
12 of an alert to the patients or maybe you would have to
13 educate them. I seem to recall--I don't know much about it
14 recently, but there have been diabetics who have gotten into
15 trouble by changing the doses, the concentration of insulin
16 that they use, and using the same volume of double
17 concentrate and getting into difficulty.

18 I think that most of them are now trained or maybe
19 the doses are all the same now. I don't know. That's one
20 thing. Then the other thing that occurred to me--Dr.
21 Feldman, I think, from Centeon raised the possibility of
22 some type of a conference that might look at the pros and
23 cons of the chromogenic assay versus a clotting-based assay.

24 If the chromogenic assay were likely to become
25 pretty universal, then the price would likely come down. At

1 least that has been something that has happened in the past.
2 I think if there were some interest in that at the level of
3 the FDA or other portions, the NHLBI, at least would be
4 willing to discuss the possibility of such a conference that
5 might come up with some recommendations that could be
6 published.

7 MS. COURTER: If I could address your first issue
8 about the patient treating at home. I actually don't think
9 the patient treating at home would treat differently. It is
10 only in the monitoring situation that this assay artifact
11 appears.

12 At home, what the previously treated patient data
13 showed you is that the same dose as was used with products
14 labeled on one-stage was used with this product labeled on
15 chromogenic. We saw a similar efficacy profile. So it is
16 not confusing to the patient in the home setting.

17 It would be when you have that plasma factor-VIII
18 activity in front of you after you gave a dose as to how
19 that would relate one-stage to chromogenic.

20 DR. FRITSCH: Also, to maybe comment on the second
21 part of the question, certainly the appropriate assay to use
22 has been an ongoing discussion for a number of years and
23 primarily climaxed, I think, at the SSC a number of years
24 ago. But they did recommend the chromogenic assay.

25 But, since then, of course, there is still the

1 issue of what is the right standard to use and it has been
2 an ongoing debate. So I think this is still progressing. I
3 think I agree with Dr. Kessler, the biggest problem is cost
4 and then just the inertia of overcoming the fact that
5 everybody is currently using the one-stage assay.

6 But, ultimately, we believe that the chromogenic
7 will be the most appropriate assay to use.

8 DR. HOLLINGER: Some of it is very similar to what
9 I view as sort of heparin or low-molecular-weight heparin.
10 In heparin, you would use a PTT to see what is going on. In
11 low-molecular-weight heparin, I understand, you are using
12 factor Xa. You have an assay sort of for that or something
13 else, but physicians still have to know that.

14 To them, many of them, they are using heparin.
15 They might say, "Well, I can monitor this with a PTT," when
16 they use the low-molecular-weight heparin. So it is a
17 matter of physician education that has to be done here.

18 Somewhere or other, the question is on the
19 labeling for this stuff, does this have to be--how many of
20 the physicians would look at the insert if it was in the
21 insert versus whether it ought to be on the box and say
22 there are some differences here.

23 Fortunately, I think what Dr. Hoots has mentioned,
24 and others here, is the fact that it does seem to me that
25 the error is in the right direction. That is probably a

1 critical issue here more than anything else.

2 DR. HOOTS: In terms of how would you address your
3 concern outside of the major life-threatening and surgical--
4 I think it may have Dr. Feldman or Dr. Gomperts, I can't
5 remember who, but somebody suggested this morning a very
6 good way to assess it which is since now children, by and
7 large, are on prophylaxis, a very good way would be to do a
8 random crossover study between full-length factor VIII and
9 b-domainless factor VIII and look for breakthrough bleedings
10 over a year or two or three.

11 You would expect, if everything we have heard
12 today is accurate, that there would be zero difference if
13 you dosed according to the chromogenic for this product and
14 the one-stage label for the other product.

15 DR. KOERPER: To answer your question about the
16 physician reading the package insert, most of the time, at
17 least in this setting we are talking about with the patient
18 on the ward or in the operating room, the physician is not
19 even the person who is mixing up and administering the
20 factor. It is the nurse who is doing that. The physician
21 writes the order and then walks away.

