Wednesday, 3 November 2021

(10.00 am)

Presentation by Counsel to the Inquiry relating to knowledge of and response to risk by pharmaceutical companies involved in blood products

SIR BRIAN LANGSTAFF: Yes.

MR HILL: Sir, we continue from August 1983, with a document that we were discussing last night. It comes from a Congressional hearing that took place on 1 and 2 August, before a subcommittee of the House of Representatives Committee on Government Operations. The hearing was about the AIDS epidemic as a whole, and focused on the Federal Government's response to it. The document to which I would like to take you is a written statement that was submitted to the hearing by Dr Edward Brandt, who was the Assistant Secretary for Health at the Department of Health and Human Services. Soumik, it's JREE0000006, and it's electronic page 306.

In his statement, Dr Brandt said this:

"1. How is AIDS transmitted?

"Based on the best available information, we believe AIDS is transmitted sexually, particularly among homosexual partners; less frequently, through transfusion of blood or blood products; or by the misuse of needles. We have no evidence that the disease is spread through air, food, water, or 'casual' contact. To the contrary, AIDS is a difficult disease to contract.

"2. What is the risk after acquiring AIDS through a blood transfusion?

"At present, the risk of acquiring AIDS through blood transfusion appears to be extremely small. Although as many as 10 million Americans received transfusions during the 3 years of the AIDS epidemic, CDC is investigating approximately two dozen AIDS cases in which transfusions may be a risk factor. We believe that the PHS recommendations issued in March 1983, which suggested that members of the groups at increased risk not donate blood, will decrease the current risk."

Those are the Public Health Service recommendations that were subsequently replaced by the FDA recommendations.

"3. What is the cause of AIDS?

"Although we do not yet know the cause of AIDS, the evidence is strong that we are dealing with an infectious agent with a long incubation period. Public Health Service laboratory scientists are using the most sophisticated methods available in the search for this putative agent. The most plausible agents are viruses. The absence of illness in animals already inoculated with specimens may be a reflection of the long incubation period or may indicate that the 'AIDS agent' affects only humans. Unfortunately, it is not possible to predict when the cause of AIDS will be found."

Then if we could go forward in the statement, please, to electronic page 325. If we could highlight the paragraph beginning "At its July 19 meeting". By this point in his statement, Dr Brandt has moved on to discuss some of the debates that have been taking place within the American scientific community:

"At its July 19 meeting, FDA's Blood Products Advisory Committee discussed the safety of plasma derivatives. This is of concern because haemophiliac patients require treatment with a product, antihemophiliac factor ... derived from plasma ..."

SIR BRIAN LANGSTAFF: I think it ought to be "antihemophilic factor", after all the factor is not supposed to be anti-haemophiliac, is it?

MR HILL: No, it's not supposed to be, it should be "antihemophilic factor":

"... derived from plasma which is pooled from thousands of donors. However, I would emphasize that the risk of transmitting AIDS to an individual hemophiliac from a special lot of AHF is very small, if it exists at all. The Committee recommended that no regulatory requirements regarding the recall or destruction of lots of AHF, which may contain plasma from an AIDS donor, be developed but that any cases that are identified be examined individually. In reaching such a conclusion, a number of variables must be considered, such as: the degree of specificity of the diagnosis, the time of onset of symptoms in relation to the time of donation, the potential effect upon the immediate supply of AHF and the long-term productions of this essential plasma derivative. Let me emphasize that the health of the individual hemophiliac patient will be a continuing concern for the [Public Health Service]."

I pause there to note that that is the reason that we were looking at yesterday and the summary that is contained in Dr Brandt's statement to Congress draws seemingly from Dr Donohue's memorandum that we looked at yesterday.

Going back to the statement, Dr Brandt continues:

"Additionally, through these collaborative efforts, progress in developing new procedures for

increasing the safety of clotting factor concentrates have been accelerated. One such product is currently available and others are at a late stage of development. This ongoing cooperative effort will continue to monitor the nation's blood supply in attempts to insure maximum safety and at the same time maintain adequate supplies of blood and blood products."

I take the reference, sir, to the new procedures to be references to heat treatment.

There was, of course, much other testimony heard at the Congressional hearing, I won't take you through it. The purpose of bringing up Dr Brandt's -- or parts of Dr Brandt's statement is that it contains a summation of what the Federal Government's position was at the time and, as we mentioned yesterday, we know that the hearing was reported back to the DHSS in the UK.

SIR BRIAN LANGSTAFF: Could you just go down to the bottom of the page that's in front of us at the moment, the last paragraph, "The National Institute of Mental Health"?

MR HILL: If I read out that paragraph, sir:

"The National Institute of Mental Health (NIMH) held a research planning workshop on August 1, 1983 to

address the mental health aspects of AIDS. Research will be encouraged in several areas: (1) the effects of stress on the immune system; (2) the psychological effects of AIDS on high risk groups; (3) how to meet the psychological and emotional needs of AIDS patients; (4) anxiety in health care workers; and (5) the role of community and family in providing emotional support. A workshop to address the emotional concerns and support needs of AIDS patients, relatives and health care providers will be held on August 3, 1983."

SIR BRIAN LANGSTAFF: I appreciate this is dealing with AIDS victims generally, not specifically those who had contracted the AIDS through taking a blood product, but it looks as though, in America, at any rate, there was almost immediately concern for the mental health, psychological consequences, of infection.

MR HILL: Yes, sir. A document that I didn't take you to yesterday, but, is referred to in the written statement, comes from the Alpha pack of documents that was sent out in December 1982. We looked at the document which was given to the donor in order to educate the donor, and the donor was asked whether or not they were in any of the high-risk groups. There was a further document that was provided in

December 1982 to any deferred donor, offering that donor a short piece of advice about the steps that that donor may wish to take in light of the fact that they had been deferred because of the ongoing element of -- or the ongoing risk of AIDS. That is another example, perhaps, of how such considerations were in the minds of at least some of those involved in this area in the United States at an early stage.

SIR BRIAN LANGSTAFF: To what extent was there anything comparable in this country? I don't think the Inquiry has heard, has it, of any similar concentrated effort to address the psychological consequences this early.

MR HILL: I certainly can't bring one to mind.

SIR BRIAN LANGSTAFF: Well, if there is anything which comes to mind let me know about it in due course.

MR HILL: We will look into that, sir. Thank you.

Thank you, Soumik, we can take that down now.

Moving to the autumn of 1983, according to Dr Evatt in his Tragic History, by the end of August 1983, 26 patients with haemophilia and 26 patients who had received transfusions had been diagnosed with AIDS in the United States. You will have seen the reference to a couple of dozen of transfusion patients in the evidence of Dr Brandt.

The following month, so September 1983,

Dr Luc Montagnier attended a conference in New York where he presented his team's findings that suggested that the virus he had isolated, LAV, was responsible for AIDS. This began a period of cooperation between Dr Montagnier and the CDC, which led to the CDC developing assays that would be used in testing viral inactivation, particularly in heat-treated products. I just flag that now, the discussion we will have later about those products.

SIR BRIAN LANGSTAFF: I mean, he had already reported his results in May, had he not?

MR HILL: Yes, he had.

SIR BRIAN LANGSTAFF: So that hadn't been picked up until now, it seems.

MR HILL: I wouldn't like to say that it hadn't been picked up. I'm not sure of the extent to which the CDC had been aware of those findings. But it seems to have been from September that there is personal contact between Dr Montagnier and the CDC, which leads to the development of their cooperative work together.

SIR BRIAN LANGSTAFF: Okay.

MR HILL: In the same month, September 1983, Hyland and the American Red Cross withdrew some fractionated blood products because of a perceived AIDS risk.

Cutter did the same in November 1983. So these were the second and third product withdrawals from US companies. We have an internal memorandum from Armour, commenting on the Cutter withdrawal, and if we could have that on screen, please, it's ARMO0000302.

The memorandum is dated 7 November 1983, and it's to Mr Bishop, from whom you'll be hearing tomorrow. He's part of the UK subsidiary of Armour. What the memorandum says is this:

"Cutter recalled 16 AHF lots (6,400 vials, 2.2 MIO [I think that's 2.2 million international] AHF units) distributed to 33 countries, including Japan. Several other lots are on hold. One of Cutter's plasma donors recently died because of AIDS. The man donated about 5 liters of plasma over the time, but apparently failed to indicate any information about his disease during that time. We will probably have to expect very detailed questions regarding donor screening/selection of donors during the BGA hearing at ..."

Unfortunately, this is obscured, and I'm not quite sure what that next word is.

COURT: It's not Berlin, is it?

MR HILL: It could well be Berlin, sir, yes. The BGA was the German regulator so, yes, Berlin fits:

"I am also concerned about suggestions that paid donors are less likely to be truthful when asked questions which would disqualify them as donors. Under the circumstances I suggest that we have a meeting at 1:00 MP [I think that should be PM], Sunday, the 13th, prior to the BPI meeting at 3 PM, at the Hotel Kempinski. The Cutter incident is under investigation now and Dr Rodell will be have detailed information available for our meeting.

"We regret the unfortunate circumstances of the Cutter incident. However, a possibility of something like that happening to any plasma manufacturer cannot be excluded. It should be to our advantage to [remind] our customers in an appropriate form, that Armour processes plasma from our wholly owned and fully [controlled] plasmapheresis centres. Plasma Alliances has a worldwide reputation for excellent quality and highest standards. Although it is obvious but is it actually not known how to avoid transmission of AIDS, it should also be emphasized that we have recently introduced factorate HT to improve the safety of our project.

"We will keep you informed on this matter and would appreciate any feedback. Regards ..."

And it's from an I Regier.

Factor VIII HT is the heat-treated product.

On 22 October 1983, after these products had been -- or at least after the Hyland and American Red Cross recall but before the Cutter recall, on 22 October 1983, the National Hemophilia Foundation issued a recommendation in effect restating its formal position from the July 1983 meeting, namely automatic recall of products manufactured from plasma donated by a person who was later identified as having AIDS or characteristics strongly suggestive of AIDS.

You will recall, sir, that that proposition was put at the July meeting, but was somewhat undermined by Dr Aledort immediately saying that he personally didn't agree with it. The NHF, however, restated it in October of 1983.

It did not lead to any change in regulatory policy at that time, so that continued on a case-by-case basis.

In the same month, this is October 1983, Hyland took a policy decision to cease using plasma from prisons in the manufacture of coagulation factors. We can look at a document which we've seen before but I think is worth looking at again in the context of the wide debate of what should be done.

It's CGRA0000291.

It is from Dr Srigley to D Castaldi dated 20 October 1983, so an internal Hyland document. It refers to a telecon with Dr Donohue of the FDA. What the document says is this:

"Attached is the text which I used to define for Dr Donohue Travenol's policy with regard to the use of plasma from prison centers.

"He expressed his satisfaction with the policy and appreciation that we responded promptly to him. He asked that we not send it to him in writing at this time."

Then he says:

"If you have any additional questions ..."

Let him know. If we could turn over, please, to the next page, you can see this is the text that was used, it's marked as "Proposed Text" but we know from the memorandum that it was used with Dr Donohue. What it says is this, and I quote:

"We had previously made the decision to discontinue the purchase of plasma from licensed centers in prisons. To that end we have chosen not to renew any pre-existing contracts with such centers after this year. Following my conversation with you yesterday, we have decided that we will promptly discontinue the use of such plasma for the manufacture

of coagulation factors. We have pools in process this week which contain plasma drawn in prison centers. As of the end of this week, we will not make any coagulation factors from any of the prison plasma which remains in our possession or which we are contractually bound to purchase through the remainder of the year; no further plasma pools used for coagulation factors will contain prison plasma. Any intermediate fractions manufactured from plasma pooled this week, or in previous weeks, would be processed to final product."

Then there is an offer to put that policy in writing, which we know Dr Donohue did not take up.

We discussed this document before, sir. It is clear from the statement that Hyland Travenol had previously manufactured coagulation factors from plasma taken from prisoners, and that they were continuing to do so up until that very week. This is October 1983.

The document doesn't specify whether or not that plasma was used in any particular set of products or whether it was sent to any particular markets. There is nothing in the document to say that it was treated any differently from the plasma that was used generally by the company.

SIR BRIAN LANGSTAFF: Well, I think it does indicate, doesn't it, that the pools were used for coagulation factors?

MR HILL: Yes.

SIR BRIAN LANGSTAFF: So --

MR HILL: It was certainly used for the creation of factor products --

SIR BRIAN LANGSTAFF: Yes.

MR HILL: -- and there is nothing to say that those factor products were treated in any way differently to any other factor products that the company made.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: Just to break sequence slightly, on 7 January 1983, so nine months before, 16 cases of AIDS in prison inmates had been reported to the MMWR.

If we could have on screen, please, JREE0000019, page 76. This is taken from the Institute of Medicine report, and they've helpfully set out a table which shows the number of cases reported in different risk groups from across the United States.

We can see, 7 January 1983, risk groups 16 prison inmates, and there is a snippet of the report, which says:

"Since male homosexuals and IV drug abusers are known to be at increased risk for AIDS, the occurrence

of AIDS among imprisoned members of these groups might have been anticipated."

That comes from January 1983. Thank you, Soumik, we can take that down. I'm sorry, just at bottom there.

Moving on to December 1983, there is discussion of the issue of surrogate testing. A joint meeting was convened on 15 December 1983 by the National Heart, Lung, and Blood Institute, and the Office of Biologics. It took place to consider work that had been done by that time on surrogate testing, the trials had been running in different parts of the country. In particular, it considered anti-hepatitis B core antigen testing, so the antibodies for hepatitis B core antigen.

The Krever Report summarised the meeting in a helpful way, which I will now take us to, it's KREV0000001, electronic page 770, please. From the top of that page, this is what Mr Justice Krever said about that meeting:

"In December 1983, the Food and Drug Administration's blood products advisory committee reviewed the research on various surrogate tests, including several pilot tests performed at blood banks in high-risk areas. Four studies had been done on

anti-core testing, two on Beta-2-microglobulins, and single studies had been made of cytomegalovirus, EBV [which is Epstein-Barr Virus], immune complexes, Neopterin, T-cell ratio measurement, Thymosinal, and Alpha interferon."

So these are all different surrogate tests have been considered in various studies:

"Most of the discussion focused on the usefulness of anti-core testing. Dr Johanna Pindyck, for example, summarized the results of anti-core testing done at the Greater New York Blood Program. She reported that 5.5 per cent of male donors under thirty-five years of age were core antibody positive, as were 7.7 per cent of those over thirty-five years. The estimated cost of the test was three dollars, but the cost of discarding the units as well as recruiting efforts to replace the donor required further evaluation. Data from testing 8,049 donors at Irwin Memorial Blood Bank were also discussed. They demonstrated that donors living in an area of homosexually active men were likely to be positive for anti-HBc and that the test could identify 89 per cent of those most at risk of contracting AIDS. The committee members asked whether these data constituted 'sufficient evidence to substantiate testing for

anti-HBc,' and expressed concern about the potential cost of such testing."

If we can go to the next paragraph, please:

"Although Dr Donohue, the director of the Food and Drug Administration's division of blood and blood products, had recommended to the committee that anti-core testing be implemented, Dr Michael Rodell, a representative of Armour, suggested that a task force be struck to consider the potential application of the anti-HBc test as an additional risk-reduction measure and to report within three months. This suggestion met with universal approval from the committee members; many representatives of blood products manufacturers had met the previous evening and agreed that the task force would 'provide a delaying tactic for the implementation of further testing', which they expected would become a requirement later that year."

We're going to look at a different source from the same meeting in a second but, before I do, I flag the point that Dr Donohue of the FDA had, at the start of 1983, expressed some reservations about hepatitis B core testing. From the summary that we see of that meeting, and indeed from other sources, we can see that, by this stage, December 1983, Dr Donohue's

position had changed and he was recommending that such testing be introduced.

The reference to the meeting of the fractionators appears to be drawn from a note of the meeting prepared by Dr Ojala of Cutter, we've seen many of his memorandums in the last day or so. The reference is UCSF0000034. The memorandum is dated 19 December, it's sent to a number of people within Cutter, and it is a report on the meeting that took place on 15 and 16 December, the meeting that we have just been discussing.

If I could pick it up from the third paragraph, starting "Donohue recommended", this is Dr Ojala's account of the meeting:

"Donohue recommended that Anti-core Hepatitis B testing be incorporated for routine plasma screening (in addition to current requirements) since it would identify 90% of all potentially infectious (or high risk) donors. The Anti-core testing would add a further measure of confidence in product safety at a relatively low cost for the products involved. He reviewed the AHF market withdrawals that had been conducted and indicated that core testing and heat treatment could eliminate this potential for the future.

"The advisory committee agreed with this recommendation, with the dissension of the Acting Chairman, Bill Miller of the St Louis Red Cross. Dr Miller stated that he believed that any testing required for plasma should also be required for whole blood. The committee is aware of a scheduled January publication in the New England Journal by the CDC indicating AIDS transmission in more than 30 transfusions. Several members of the audience objected to the proposal for one reason or another, but Mike Rodell of Armour proposed a Task Force to deliberate the details of the recommendation and provide further in 3 months."

Go over to the next page, please:

"This proposal was one that had been agreed upon by all of the fractionators the previous evening. The general thrust of the task force is to provide a delaying tactic for the implementation of further testing. It was generally agreed that core testing would eventually become a requirement.

"The addition of core testing is expected to eliminate approximately 15% of plasma donors, and 6-7% of whole blood donors if used by blood banks. Some blood bankers mentioned that public pressures would certainly be a motivating factor for core testing at

their facilities.

"The fractionators met with Donohue following the meeting and, although Donohue was not completely satisfied with the task force approach, he agreed to it. He stated that we should also take on the responsibility for all testing of recovered plasma. Rodell was named chairman of the Task Force and a meeting would be scheduled in January."

If you go on, please:

"John Hink [who, as we heard yesterday, is a fellow Cutter employee], in a prescient move, has already begun core testing at Cutter centers. We recommend that the implementation of core testing be accelerated to the maximum degree possible to obtain a competitive advantage in the marketplace. The approval of our heat-treat submission, in conjunction with core-screened plasma could present us with a potent marketing advantage. We made no mention of our plans to the others.

"In summary, the conclusion of this meeting was that the time had come for Hepatitis core anti-body testing for plasma. Implementation will probably be achieved during 1984 for the industry."

We will come back to Cutter's approach to hepatitis B core testing in due course.

We have reached the end of 1983 and, in summary, the year saw the introduction by all fractionators of enhanced donor screening processes. Following the publication of the FDA recommendations in March 1983, blood banks also introduced further steps, but they continued to be less robust with the ones that were put in place at the plasmapheresis centres.

The five firms that supplied the United Kingdom gave undertakings to the DHSS that, going forward, they would only supply products that had been manufactured from plasma after the introduction of their new enhanced screening processes. That commitment was prospective. Products that had already been produced were not affected and were not withdrawn, nor did the DHSS or the American authorities insist upon such products being recalled or withheld from distribution.

One firm, Hyland, continued to fractionate from prison blood until October 1983.

The wider issue of when product should be recalled had been discussed at length but no consensus had emerged. The fractionators had argued that a policy of automatic recall would jeopardise supply, and even the continuing existence of some firms. Their arguments were effective in that the FDA was not

advised to, and did not, take formal regulatory steps in this period; instead, recall was considered on a case-by-case basis. There were three such recalls in 1983.

In July of 1983, the NHF had formally called for a policy of automatic recall, but, as we have seen, it was somewhat undermined by Dr Aledort's personal views. His approach, as expressed at the meeting in July, was similar to that of the fractionators; however, the NHF restated its official position in October 1983.

On surrogate testing, the fractionators had successfully argued for further consideration through a task force, something that Dr Ojala has referred to as a "delaying tactic". His company, Cutter, had unilaterally begun to test plasma for anti-hepatitis B core antigen, something that he thought would steal a march on his rivals.

1983 also saw the first heat-treated product being licensed. That was Hyland's Hemofil-T. Armour, Cutter and Alpha had all applied for licences during 1983, and, as we will see, they were granted early in 1984.

Meanwhile, products continued to be recalled, the number of cases of AIDS among people with

haemophilia and people having blood transfusions continued to grow.

Turning then to the first six months of 1984. January saw the publication in the New England Journal of Medicine of a study of 18 AIDS cases where the only risk factor identified was exposure to blood components within five years of the onset of the illness. The lead author was Dr Curran of the CDC.

Mr Justice Krever placed some weight on this application, and he quoted the evidence of Dr Thomas Zuck, of the FDA, who said that the article, and I quote:

"... put the whole medical community and perhaps the world on notice that AIDS is transmitted by blood transfusions ... the debate [was] over."

That was Dr Zuck's view in his evidence to the Krever inquiry.

The same month, January 1984, saw Alpha recall factor concentrates as a result of the donor later developing AIDS, so this was the fourth such withdrawal. Hyland, in May 1983, Hyland and the Red Cross in September 1983, Cutter in November 1983, and now Alpha in January 1984.

Cutter and Armour products received FDA licences

for heat-treated products in January. Those are the pasteurised form of Koate HT and Armour's dry-heated Factor VIII HT. In the following month, February 1984, licences were granted by the FDA to a different heat treatment method from Cutter, that's Koate HT dry-heated and Alpha's Profilate HT. We will come back to those products in the heat treatment processes in due course.

On 9 February 1984, a meeting was held at the UK's National Institute for Biological Standards and Control, NIBSC. It was a meeting that was entitled "Meeting on the Infectious Hazards of Blood Products", and it was attended by a number of US and UK fractionators and officials. Among those present on the UK side were Joseph Smith of the Committee on the Safety of Medicines, he seems to have taken a convening role at the meeting, Duncan Thomas of the NIBSC, and as we saw yesterday Dr Thomas had been present at the some of the meetings in the United States that had taken place the previous year.