22 The physician may not even realize whether the
23 patient is getting ReFacto versus Recombinate or Kogenate
24 unless they have taken the time to call the pharmacy and
25 say, "Which product are you presently stocking in the

1 pharmacy?"

2 So physicians, I would say 90 percent of the time,
3 are not even the ones who are handling the box and doing the
4 reconstitution.

5 DR. CHAMBERLAND: Actually, I was thinking the
6 very same thing after I made my earlier comment that you
7 have to know what is on formulary in your institution and
8 then you have to know specifically what that particular
9 patient you are ordering is getting. I don't even think
10 this is possible, but it is almost when the results come
11 back of these tests that you need to have in parenthesis
12 what the normal range is and it would vary depending on the
13 product that is being used.

14 DR. KOERPER: But then the laboratory has to be
15 told what the patient is using. We even have trouble with
16 the laboratory understanding whether the patient is on
17 heparin or not, whether they need to add HepAbsorb to the
18 specimen because the patient is on heparin.

19 So, trying to get the lab to be clued in on what
20 product the patient is on is going to be very difficult.
21 And what product the patient is getting might vary from one
22 day to the next depending on what the pharmacy chooses to
23 send up, depending on what dose was ordered for that day.

24 DR. RICK: I think that is true. I think,
25 however, that with the computer age, most of us are finding

1 that we are putting our orders into a computer. That page
2 can be modified very easily to not accept your order unless
3 you put in the information.

4 But you are right. If the pharmacy has several
5 different items they are using, then it is a problem.
6 However, I think you could probably get around the practical
7 issue.

8 DR. KOERPER: It is not a problem for those of us
9 sitting at this table. The issue is for the people who are
10 not as intimately involved in hemophilia care as those of us
11 sitting at this table.

12 DR. RICK: Right. But I think most hospitals do
13 have a computer system now and I think that part we could
14 probably, with some manipulation, work out. It maybe would
15 make people aware more of what is going on as well, part of
16 the education process.

17 DR. KOERPER: Exactly.

18 DR. RICK: And the results, again, in those pages
19 that are returned would have to indicate what level,
20 perhaps, if you are using a one-stage, ReFacto versus
21 others. It should be on the insert that way as well.

22 DR. HOLLINGER: I am going to call for the
23 question to be voted on here. Actually, the FDA has heard
24 many of the comments here. I think one of them, most
25 importantly, Craig brought up very nicely, has to do with

1 that table which might be confusing in terms of the percent
2 that you are shooting for particularly with this product.

3 But the question is fairly straightforward. I
4 would like to see at least us vote on it and then decide if
5 there is anything else that needs to be done or add to it.
6 You all have the question in C55 which is, "Is the
7 information supplied in the dosage and administration
8 section of the proposed product label (attachment 2)
9 sufficient to dose and monitor this product appropriately?"

10 But then they used a proposed labeling difference
11 that they would like because attachment 2 talks about
12 50 percent of the values.

13 Now, the paragraph which they have on C57, I think
14 is what they expect to be and what would have been
15 attachment 2--correct me if I am wrong--which is that they
16 take out the 50 percent. The rest of it is essentially the
17 same with a few minor derivations. But, basically, it says
18 that the one-stage clotting assay yields results which are
19 lower than the values obtained with the chromogenic assay
20 rather than consistently yields results which are
21 approximately 50 percent of the values obtained with the
22 chromogenic assay.

23 MS. COURTER: May I just add one clarifier. We
24 moved the 50 percent into the clinical pharmacology section
25 and bolded it.

1 DR. HOLLINGER: Which we looked at just a few
2 minutes ago.

3 So with that change in mind, I would like to see
4 if the committee would vote on this. I would like to ask if
5 those who agree, are going to vote yes on, is the
6 information supplied sufficient to dose and monitor this
7 product appropriately as found in this proposed labeling
8 which is in C57, to raise your hand.

9 [Show of hands.]

10 DR. HOLLINGER: Those who disagree with the
11 statement.

12 [Show of hands.]

13 DR. HOLLINGER: Those abstaining?

14 [One hand raised.]