Also present from the UK: Dr Craske, Dr Richard Tedder, Dr Richard Lane, the director of the Blood Products Laboratory, Dr Terry Snape, his colleague at BPL, Dr Brian McClelland and Dr John Cash of the Scottish National Blood Transfusion Service.

US attendees included Dr Petricciani, and representatives of Cutter (Dr Ashworth), Armour (Dr Rodell) and Alpha (Dr Carr).

A European representative of Hyland Travenol attended, Mr J Van Kalster, as did Dr Eibl of Immuno.

I'm going to ask Soumik to bring up the minutes of the meeting that were prepared by Dr Thomas. They are at PRSE0003071.

We've looked at parts of these minutes before. Although they're noted to be draft minutes, we know from other documents, which are set out paragraph 173 of the written presentation, that Dr Thomas circulated these minutes, and there are one or two corrections to specific points of detail but generally they were agreed.

I'm not going to take you through all of the document. At paragraph 184 of the written presentation there is a summary of the issues that were discussed.

Dr Smith opened the meeting by speaking about how the benefits of factor concentrates were assessed against what he called the "well recognised side-effect" of hepatitis, and against the emerging knowledge of AIDS.

The meeting recorded that 21 people with

haemophilia in the US, 11 in Europe, including two in the UK, had contracted AIDS. There were 21 in the United States, 11 in Europe, which included the two in the United Kingdom.

SIR BRIAN LANGSTAFF: Did you say to me just earlier that there had been 26 identified?

MR HILL: Yes. That was Dr Evatt's figure.

SIR BRIAN LANGSTAFF: 26 of transfusion and 26 from --

MR HILL: 26 from.

SIR BRIAN LANGSTAFF: -- haemophiliacs.

MR HILL: That's Dr Evatt's figure by the end of August 1983. I'm afraid I can't explain the difference between that figure of 26 and the figure of 21 that was given in the minutes of this meeting.

The discussion included an examination of pool sizes that were used in fractionation, and we looked at that during September, the point being made that pool sizes could range anywhere from 1,000 to 20,000 litres of plasma.

If we could go to page 3 of the minutes, please. To the final paragraph of that section. This is recording a comment made by Dr Tedder:

"In considering current views on the aetiology of AIDS, Dr Tedder (Middlesex Hospital, London) pointed out that AIDS is manifested as a profound

deficiency of both cellular and humoral immune systems. One possible explanation is that the occurrence of AIDS in recipients of blood and blood products is due to a filterable agent, presumably a virus. Another possible explanation is an overwhelming of the immune system by repeated infusion of foreign and possibly altered proteins. He suggested that the true explanation may lie between the two extremes, namely that there may be a transmissible agent which only becomes infective when certain conditions are met in the host."

Then there is a discussion of possible viruses that may be the cause.

Dr Tedder was presenting a paper which he had prepared for the meeting.

If we then move on to the next page, this is dealing with Dr Petricciani's paper, and his presentation to the meeting. If we go down to the paragraph starting "Dr [Petricciani] (FDA ...)":

"Dr [Petricciani] (FDA, Bethesda, [Maryland]) outlined the current strategies adopted by the FDA for the identification and exclusion of high-risk donors. Four strategies have been considered: 1) voluntary limitation by high-risk groups; 2) exclusion of high-risk donors; 3) laboratory testing ..."

I take that to be a reference to surrogate testing. And:

"... 4) a combination of the above. Currently, there are no specific laboratory tests that are able to identify a possible AIDS carrier. Although anti-hepatitis B core antibody is positive in more than 90 per cent of AIDS cases, it is also positive in approximately five per cent of normal individuals. The approach adopted by the Office of Biologics since March, 1983, was for plasma connect centres to give information to each donor on AIDS, to encourage self-exclusion, and to examine donors for lymphadenopathy. The New York Blood Center had introduced an additional option, allowing donors to indicate privately that their blood should be used only for research purposes."

There is a longer paper that the Inquiry has, which is at BAYP0005158. I won't bring it up, sir, but it's the full text of the presentation that Dr Petricciani made. It describes many of the matters that we went through yesterday, summarising the US debate on them, and the position reached as of February 1984. I flag it merely as a helpful resource in understanding what information UK officials had received as of that time from the US, their

US counterparts. The minute there is a summary of that paper.

If we could now turn to page 5, please, of the document, right, at the bottom Dr Ashworth:

"Dr Ashworth (Cutter ...) described collection procedures at plasmapheresis centres used by the four main US companies."

Go to the next page, please:

"There are some 340 plasmapheresis stations in 42 states, employing 6,000 people. Approximately a third of these centres are owned by the companies, and the rest supply plasma under contract. All plasmapheresis stations in the United States are licensed by the FDA, as is the centre in Belize. Dr Ashworth described the donor records in detail, including questions intended to identify and exclude AIDS carriers. The detailed system exist which allows easy identification of product batches that contain material from a particular donor. Some companies are now avoiding taking plasma from centres in high-risk areas of the United States, although he pointed out that not all donors who contracted AIDS lived in these areas. For example, both Cutter and Alpha Therapeutics have each had one donor who was later shown to have developed AIDS; in both cases, the

donors were from Texas, which is considered a low risk area."

SIR BRIAN LANGSTAFF: Just as a point of detail on that account, you showed me earlier the memo when Hyland decided to stop taking plasma from prisons. It showed that Hyland had a contract with the donor centre at the prison --

MR HILL: Yes.

SIR BRIAN LANGSTAFF: -- and the contract would persist, and therefore they'd have to pay, even though they were not going to use the plasma which they then received until the contract expired. It would follow that the centre, or some of the centres concerned at any rate, were not directly owned by Hyland.

MR HILL: Yes.

SIR BRIAN LANGSTAFF: And it would also follow that they were going on operating. But it was the FDA that was asking Hyland to stop taking plasma from prisons, and yet, if this is right, it looks as though, in the absence of further information, there were plasmapheresis stations in the United States operating in prisons, collecting plasma, which remained licensed by the FDA despite the knowledge or belief that those in prison would disproportionately be affected by hepatitis and by AIDS.

MR HILL: Yes. The FDA's conversation with Hyland was about the use of prison plasma specifically in factor concentrates. It is possible that plasma from prisons might have been used in other blood products which were thought or known not to pass on infectious diseases. So that may be an economic reason why those centres could continue. But certainly the FDA would have been aware of those centres, and would have been regulating them.

SIR BRIAN LANGSTAFF: Yes. Yes.

MR HILL: Going back to the document, the following paragraph -- sorry, just before we do move to the next paragraph, I just flag up the reference there to a donor from Texas that had led to recalls -- or donors from Texas that had led to recalls of product by Cutter and Alpha.

You will recall that yesterday, I showed you a document from February 1983 from the Alpha company, a committee of Alpha, which discussed a Dallas donor who had, and I quote, "some AIDS symptoms". That was February 1983. We know that the Alpha withdrawal of product was in January 1984, and in the following month, February 1984, there is reference to a donor from Texas being responsible for that recall, what we don't know is whether or not that Texas donor is the

same as the Dallas donor who was being discussed a year earlier.

Going on to the next paragraph:

"In discussion, Dr Cash commented that paid donors are perhaps less likely to be truthful about their activities than volunteer donors. Dr Rodell disputed this, and pointed out that in three of the four instances of blood donors contracting AIDS, leading to subsequent withdrawal of product, the donors were in fact non-paid volunteers. Furthermore, the payment to plasmapheresis donors probably sufficed only to cover their expenses."

If we -- yes, I think we can go to pages 9 and 10 now of the document. There was a discussion from Dr Lane and Dr Snape about fractionation, and there were also discussions about hepatitis B testing.

I'd like to turn now to the bottom of page 9, and the section of the minutes that deal with an open discussion that took place after the formal presentations had occurred. It says that the discussion focused on four main issues, and I quote:

"1. What should be done about blood products made from plasma pools when one of the donors to that pool subsequently developed AIDS? This has already happened to US manufacturers, leading to withdrawal of

the affected batches. Dr Thomas asked Dr Petricciani whether the FDA had specifically requested the manufacturer to withdraw batches that had been made from an affected pool. Dr Petricciani replied that no formal instruction had been issued by the FDA, but the withdrawal had taken place as a result of informal discussion and agreement. The general feeling of the meeting was that if the diagnosis of AIDS in a donor is definite, then products prepared from pools to which the donor had contributed should be withdrawn. If a donor is found to have symptoms and signs, such as lymphadenopathy, which were associated with incipient AIDS, but were neither diagnostic nor specific for the condition, the recall of material to which the subject had previously contributed plasma was not justified. It was recognised that the scientific rationale for this course of action left much to be desired, but that no other action could be taken which would not imperil the supply of Factor VIII.

"2. As far as laboratory tests for screening for AIDS are concerned, it was generally agreed that, on present evidence, only the test for hepatitis B core antibody was thought likely to be of value. However, there was no general agreement that such

testing for core antibody should be part of the routine screening carried out on all donors.

"3. There was much discussion about the optimal size of plasma pools, but no agreement that reduction of pool size would either a practicable or a successful way to reduce the transmission of either hepatitis or AIDS."

I will leave that document there, sir, and instead turn to the other source that we have for what was said at that meeting, which was a memorandum prepared by Dr Carr of Alpha. That gives a slightly different perspective on some of the passages that we have just read.

If we could have on screen, please CGRA0000610. This is dealing with the same section-- sorry, page 6. You can see from that first page that it's an internal Cutter memorandum -- sorry, an internal Alpha memorandum.

We're looking now at Dr Carr's summary of the general discussion and suggested recommendations. This is the same part of the meeting that we've just been looking at. What Dr Carr wrote is this:

"a. Identification and exclusion of high-risk donors:

"Dr Smith [that's Dr Joseph Smith] stated that

he was very reassured by the clear policies in the US and the UK. He expressed concern over what is done when the donor is identified as an AIDS donor and additionally as a suspect AIDS donor. Dr Petricciani stated that we were still struggling with the question as to what should be done. The four US market withdrawals were discussed and we explained that we were all still making decisions on a case-by-case basis. The decisions were not being made based on scientific information, but simply because of emotional and political considerations. During this discussion it was very emphatically noted that three out of the four market withdrawals involved volunteer donors not paid donors.

"b. Fractionation and processing methods:

"There were some concerns expressed over the safety of heat-treated products. Dr Bloom as a consultant to NIBSC stated that he was not sure that there was enough data on the potential immunogenicity of the heat-treated products. A brief explanation of the types of animal immunogenicity data collected was described.

"There followed a very lengthy discussion on the value of small pool size versus the use of large pools. We were finally able to show them that even

with a small pool size because of the fact that they are collecting individual donations the exposure of the hemophiliac to numerous donors would still be there. Dr Smith summed up this discussion by stating that they should encourage the development of fractionation and procession controls for lowered infectivity, ie physical and chemical inactivation."

Go to the next page, please:

"Dr Smith asked Dr Bloom whether or not dosage guidelines should be developed. Dr Bloom stated he did not see how they could develop them when they do not have enough NTS [I think that should probably be NHS] material and hemophiliacs must either go untreated or they must use foreign material. Dr Petricciani noted that AHF was not considered overused in the United States and this was not an issue. Rather there was some concern that it was being underused.

"c. Laboratory test procedures. Dr Smith summed up this item with practically no discussion at all stating for the attendees that no laboratory test procedures can be recommended at this time."

If we go to the bottom, the last couple of sentences. There is a discussion about the safety of hepatitis B immune globulin, then this:

"Finally, it seemed apparent to me that the British will watch very closely what is done in the US and in this case seem to be tending to follow our lead. In talking privately with Dr Thomas before the meeting he told me he wasn't sure that we should have withdrawn our product but postulated probably our lawyers would advise us that we had to. From his [point of view] he did not think we should have."

That's Dr Carr's record of the final stages of that meeting in February 1984.

Moving back to the United States. The task force, or what's sometimes referred to as a study group, on anti-hepatitis B core testing that had been established in the December 1983 meeting -- that's the body that was seen by Dr Ojala as a delaying tactic -- met on 6 March 1984, Dr Rodell was in the chair. A full report from the committee, or the task force, wasn't presented until July 1984 but, following the 6 March meeting, the group provided an interim report and recommendations. If we could have a look at those, please, they're at MHRA0000076_010.

You can see that this is entitled "Interim Summary Statement of Hepatitis B Core Antibody Testing Study Group, by Michael B Rodell, Chairman". What the interim statement says is this:

"On March 6, 1984, the Study Group, formed subsequent to the December, 1983 meeting of the FDA Blood Products Advisory Committee, met to discuss the issue of testing potential blood and/or plasma donors for core antibody and to hepatitis B ... Membership of the Study Group consisted of representatives of the commercial and noncommercial fractionation industry, the plasmapheresis community, nonprofit blood collection and processing organisations, and the Food and Drug Administration.

"The purpose of the meeting was to review all aspects and ramifications of the use of testing for Anti-HBc as an additional means of determining whether potential donors were members of high risk groups associated with Acquired Immuno Deficiency Syndrome. Although a full report of the Study Group's deliberations and exclusion will be furnished to the Food and Drug Administration in the near future, it was felt that an interim statement should be made available at this time."

The Study Group was divided in its position on testing for Anti-HBc as a means of identifying AIDS high risk group members, with the majority believing that such testing was not appropriate for that purpose. However, members of a majority group

indicated that they would likely be compelled to follow suit if any of the organizations represented initiated Anti-HBc testing programmes. The report to be prepared will contain position papers summarizing the majority and minority opinions on this issue.

"It was clearly recognized by the Study Group that a positive finding of Anti-HBc in an individual was not necessarily indicative of AIDS or the future development of the disease state; rather, it was viewed as a possible mechanism of identifying high risk group members, a number of whom are positive for this serologic marker. It without the prevailing opinion of the Study Group that if testing programs for Anti-HBc are employed, they should not be confined to the plasma donor population, but should extend to whole blood donors as well.

"There was unanimity on two additional issues that the Study Group addressed. First, the Study Group recommended the initiation of a pilot study in at least two metropolitan areas to ascertain the effectiveness of allowing plasma donors to privately provide a written indication as to whether their plasma should be used in the manufacture of products used in haemophilia treatment, analogous to the system currently utilized by the New York Blood Center in

whole blood collections. Secondly, the Study Group recommended that pilot studies involving testing for [Beta-2-microglobulin] levels be designed, since the presence of this analyte appears to offer a higher degree of correlation with prodromal or active AIDS."

Thank you, that can be taken down.

That is the formal record as prepared by Dr Rodell, the chair of the group. We also have an account of the meeting from an internal Cutter memorandum prepared by Dr Hink. That is at CGRA0000319, please. This is dated 13 March 1984, it refers back to that meeting held on 6 March. The first thing note, the people who are on that working group: it's Marietta Carr from Alpha, whose memorandum we just looked at; Dr Donohue from the FDA; Dr Marilyn Horowitz from the New York Blood Center; Dr Peter Page of the American Red Cross; Dr Robert Gerety, again of the Bureau of Biologics, we mentioned him yesterday; Dr Hink himself from Cutter; Dr Johanna Pindyck, of the New York Blood Center; Dr Bob Reilly of the American Blood Resources Association; Dr Toby Simon, the American Association of Blood Banks, so a blood banking industry body; Dr Rick Srigley of Hyland; Dr Mike Rodell of Armour, who was the chair.

We begin with this summary. Paragraph 1, what

Dr Hink wrote is this:

"On the question of beginning Hepatitis B Core Antibody (anti-HBc) testing of Source Plasma Donors: following 5 hours of discussion, a vote was taken. Donohue, Srigley and Hink voted in favor. All others (with the exception of Gerety who I believe abstained) were not in favor."

I pause there to note, sir, that Dr Donohue of the FDA is therefore in favour of the testing, as are the representatives of Hyland, Dr Srigley, and Cutter, Dr Hink. Dr Gerety is believed to have abstained. Everybody else, being the representatives of Alpha and of Armour, voted against. The summary goes on to mention the position papers that will be prepared and the pilot studies and investigations that the working group had recommended. If we go to point 5, please:

"Immediately prior to the conclusion of our meeting it was recommended that the Industry should refrain from starting anti-HBc testing. Carr was adamant that Alpha would not begin, Rodell said Armour would not use the test unless a competitor was using it to competitive advantage. Srigley indicated he could not speak for his company management, and I parroted his comment."

I pause there note to, sir, that we know from

the memorandum that, by this stage, Cutter had already commenced some form of anti-HBc testing.

If we go over to the next page, please, page 2, electronically. If we can pick up some of the contributions that were made to the test -- sorry, to the debate. It began with Dr Donohue setting out his concerns. I won't go through that. If we can pick up from Dr Hink, and I quote:

"... additional screening is necessary to reduce the risk of coagulation product withdrawal/recall. Recalls are not only costly but could create a shortage of material available to hemophiliacs. Anti-HBc testing can be carried out in high volume by the Industry and by the volunteer segments, if desirable. CDC reports that over 75% of the high risk AIDS groups are positive and as a marker for hepatitis it is reported that the exclusion of positive units has reduced the incidence of non-A non-B hepatitis from blood transfusion. If the test is implemented for SP(H) it should be agreed that the coagulation products manufactured from core antibody negative plasma would not be subject to AIDS related recall."

Dr Srigley said, and I quote:

"Srigley -- agrees that additional plasma screening is necessary and anti-HBc is a likely

candidate. When questioned about certain current AIDS investigations at Hyland he thought, but could not be certain, that of 7 cases only 3 or 4 were anti-HBc positive."

Dr Pindyck is quoted or cited next, she was from the New York Blood Center. I quote -- I won't go through everything which she said, but I quote:

"Anti-HBc has low selectivity, not worthwhile for volunteer segment."

I take that to be a reference to voluntary blood donor blood banks:

"Suggests there may be better tests being developed."

So that was her view.

Gerety, this is Robert Gerety of the FDA's hepatitis branch, and you may recall, sir, that we looked yesterday at the scepticism that Dr Gerety had expressed about anti-hepatitis B testing in the January 1983 meeting but, rather like Dr Donohue, we see that he had, by this time --

SIR BRIAN LANGSTAFF: I think we may need to move on to the next screen.

MR HILL: Sorry, it's electronic page 3, so Gerety there. If we pick up from the top of that:

"... AIDS cases remain with high risk groups.

Concerned about anti-HBs level in plasma pools if anti-HBc positives excluded."

So that's the concern that we discussed previously, that the inadvertent effect of this might be to reduce the protection against hepatitis B:

"However, only small amount necessary to provide antigen 'complex' safety. Feels elimination of anti-HBc positives would improve HBV [hepatitis B virus], non-A non-B hepatitis virus and AIDS safety of coagulation products. Questions mechanics/validity of test with 50% cut off. Suggests a 75% cut off ... It would reduce the 15% positive rate now experienced."

I pause there note to that this now seems to be a suggestion that, instead of excluding any donation which tested positive, a certain level would be imposed, and if it was above that level then that plasma would be excluded, which would reduce the amount of plasma that would have to be discarded -- that's the 15 per cent positive rate -- that there is then a discussion that goes on about whether or not that is a good idea.

Looking at some of the other contributions --

SIR BRIAN LANGSTAFF: Just go on, I think.

MR HILL: "(... It would reduce the 15% positive rate now experienced).

This is still Dr Gerety, yes, sorry:

"High percentage (up to 90%) of haemophiliacs now dying of liver disease. If anti-HBc testing implemented, antibody positive plasma should be used in manufacture of gamma globulins."

Presumably that was on the basis that those products wouldn't pass on infectious diseases and it would avoid the waste of plasma that would otherwise take place.

I note there, sir, that Dr Gerety was thought by Dr Hink to have abstained during the subsequent vote. It was certainly a softening of his position compared to where he was in January 1983.

The next contribution is from Dr Peter Page of the American Red Cross, and I quote:

"... doesn't think we should start with low specificity anti-HBc test now. If begun we could be stuck with it even if better test developed."

Dr Gerety appears to have intervened at this point. The record says:

"(Gerety sees no reason anti-HBc should be continued if better test implemented at later date.)"

Dr Carr of Alpha, and I quote:

"... sees problem with volunteer plasma if anti-HBc test conducted with SP(H) only. Suggests

plasma shortage if test implemented."

Then it says that:

"Alpha is currently conducting 8,000 HBsAg tests/day ..."

The next contribution is from Toby Simon of the American Association of Blood Banks, and I quote:

"... whatever test is imposed on Industry would impact (be required) for volunteer segment. Earlier pilot study with anti-HBc identified only 38% of known gays as positive. Evatt of CDC told him only 50% of key blood donors (suspected of transmitting AIDS) were found anti-HBc positive."

So Dr Simon casting some doubt on the figures that had been elsewhere cited of 90 per cent.

Rodell made a contribution --

SIR BRIAN LANGSTAFF: This may go back to link what you showed me yesterday as the expanded table which Evatt produced, where he showed the greater prevalence of hepatitis B core antigen in certain risk groups and showed the high-risk groups were significantly higher in their prevalence rates than was the so-called "normal" donor.

MR HILL: Yes.

SIR BRIAN LANGSTAFF: And it must follow -- sorry, it doesn't necessarily follow that the percentage of

positivity in donors is echoed by the exact same percentage in those who suffer from the disease. It's the point I raised with you yesterday.

MR HILL: Yes. But the figures that Dr Simon cites there are not consistent with Dr Evatt's figures from that table.