15 DR. HOLLINGER: I will ask Dr. Smallwood to read
16 the results of the voting.

17 DR. SMALLWOOD: There are eleven members here that
18 eligible to vote. The voting is as follows. There were
19 seven "yes" votes, three "no" votes, one abstention. The
20 consumer and the industry reps voted in favor if they could
21 have voted.

22 DR. VERTER: I would like to ask the indulgence of
23 the committee for two minutes to make a statement to the
24 FDA. If this were down on the Hill, and I hate to use that
25 analogy, anything that the witnesses brought forward, even

1 though it wasn't in the prime question, we would be allowed
2 to cross examine, so to speak.

3 I feel particularly frustrated but I didn't bring
4 up the comments during the regular discussion because the
5 question was very specific. It said, "In the dosage and
6 administration section of the proposed product." My
7 comments couldn't, in any way, shape or form, be bent into
8 those sections.

9 However, I would like to give the FDA some advice
10 which they probably already had from their own people, but
11 there were a number of things in the proposed label, the
12 entire label, which I would take some issue with.

13 There are statement in there which suggest
14 comparisons. There were no comparisons presented here today
15 with other products. There were a couple and, in fact, the
16 one or two that you could look at, you could actually make
17 an argument that the other product may be better that, for
18 instance, the percent needing only one dose to resolve
19 bleeding.

20 There was one slide which clearly suggested to me
21 a highly significant difference between this product and the
22 other product. The presentation of some of the safety data,
23 I think, while complete, was not quite the way I would like
24 to see it. I always like to see it on a per-patient rather
25 than over 23,000 days of dosing although I understand why

1 that is done and I am hopeful the FDA will take a look at
2 some of that.

3 It is just the continuing frustration that I have
4 expressed before in this committee that the standard of
5 evidence for what is called clinical trials in this
6 committee I think is quite different from the standard of
7 evidence that is used by other FDA committees in phase-III
8 clinical trials.

9 I understand that this is an orphan-drug
10 situation, that there are, at most, 15,000 to 20,000
11 patients who may be eligible instead of a half a million a
12 year who have MIs or 450,000 who have CABGs or coronary
13 bypasses, but I still think that, within the confines--you
14 guys are up to bat today but, clearly, there were two others
15 who got products on the market that I didn't get a chance to
16 critique so please try not to take it personally, but I
17 think there is a real need in the blood-products area to
18 design better studies.

19 I think there is an opportunity to do trials with
20 better comparisons. You may have to go to something which
21 are called the historical comparisons which are very
22 difficult to do and much harder than a truly randomized
23 trial. But I think, even within the fields that you are
24 dealing with, there is an opportunity to design and carry
25 out better phase-III randomized trials which would better

1 serve the public.

2 Thank you.

3 DR. HOLLINGER: Thank you, Joel.

4 DR. OHENE-FREMPONG: Joel, just a little comment
5 on that. I am not sure whether there was any comparison
6 between this product and another recombinant.

7 DR. VERTER: Yes; there was.

8 DR. OHENE-FREMPONG: I thought it was mostly
9 plasma-derived.

10 DR. VERTER: No. It is on C41, I think. Look in
11 the booklet. There was a comparison between some sort of--
12 one bleeding episode or two bleeding episodes. There is
13 also another comparison further on. There are two or three
14 of them. They weren't stated that way, by the way, with
15 significance tests. I did the tests.

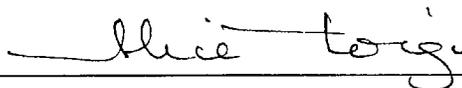
16 DR. HOLLINGER: Does anyone else wish to make a
17 comment before we adjourn this meeting? I want to remind
18 the committee members that the next planned meeting for the
19 Blood Products Advisory Committee is on March 25 to 26 of
20 1999, a tentative date. Dr. Smallwood will be getting back
21 with you again.

22 If there is nothing else, then this meeting is
23 adjourned.

24 [Whereupon, at 2:40 p.m, the meeting was
25 adjourned.]

C E R T I F I C A T E

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