SIR BRIAN LANGSTAFF: What does he say in the table for those who were --

MR HILL: If we could bring up, please -- can we do a split screen, please, Soumik, and have CVHB0000042, page 5. If we put that on one side and then the document that we've just been looking at on the other.

Sorry, I'm throwing this one at you at the last minute. CVHB0000042. And it's electronic page 5 of that document.

SIR BRIAN LANGSTAFF: We can come back to it later. At the moment we're just getting each page in turn -- we can see enough, I think, from that, if we just enlarge the table at the bottom.

MR HILL: I have the figures from Dr Simon in front of me, so I can remind you of those in a second, sir.

SIR BRIAN LANGSTAFF: Thank you.

So let's just enlarge the table at the bottom and see what he was saying.

MR HILL: This is from 1982, and the first cohort of

population is labelled "AIDS cases", so presumably people who have been identified as having AIDS.

It's the left-hand column we're interested in: "Anti-HBc% positive".

SIR BRIAN LANGSTAFF: Yes.

MR HILL: 88 per cent of people who had AIDS and who were homosexual or bisexual; 100 per cent of people who had AIDS and were drug users intravenously; 86 per cent of people who had AIDS and were Haitians; and the "Others" group, we don't know what that specifies. One can perhaps surmise that this is probably people who have developed AIDS through person-to-person contact, or possibly through blood transfusion and the use of blood products. The "Others" group is 42.9 per cent.

SIR BRIAN LANGSTAFF: I mean, the issue is knowing for those who made donations, as opposed to those who actually were AIDS cases, so the group, the risk group, the Haitians are 36 per cent, so they're seven times more likely to have hepatitis B than -- hepatitis or to be anti-HBc positive than are normal controls, homosexuals are 80 per cent roughly.

MR HILL: Yes.

SIR BRIAN LANGSTAFF: Four out of every five are likely to be. It doesn't take an overall figure across the risk

groups, does it?
MR HILL: No, it doesn't, but the figure that is given by Dr Simon was that Dr Evatt of CDC told him only 50 per cent of key blood donors suspected of transmitting AIDS.
SIR BRIAN LANGSTAFF: Yes, it's a very difficult description to mine, to understand precisely what is being said.
MR HILL: Yes. And also the other point to make about it is that Dr Simon was saying that in March 1984. This table comes from 1982.
SIR BRIAN LANGSTAFF: And the person who is saying it has a particularly vested interest in not wanting to do the test.
MR HILL: Yes. And voted against it.
SIR BRIAN LANGSTAFF: Yes.
MR HILL: We do have some later figures that I will come to about anti-hepatitis B core testing, but that is, I think, as far as we can take it from that document.
SIR BRIAN LANGSTAFF: But it shows that my initial suggestion that it refers back to that table, it doesn't necessarily.
MR HILL: No. No.
Dr Simon also refers to a pilot study. We don't know which pilot study that was, but that was said to

have identified only 38 per cent of "known gays" as positive. What is meant by "known gays" is not explained in this document.
Just to finish off the meeting from 13 March, Dr Rodell, and I quote:
"Rodell - questions if anti-HBc test is sufficiently specific to be effective. It would exclude only 50% of donors with AIDS [prodrome]. Provided figures show anti-HBc testing and rejection of positive donors should cost several million $ per year."
So that's -- Dr Rodell provided those figures:
"14 to 15 Plasma Alliance centers collecting about 850,000 liters per year. Armour currently derives all plasma from Plasma Alliance, no contract centers."
What isn't clear from that note is whether the cost of several million dollars per year is intended to refer just to Armour's costs, or to the costs across the industry. But what is perhaps notable is that the figures of $100 million and $150 million per year, which we saw yesterday, aren't repeated at this meeting, at least according to the records that we have of it.
Finally on that meeting, Dr Rodell provided

a copy of his summary report to Dr Thomas of NIBSC in March 1984, following up on the meeting that had taken place on 9 February.
I'm about to move on to a related but distinct topic of Cutter's approach to hepatitis B core testing, and I note the time, sir.
SIR BRIAN LANGSTAFF: Well, shall we have a morning break then until 11.55. 11.55.
(11.23 am)
(A short break)
(11.55 am)
MR HILL: Sir, you will recall from the memorandum of Dr Hink that I read before the break that there appears to have been some discussion at the end of the meeting about the industry as a whole not introducing anti-HBc testing, and Dr Carr from Alpha saying that they wouldn't begin, Dr Rodell from Armour saying they wouldn't begin unless they were forced by a competitor doing so. You will also recall that Dr Srigley from Hyland said he couldn't speak for his company management and Dr Hink gratefully parroted that line.
We know that a few weeks later, on 2 April 1984, Cutter publicly announced that it would commence testing all donated plasma for anti-hepatitis B core antigen. The company declared that:

"Until a specific test for any AIDS agent has been discovered ... Cutter intends to take these precautionary measures to protect those with haemophilia who depend upon our products."
The reference is at paragraph 198 of the written presentation.
A document from May 1984 shows the debate that took place within Cutter that month, when the policy was reviewed, it's a helpful document, because it literally sets out the arguments for and against hepatitis B testing, and it does so in the context of an internal company document, so it's something not for public consumption, but for the company itself to cogitate upon before deciding whether or not to continue the policy that it had announced of anti-HBc testing.
If we could have on screen, please, CGRA0000362. We can see that the memorandum is dated 25 May 1984, and it comes from John Hink, and it is sent to the members of a committee within Cutter, which was responsible for making decisions on matters such as these. It refers to the materials that have been provided ahead of the meeting on 31 May.
If we turn over to the second page, please. We can see a document headed "Arguments Advocating

Continued Hepatitis B core Antibody Testing". Not to give anything away but, on the following page, there is a heading "Arguments for Discontinuing Hepatitis B Core Antibody Testing", so the pros and the cons being set out. I'll read through this document from the top:

"Arguments Advocating Continued Hepatitis B core Antibody Testing of Cutter Plasma

"1. Exclusion of [HB core antibody] positive plasma from use in the manufacture of coagulation products will reduce the risk of further product withdrawals.

"a. National Hemophilia Foundation and FDA agree that coagulation products 'contaminated' with plasma collected from a donor subsequently diagnosed with AIDS must be withdrawn and/or withheld from market. Until proof that the AIDS agent is inactivated by heat treatment or other means, it is unlikely that this position will be changed.

"b. Donor populations at greatest risk for AIDS are homosexuals/bisexuals and IV drug users.

"c. Screening my interviews and lymphadenopathy have been effective only partially in eliminating 'high risk' donors.

"d. CDC reports 88% of homosexuals/bisexuals

and 96% of IV drug users with AIDS are [HB core antibody] positive. 78% of individuals with AIDS prodrome are positive. A high percent of populations considered 'at risk' for AIDS have been shown to be [HB surface antibody] positive."

We'll come back to those figures later, sir:

"2. Cutter has an obligation to use all reasonable means to provide safe effective products.

"a. [Hepatitis B core antibody] is a 'marker' for hepatitis and in indication for exposure to multiple infectious diseases. [Hepatitis B core antibody] positive plasma may be expected to have greater virus contamination than untested plasma.

"b. Retrospective studies show 25% to 50% of [hepatitis B core antibody] positive blood can cause post [transmission] *[sic]* non-A non-B hepatitis. Coagulation products derived from [hepatitis B core antibody] negative plasma should transmit less non-A non-B than those produced from conventional plasma.

"3. [Hepatitis B core antigen] positive plasma exclusion from coagulation products should result in high customer acceptance with increased sales at appropriate prices.

"a. Cutter ([without] chimp data) needs to differentiate itself from the other manufacturers to

gain back market share.

"b. If HTLV-III screening test is available at years end '84, Cutter will have 8 months production from core screened plasma available before any HTLV-III screened products are available.

"c. If HTLV-III screen test is delayed Cutter will have even more advantages over competition."

On the next page:

"d. Core screening is just one advantage we can offer with Koate that competition cannot.

"4. Separation of HBcAb positive plasma provides the opportunity to more efficiently identify plasma donors with high levels of other hepatitis 'marker' antibodies, ie [cytomegalovirus] and HB [surface antigen]."

Sorry, I think that might be HB surface antibody rather than antigen.

"5. It may be possible to fractionate core positive plasma to concentrate. If later development in AIDS screening (for example HTLV-III) can be used to test the concentrate, much of it can be salvaged.

"6. Startup costs are already sunk and testing costs are not financially significant -- the exclusion of a plasma allocation of $13.25 per liter is the real expense.

"7. We may be able to make stronger claims concerning Non A non B Hepatitis risk from core screened products."

So those, sir, are the seven reasons in favour of continuing the testing. Arguments for discontinuing were then set out, and I quote those now:

"1. Cost.

"a. Implementation of HBcAb testing has cost somewhat more than [US] $100,000. Continuation of this testing will add approximately $0.03 to all liters procured.

"b. 15% of plasma tested has been HBcAb positive. Exclusion of this plasma from coagulation products and quarantine of HBsAb positive AHF concentrates will have significant but indeterminate costs.

"2. HBcAb is a marker for hepatitis B and a potential indicator of population groups at risk for AIDS. It is not an AIDS specific test and will not identify all potential AIDS victims. Even with continued HBcAb testing we are at risk for product withdrawal due to AIDS 'contamination'.

"3. More specific AIDS screening tests will be available in the future. HTLV-III is assumed to be

the causative agent for AIDS. Press announcements indicate that an HTLV-III antibody test will be available by Oct 1984."

I pause there to say, sir, that we will be looking at the screening tests shortly:

"It is contentious whether this target will be met for commercial availability in quantities approaching/plasma screening requirements (ie 1.5 million per month). Coagulation product derived from HTLV-III tested plasma could be commercially available 8 to 11 months following implementation of testing.

"4. The Cutter dry heat treat method may demonstrate inactivation of HTLV-III. Use of HBcAb negative plasma plus [heat treatment] of coagulation products would then be considered a 'belt and suspenders' redundancy.

"5. Exclusion of [hepatitis B core antibody] positive plasma from coagulation products should reduce the already low level of HBcAb, thereby potentially increasing the risk for transmission of hepatitis B virus.

"6. Flexibility of Plasma Procurement operation is considerably reduced by the requirement for HBcAb testing. Many suppliers to our industry are unable to

comply (or will not comply) with procedures necessary for separation and control of tested plasma.

"7. Identification, separation and isolation of HBcAb tested plasma has placed a large burden on Cutter employees and staff. Blending of [hepatitis B surface antibody] positive and [hepatitis B surface antibody] negative Fraction II to assure normal ISG will increase this burden."

So those are the pros and cons set out. I will come back to the figures that are contained in a second. I would just note that the company agreed to the continuation of the testing programme in a meeting on 25 June 1984, a reference to that is at paragraph 202 of the written presentation.

SIR BRIAN LANGSTAFF: The document that you're showing me, I think it was anticipating a meeting which took place on 31 May.

MR HILL: It is. I don't know why it was that the decision was delayed until 25 June 1984. We can trace that through if necessary. But the overall point is that Cutter continued that programme.

SIR BRIAN LANGSTAFF: I mean, just to fit in what had happened between the starting of testing for anti-HBc by Cutter on 2 April, and this document which is at 25 May '84, is that on 21 April there was a press --

or Gallo announced his discovery that the HTLV-III was, he claimed, the cause of AIDS, and two days later there was a press conference with the Secretary of State for Health to announce it --

MR HILL: Yes.

SIR BRIAN LANGSTAFF: -- and to announce that tests would be forthcoming.

MR HILL: Yes. The somewhat optimistic statement on 23 April 1984, by Secretary Margaret Heckler was that the tests would be available within six months, and that is why I think there is a reference in the document that we've just looked at to the tests being available in October.

Scepticism is expressed -- justified scepticism it turns out -- about whether or not that target could be met if what Secretary Heckler meant was that these tests would be available across the country at the level that the industry required. That, in fact, didn't take place until the early and mid part of the following year, 1985, and we'll come on to that in due course.

The decision then by Cutter is to continue the testing. The meeting on 25 June 1984 also contains an interesting detail, that an insurance claim had been made for a sum for the -- to cover the costs of the

withdrawal of 16 lots of Koate and Konyne the previous year, that's the product withdrawal that we mentioned earlier. The insurance claim was for $4.9 million. That was for 16 lots of the product.

If we could just go back, Soumik, to the second page of the document that we were just looking at, CGRA0000362. If we could go to 1.d.

Now, this is the Cutter rendering of the CDC position as of the time of this document, which is May 1984. There, it is saying that:

"CDC reports 88% of homosexuals/bisexuals and 96% of [intravenous] drug users with AIDS are HBcAb positive."

That contrasts with the figures given by Dr Evatt in 1982, which were -- and I'll just read them to you rather than putting them up on the screen. The figure for homosexuals and bisexuals with AIDS in 1982 was 88.2 per cent, so a very similar figure to the one that is contained in that document.

The figure for intravenous drug users with AIDS in 1982 was 100 per cent, so all 21 such cases. That has fallen slightly, but it is still very high: 96 per cent as of May 1984.

The figure given in 1982 for probable AIDS -- and the test then was lymphadenopathy, so swollen

lymph nodes -- was 81.3 per cent; a very slight decrease by 1984 of 78 per cent of individuals with AIDS prodrome are positive.

That might not be comparing precisely like with like, but the figures, you may feel, sir, are strikingly similar.

SIR BRIAN LANGSTAFF: Yes. I mean, for no numbers you'd speculate that they would be bound to be within the same confidence interval, speaking statistically.

MR HILL: I wouldn't disagree with that at all.

Those figures are notably different from the ones that were cited at the meeting that we have just looked at. I won't take you back over those.

What I would add here is that according to the Krever Report, and it's electronic page 772 of that report, I won't take you to it, but Mr Justice Krever said that in early 1985 the CDC published a study that demonstrated that 62 per cent of donors to whom CDC had traced a transfusion-related AIDS case had tested anti-HBc positive. So that figure of 62 per cent seems to relate to all AIDS cases. And as we saw earlier, the correlation between anti-HBc positivity and the Haitian community was lower than that --

SIR BRIAN LANGSTAFF: Well, it's looking at something a bit different there, isn't it, because that's

looking at donors, whereas I think what you've just been showing me has been looking at cases.

MR HILL: Yes. That's correct, yes.

SIR BRIAN LANGSTAFF: So they're two different communities.

MR HILL: Two different -- those are donors to whom AIDS cases had been traced.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: But, yes, they are a different community, and it would include donors who might fall outside the groups of intravenous drug users and homosexuals.

But I stress that study had not been reported publicly at the time of this meeting.

You may also feel, sir, that it is unlikely that the CDC would have made figures, their figures, available only to Cutter. There would have been no purpose in them doing so.

Moving on from that meeting, and this is -- you've said, sir -- between those two meetings you have the announcement from Dr Gallo and then Secretary Heckler about the isolation of HTLV-III.

By June 1984, 49 cases of AIDS in people with haemophilia had been identified in the United States. The following month, on 13 July 1984, there was a publication in MMWR, which was a preliminary report

prepared by the CDC, using the first generation of LAV tests, so the tests that they have developed with Dr Montagnier. That showed that 18 of 25 asymptomatic people with haemophilia tested positive for LAV, as did two-thirds of a larger sample size, the references for those are at paragraph 205 of the written presentation.

On 16 July, the study group that had been chaired by Dr Rodell on anti-HBc testing presented its final report. The majority continued to oppose the introduction of the test, they cited the lack of specificity, the 6 to 20 per cent rejection rate for plasma, an increased risk of hepatitis B transmission, plasma shortages and price increases. The minority argued that the tests would have identified 60 to 80 per cent of homosexual men, but they accepted that it would no longer be worth implementing anti-hepatitis B core testing in light of the identification of HTLV-III and the prospect of a screening test that was specific for AIDS.

Later that month, July 1984, there was some discussion of an industry-wide public relations campaign. You've seen the documents in respect of that, sir. We don't know how far that campaign went, but the references are at paragraph 207 of the written

presentation, if people wish to pick them up.

So that takes us to the end of July 1984, which is where we're going to break with the strict narrative, chronological narrative, that we've had so far, to summarise the position at that point: the debate about the safety of blood products in the first half of 1984 had predominantly been about anti-hepatitis B core testing.

The coalition of two of the fractionation companies, Armour and Alpha, and a number of blood banking organisations had successfully resisted calls from the FDA to introduce such testing, and had done so until a point in time when even advocates of testing were resigned to waiting for the emergence of a specific test for HTLV-III. However, two companies, Hyland and Cutter, had taken a contrary view. The latter had unilaterally introduced anti-HBc screening tests, despite pressure not to do so.

Product withdrawals had continued in the first six months of 1984, as had the increased number of AIDS cases identified among people with haemophilia. Initial results on patient testing had also provided evidence of devastating rates of infection within that community in the United States.

SIR BRIAN LANGSTAFF: Do we actually know how many

withdrawals there were in this part?
MR HILL: Up until this point, four.
SIR BRIAN LANGSTAFF: In 1984?
MR HILL: Yes.
SIR BRIAN LANGSTAFF: They're the four you mentioned earlier.
MR HILL: The four that we mentioned earlier, yes.
SIR BRIAN LANGSTAFF: So when you say product withdrawals had continued --
MR HILL: They had continued -- the last two of those withdrawals had been in the early months of 1984.
SIR BRIAN LANGSTAFF: Thank you.
MR HILL: The year had, however, seen the announcement of the isolation of the HTLV-III virus, and the granting of licences for heat-treated products, all four companies had a licence for heat-treated products, and it's to heat treatment that we will now turn.

In the written presentation I set out why it is that no effort is made today to try to provide a comprehensive presentation on the development of the heat treatment, it is a very complicated and dense story. The main narrative events are the ones that I will seek to highlight today.

There is an abundance of evidence, you may feel, sir, that during the 1970s, Factor VIII and Factor IX

were considered to be highly heat labile proteins, such that they would not survive the sort of heat treatment that was used as a method of viral inactivation on, for example, albumin, and you'll recall the evidence of Sarah Middleton. However, in 1977, the German company, Behringwerke commenced work on heat treatment studies with a view to providing factor concentrates with lower risk of hepatitis transmission. So that's 1977 that we have a date for Behringwerke beginning these studies.

By the following year, 1978, Hyland had begun some form of research on heat treatment of Hemofil. There is a memorandum dated 26 April 1978, stating that that work required additional funding and manpower if it was going to be progressed. Hyland's parent company, Travenol, appears to have obtained information from its German subsidiary about the Behringwerke process, but encouraged further efforts in that field.

If we could have on screen, please, CGRA0000222. This is an internal Hyland document marked "Confidential Division Priority List September 1979." The division, I take to be Hyland division of Travenol. 1, top of the priority list is Autoplex, which was the product intended for patients with

Factor VIII inhibitors:

"2. [Antihaemophilic] Hepatitis Risk Removal

"A. Heat Inactivation/Radiation

"B. Ultrafiltration/Glycine."

So two different methods of viral inactivation which are the second item on Hyland's division priority list as of September 1979. Other documents are referred into the written presentation as well.

Behringwerke obtained a German licence for its product in early 1981. That product was pasteurised, so that's heated in a solution, at 60ºC for 10 hours. It's important throughout this section to keep in mind the different methods of heat treatment, as well as the different temperatures used. Behringwerke's was a true pasteurisation technique which means that the product was heated in a solution.

That product was not, at that time, licensed or marketed in the US and the UK, and there were various drawbacks to it, including the fact that there was very low yield. At about the same time, early 1981, Hyland were proceeding to clinical trials in humans of Hemofil-T. We heard a little about that from the evidence of Dr Kingdon that we looked at in September and October.

Other companies had also commenced work on

heat-treated products by this time. There is a Cutter budgeting document from 1983, I won't bring up the document but I will just summarise what we have taken from it, and it's at paragraph 215 of the written presentation. That document suggests that in 1981, the total amount spent on research and development by the drug research and development division was $4.2 million, or $4.27 million. Of that, $293,000, 6.9 per cent of the budget, was spent on hepatitis-free product development.

In 1982, an estimated $558,000 of the same budget was forecast to be spent on that project, which was 9.2 per cent of the total. In addition, an estimated $102,000 was estimated to be spent from the technical operations division on the project, which was 5.1 per cent of that budget. The notes to the budget describe the project as being, and I quote:

"... a defensive move necessary to maintain AHF market share."

The 1983 budget included a projected $632,000 under the international division budget, which was 36 per cent of that total budget, which seemed to be earmarked for applications for a Japanese licence and for testing in the first quarter of 1983. Now, we don't suggest, sir, that these numbers are the sole

figures for what was spent by that company at that time, they're what we can discern from the document that we have.

If we could have on screen, please, Soumik, JREE --

SIR BRIAN LANGSTAFF: Just before you do that, this is looking at Factor VIII?

MR HILL: The project is referred to as hepatitis free product development.

SIR BRIAN LANGSTAFF: Because in -- I have a note to myself that -- the reference is BAYP0003708 -- that the Cutter's "Biochemical Research Department Quarterly Progress Report for April to June 1972", so 10 years earlier, more or less, showed that experiments had been conducted to see if the virus with which Factor IX had been spiked could be inactivated without the Factor IX losing its activity, and suggested that the activity was indeed maintained if certain salts were used; in other words, the Factor IX could be stabilised and I think the virus in that experiment remained active.

But it may indicate that there were certainly moves in the early '70s to look at whether heat and stabilisers might be an answer, so far as Cutter was concerned.

MR HILL: Yes. I think it's fair to say that the heat development techniques that were developed in the early 1980s were generally applied to both Factor VIII and Factor IX, but there were additional difficulties with Factor IX, particularly in establishing that the resulting product didn't cause blood clots. You heard a little about that from Dr Middleton. There was a considerable concern amongst the clinicians about thrombogenicity.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: But the way -- when we looked at the licensing of these products, we would often see that the same heat treatment regime was applied both to Factor VIII and Factor IX, and so I have taken it that the work in the early '80s was being done generally on factor concentrates, and then the licences would be applied for specifically the Factor VIII and Factor IX --

SIR BRIAN LANGSTAFF: I think my question was directed towards activity on the research front anyway, during the 1970s, given that there had been some evidence of some in 1972.

MR HILL: Yes. As I understand it, the concern in the 1970s, and it's often in the papers presented as a received wisdom --

SIR BRIAN LANGSTAFF: Do we actually have any documents

about this that you're aware of, so far as pharma are concerned?

MR HILL: There are many thousands of documents that we have and there will be some references to -- or there are -- certainly from Cutter, there are a large number of documents in which do refer to research products.

SIR BRIAN LANGSTAFF: Because, in due course, I will be quite interested in the progress of research into inactivation of virus in products during the 1970s.

MR HILL: That is something that we can look into, sir, as I say, it's a fairly significant.

SIR BRIAN LANGSTAFF: This is now, I think, not the time to deal with it.

MR HILL: No, I certainly won't be able to do it on an *ex tempore* basis.

If we could have JREE0000019 on the screen, please, page 106.

This is taken from the Institute of Medicine report, and it's a helpful table which sets out when licences were applied for and when they were granted.

I've mentioned these as we went through, but it's perhaps helpful just to look at this now.

Baxter, which is the parent company of Hyland, the application for a licence was made in June 1982, and it was granted in March 1983, a period of

nine months.

We then have Miles, which is -- perhaps -- I think it might be more helpful actually to take it chronologically. So:

Baxter, June 1982, granted March 1983.

Armour, this is Factor VIII, December 1982, granted January 1984, so 13 months.

Alpha, which is -- I should have mentioned the Factor VIII is dry heated. The Hyland product was dry heated. There was a different -- both were heated at the same temperature, 60 degrees. Hemofil was heated for 72 to 74 hours. And Factor VIII was heated for 30 hours. That may be of some significance later.

Alpha applied for its licence for Profilate in December 1982, and it was granted in February 1984. It's referred to as "wet heat" there.

As we've discussed before, sir, it was heated in suspension, so not a true pasteurisation, but a suspension. But 60ºC for 20 hours.

Then we have Cutter. They applied for and received two licences. The first was for a pasteurised product, heated at 60 degrees C for 10 hours, so similar to the Behringwerke product. That's applied for in August 1983, and approved in January 1984. And then a dry-heated product, 68ºC for

72 hours, applied for in November 1983 and granted in February 1984. So the speed at which these licences are granted increases in late 1983.

I also point out there that the Miles dry heat treatment was heated at a higher temperature, 68 degrees, than both the Hyland and the Armour product, and it was heated for 72 hours, which was longer than the Armour product, and about the same time as the Hyland product.

Immuno don't appear to have sought an FDA licence for their heat-treated Kryobulin. Their UK application was made in December 1984, and it was approved in February 1985. So a short period. And you will recall, sir, from the licensing section, that the DHSS were encouraging the pharmaceutical firms in the autumn of 1984 to put in applications for their heat-treated products.

SIR BRIAN LANGSTAFF: When the meeting at Heathrow Airport took place on 24 January 1983, Immuno were presenting on a method of chemical inactivation.

MR HILL: Yes, they were.

SIR BRIAN LANGSTAFF: Do we know anything more about that? Did anything come of it?

MR HILL: There are a couple of documents from later in that year, where the ...

SIR BRIAN LANGSTAFF: Just take a moment.

(Pause)

SIR BRIAN LANGSTAFF: Yes?

MR HILL: There were a couple of documents from later in that year which indicated that Immuno had given some presentations at conferences, hinting at this process and the work that they were doing on it. What appears to have happened, or may have happened, is that the heat-treated products were seen as a more likely avenue of success from later in 1983, and therefore Immuno's attention turned towards that method, and away from the chemical separation that they had been previously discussing.

I have to say the chain of documents doesn't allow for a full answer to that question. That is my analysis of what was going on.

It's a pertinent point, sir, because although we are focusing here on heat treatment, as we saw with the earlier Hyland document, there were other made of viral inactivation which had been considered and worked upon by the companies as well. But by this stage the heat treatment seems to have been the one that had gained priority from all of the companies. The New York Blood Center had worked on a solvent detergent method in the 70s and the 80s and that was

later picked up by some of the companies and taken forward.

That led to a second generation of products which were safer in respect of non-A, non-B hepatitis in particular.

It's clear from the documents, and indeed from the chronology, that the initial work that was undertaken on heat treatment was for the purpose of inactivating hepatitis, and not AIDS, it pre-dated the knowledge of AIDS. We've seen the meeting that took place on 9 September 1982, where fractionators met with officials from the US federal government and the discussion there was on hepatitis and AIDS wasn't even mentioned in the record of the meeting.

I won't go back to that meeting, but at paragraph 219 of the written presentation there is a summary of some of the topics that were discussed and some of the difficulties that the companies were having as of 9 September 1982 in heat treating their products: difficulties in plasma protein denaturation, the protein being heat labile; difficulties with chimpanzee experiments, which were described as being slow and fraught, with inherent problems; whether to change inactivation processes known to inactivate hepatitis B virus in order to seek to inactivate

non-A, non-B hepatitis; and the use of marker viruses for non-A, non-B hepatitis and the difficulties involved in using them. No consensus could be reached on that point.

Non-A, non-B, at that stage, was known to exist, but there was no test for it, which hampered an ability to assess how effective your product was.

There was also the discussion about the use of clinical trials, which -- including clinical trials following on from chimpanzee trials.

So those were some of the difficulties that were present in September 1982.

Turning back then to the period from 1983 and 1984, when the products began to come on the market. The early heat-treated products were treated with some scepticism by haemophilia clinicians. There were doubts, which turned out to be justified, about their effectiveness in inactivating hepatitis, and particularly non-A, non-B hepatitis. And doctors were concerned that heat treatment of the products could give rise to the development of inhibitors in patients. Again, Dr Middleton mentioned that in her evidence.

Dr Evatt, in his Tragic History, I won't take you to it, but I quote him from it, wrote that:

"Because of the high cost and feared risk, the [Hyland] product did not achieve widespread use."

Dr Kingdon gave similar evidence in his draft witness statement from 1990, so there was a reluctance from some haemophilia doctors to take on these heat-treated products.

Just to re-emphasise, the three areas are -- that emerged from the evidence are: questions about their effectiveness against hepatitis; concerns that they may give rise to the development of inhibitors, which would mean that patients could no longer be treated with standard Factor VIII concentrates, be they heat-treated or not; and also the factor of cost, these products were more expensive.

Similar doubts were expressed in the United Kingdom, and I've given some references in the written presentation to, for example, the letter that Dr Gunson wrote to Dr Walford on 29 June 1983. And there was also a discussion of heat-treated products on the 13 July 1983 meeting of the Biologicals Subcommittee of the Committee on Safety of Medicines.

As late as June 1984, Dr Aledort, who was by then working for the World Federation of Hemophilia, or at least working with the World Federation of Hemophilia, wrote, and I quote, that he was:

"... strongly opposed the industry's inclination to stop manufacturing non-heat-treated FVIII and FIX concentrates. He cites the possibility of neo-antigen formation with [heat-treated] products, the extra cost involved, and the fact that there is no direct evidence that heat treatment eliminates or reduces the risk of AIDS to haemophiliacs."

So that's June 1984.

Although the products were originally developed to tackle hepatitis, it was the AIDS crisis that led to them becoming more rapidly licensed and accepted for use. As we've seen from that table, the time lapse between an application for the licence from the FDA and the licence being granted shortened considerably as time passed, and we've mentioned as well the UK position in that respect.

The work done by the CDC on developing an assay to measure viral load in factor concentrates was also an important catalyst. That goes back to the cooperation that I mentioned before the break between the CDC and Dr Montagnier and his team.

According to Dr Evatt, in his Tragic History, in August 1984 the CDC presented results of studies at a conference of the World Hemophilia Congress Rio de Janeiro which showed that there was

LAV inactivation by heat treatment. And, of course, by August 1984 HTLV-III had been isolated as well, and there was some debate about whether or not the two were the same virus, but an increasing acceptance that they were.

So that's August 1984, when those results are presented.

According to Dr Evatt, clinicians still expressed scepticism and that led to further experiments taking place, particularly conducted by Dr Steve McDougal, Dr Evatt's colleague at the CDC. And Cutter and later Alpha were to provide concentrate to Dr McDougal. That concentrate was then spiked with virus, subjected to the heat inactivation techniques in a laboratory setting, and the CDC demonstrated there that there was a reduction in -- viral inactivation. That was taking place in September 1984.

Also in September 1984, Dr Jay Levy published results of his work on inactivating mouse retrovirus by heat treatment. That was reported in The Lancet, and mouse retrovirus was thought to act in a similar to retroviruses in humans.

So gathering evidence as of September 1984 as to the effectiveness of heat treatment.

Events then moved rapidly. In September 1984 a conference was held between haemophilia clinicians and the CDC, at which there was agreement that physicians should consider changing to heat-treated factor concentrates.

In October 1984, the Medical and Scientific Advisory Committee of the National Hemophilia Foundation advised physicians to "strongly consider" changing to heat-treated product. The CDC published the results of Dr McDougal's experiments in MMWR on 26 October 1984, but of course preliminary results have been discussed with the various bodies before then.

The same edition of MMWR recorded 52 cases of AIDS in people with haemophilia.

The Groningen conference of various haemophilia clinicians and fractionators took place on 1 September 1984. Further presentations made there on the efficacy of heat treatment.

In December 1984, an editorial in The Lancet advised that it was reasonable to take a pragmatic approach and switch haemophilia A patients to heat-treated products, notwithstanding the lack of clinical evidence of their efficacy against AIDS.

So until that stage the studies had been done on

a laboratory basis showing viral inactivation, they hadn't been traced clinically. But despite that, The Lancet were saying that a pragmatic approach should be taken.

In the same editorial, and in the context of a call for additional funding to purchase such products, the editorial suggested that it would be, and I quote:

"... indefensible to allow prescription and home use of material known to be at risk of HTLV-III when apparently safer preparations are available."

That is December 1984.

In February 1985, they first publish reports appeared in The Lancet again, showing the result of a clinical trial of Hemofil-T, which appeared to demonstrate that it did not transmit HTLV-III to the patients that had used it. We heard something of that from Dr Kingdon in September and October. That was Professor Mannucci's trial. Dr Kingdon points out that was the first clinical evidence of the efficacy of heat treatment, to go with the laboratory evidence which had been emerging since August 1984.

Dr Kingdon said that Hyland ceased the sale of all non-heat-treated Factor VIII concentrates in the United States in January 1985 and, on 13 March 1985,

Cutter wrote to Dr Geoffrey Savidge at St Thomas' Hospital to say that the company felt that it was "prudent to no longer affect sales of non-heat-treated product for used in the United Kingdom".

From 15 to 19 April 1985 a conference was held by the World Trade Organization in Atlanta. During the conference, the positions that non-heat-treated products should not be used was advocated but it's not clear from the documents whether that generated a consensus of opinion. The conference, however, did endorse and recommend the use of heat-treated products. So there is a distinction between encouraging the use of heat-treated products and the question of whether you should also stop the use of non-heat-treated products.

Also in April 1985, the National Hemophilia Foundation revised its treatment recommendations to recognise that heat-treated concentrates "may be the preferred products" for infants and children with severe haemophilia and for newly identified and previously untreated severe haemophilia patients.

It continued to advise the use of desmopressin or cryoprecipitate in patients with mild or moderate haemophilia, and it wasn't until December 1985 that the NHF advised that only heat-treated products should

be available for all patients. Sorry, that's all patients with severe haemophilia.

So, as well as these clinical recommendations which are going to the clinicians, the availability and use of heat-treated products and their apparent efficacy led to discussions about whether or not there should be a change in approach to the recall of products that were known to have been contributed to by a patient who later developed AIDS. In April 1985, so around the time of the World Health Organization conference, the National Hemophilia Foundation reversed its previous position and declared that it no longer recommended the recall of concentrates contributed to by a donor later found to have AIDS if those concentrates had been treated with the licensed heat-treated process. The basis for that change in position is that the heat treatment would have, and I quote "adequately killed" -- that's the end of the quote -- the virus contained in those concentrates.

The change in the NHF's position was cited by Alpha in a letter to the FDA on 30 April 1985, in which it explained that it didn't intend to withdraw vials of factor concentrate that had been produced using plasma from a donor later diagnosed with AIDS. That letter sets out a series of calculations in which

the company shows that, even on a worst-case scenario, the heat treatment proposed would, in their view, have inactivated the amount of virus that was in that product, and so they say there is no need then to recall it, and they also point to the fact that the NHF are no longer calling for such products to be withdrawn.

The letter makes it clear that the company had discussed this position with an official of the Bureau of Biologics and counsel to the Inquiry haven't identified any subsequent correspondence from the FDA saying, "No, you shouldn't do this".

While this was going on, non-heat-treated concentrates that were still in circulation continued to be withdrawn by companies. On 3 May 1985, Armour withdrew seven batches and, in June 1985, Hyland announced a withdrawal of products. These are non-heat-treated products that were still available.

SIR BRIAN LANGSTAFF: Was that in the States or here?

MR HILL: Those withdrawals were announced in the States, it's not always clear from the documents where the concentrate had gone to. We will be hearing tomorrow about an Armour withdrawal that took -- specifically of a product in the United Kingdom, and I'll refer to that a little later, but I'm not going to pre-empt the

evidence, so I won't go into that in great detail.

This was then a period where heat-treated product was becoming increasingly available and increasingly used but non-heat-treated product was still in circulation, and there is some evidence that Cutter sought to sell non-heat-treated products, including from stock held in Britain, to overseas markets that had not at that time adopted heat-treated products. If we could have on screen, please, CGRA0000583.

This is an internal memorandum from Cutter dated 10 April 1985. It is entitled "Inventory of non-heat-treated Koate in the United Kingdom", and I'll read from the memorandum:

"In a recent trip report from Jack Wood, Jack indicated that the transfer price value in US dollars of the non-heat-treated Koate inventoried in the [United Kingdom] is $395,273.53. As you know we are attempting to sell some of this merchandise into Hong Kong and Taiwan. Jack indicated that Brian Dyos will be discussing with Trevor Barrowcliffe a dating extension allowing for relabel and continuous selling into markets not yet converted to the heat-treated Factor VIII products.

"I'll keep you posted as we progress in this

project."

Jack Wood was a Cutter employee who was involved in distributing Cutter products in Europe and Trevor Barrowcliffe is a civil servant within the National Institute of Biological Standards and Control (NIBSC). We don't know at present how far those discussions with Mr Barrowcliffe got -- or Dr Barrowcliffe got.

If we could go, please to CGRA0000581, we can see that this is a memorandum from Jack Wood, who was referred into the previous memorandum, dated 15 April 1985. It's called "Koate Returns from United Kingdom". If we could just read this, it's addressed to a colleague called Gary:

"Gary,

"On behalf of Cutter UK I would like to express our appreciation for the efforts you have made in marketing to other countries their inventory of non-heat-treated Koate.

"The 4,000 vials of 250 material will significantly help in reducing this inventory, but we still have on hand close to 4 million units as listed in your letter ... Two major lots are 2,877 vials of [the product reference number is given] and 1,434 vials [of another lot of product]. We will do everything possible to sell this product in European

countries not yet converted to heat-treated product.

"Thank you again for your efforts and we look forward to the positive results that you will achieve on the rest of this inventory."

We can take that down. A similar memorandum was sent, which is referred to at paragraph 233 of the written presentation, to another Cutter employee, and that memorandum referred to the fact that Cutter would be willing to subsidise the sale of the remaining non-heat-treated product on the basis that it was better to have a lower profit than a total loss.

Such an approach is also evident within the United Kingdom in this period.

If we could have on screen, please, CGRA0000561. We can see that this is sent to Dr Tuddenham, at the Royal Free Hospital, and it's send by Linda Frith, the sales development manager at Cutter UK. It says this:

"Dear Dr Tuddenham,

"Brian Dyos asked if I would contact you regarding a lot of Koate regular products in our inventory. We have available a lot of 1,045 vials, 260 [international units] with an expiry date of 13.7.85. After speaking with our financial advisers I would like to lower the price of this material to 4.75p per [international unit].

"I hope this price is more acceptable to you. If you are interested in this batch, could you let me know as soon as possible."

Now, sir, we don't know whether or not this was heat-treated or non-heat-treated product. But the expiry date of 13 July 1985, the fact that this letter was being sent in May 1985, and in the context of the previous memoranda that we've looked at, and the very low price of the product, 4.75p per unit, might indicate that this is non-heat-treated product which is being offered on a discount basis. We don't know what Dr Tuddenham said in response.

A later memorandum, dating from 1987, recorded that Cutter sold both heat-treated and non-heat-treated products in parallel in the United Kingdom until October of 1985. So that memorandum would certainly allow for the sale of non-heat-treated products within the UK as of May 1985.

A formal letter that was subsequently sent by the company to a solicitors firm -- so one can infer that that was part of legal proceedings -- stated that after February 1985 non-heat-treated product was supplied, and I quote:

"... only in response to specific requests for

it from Haemophilia Centres."

Sir, I'm about to move on to a meeting which took place in the United States in May 1985 on the question about what, if any, non -- what regulatory action should be taken over non-heat-treated products.

That's the last section, as it were, really, on heat treatment, and will take a little bit of time to go through, so I wonder if now might be a --

SIR BRIAN LANGSTAFF: Let's take a break then, shall we, and come back at 2? 2 o'clock.

(1.01 pm)

(The luncheon adjournment)

(2.00 pm)

MR HILL: Sir, before returning to heat treatment, I realised over lunch that I skipped over, inadvertently, a piece of information that I should have given you earlier. It is about Cutter and it's the hepatitis B testing.

That testing continued until the end of October 1984. It was discontinued at that time, mainly because it was stated that there was sufficient confidence in the heat treatment process at that time to allow for the discontinuation of the anti-hepatitis testing. It was also noted in the internal company documents that a specific test for HTLV-III was

expected shortly. That's at paragraph 203 of the written presentation.

Moving back to heat treatment. On 30 May 1985, a meeting took place between the FDA and fractionators about the question of what, if any, regulatory action should be taken over non-heat-treated products. If we could have on screen, please, BAUM0000025. Please ignore the highlighting on this document, that's not ours. The date of the document is 30 May 1985, it's from Dr Ojala and, as we know, Dr Ojala is a regular source of our information for such meetings, and it's an internal Cutter memorandum.

The memorandum says:

"Dr Harry Meyer [who is a senior figure within the FDA] called this special meeting of all producers of coagulation products to discuss the use/productions/license of non-viral inactivated products."

"Non-viral inactivated products" we take to mean heat-treated products.

SIR BRIAN LANGSTAFF: No, not heat-treated products.

MR HILL: Sorry, yes, non-heat-treated products, yes. Thank you.

The attendees included Dr Petricciani and Dr Donohue from the FDA, as well as a number of other

members of the FDA, and the figures from the industry that we've become accustomed to seeing at these meetings: Dr Ojala; Dr Holst of Hyland; Dr Carr from Alpha; from Armour there is a D Marcus rather than Dr Rodell, who was usually present; also representatives of Hoechst, Immuno, the American Red Cross, and Bob Reilly of the American Blood Resources Association trade body.

If we can go back to the text:

"Dr Meyer explained that the major manufacturers of coagulation products (AHF and PTC) have been approved for a viral inactivation process for some time, and the data demonstrated reasonable performance for eliminating HTLV-III virus from the final product. He questioned the utility for a non-treated process given the current situation and requested that we uniformly send letters to the FDA stating we would no longer produce or distribute non-heated product to preclude negative reaction from the medical community and the general public. He indicated that everyone spoke as though heat treating processes had eliminated the potential for HTLV-III viral exposure from these products, and no-one had really focused on the fact that the ability to produce non-treated products still remained possible with the current licences. He

explained that although the FDA could revoke these through the regulatory process, he did not want any attention paid to the fact that the FDA had allowed this situation to continue for so long, and he would like the issue quietly solved without alerting the Congress, medical community and the public. Implicit in the discussion was the concern that the FDA felt that this action was long overdue. He wanted a date (such as June 1), for the letters from us."

Over the page, please:

"Industry responded with a list of reasons why they had particular problems with the proposal, including the value of the inventory in our control, the lack of inhibitor indication for PTC, Alpha's pending dry-heat approval, Hyland's non-approval for Autoplex, etc. Everyone had a reason and Hyland mentioned an 18 million unit AHF inventory that would have to be reworked to heat-treat product.

"The industry position was that that we would need rapid review of pending submissions and some time to review the situation with our management. Several proposed a staggered elimination of non-heat license, starting with AHF and moving into other areas as feasible, and the international situation was reviewed extensively.

"Meyer replied that he understood the situation and could sympathize with the difficulties but that did not remove the overriding concern that no one anywhere in the world should be allowed continued exposure to HTLV-III for any of the reasons mentioned. He specifically mentioned that the Japanese registration would soon occur, and he would assist with rapid review and approval for submissions, but the de-licensure of all products had to occur soon.

"I spoke with Aronson following the meeting and he reported the problem with the review was that 'there are those who seek to license heat treating processes with low temperatures and short times, which the FDA finds unacceptable'. This was briefly reviewed during the meeting and Hyland (Holst) stated that Cutter had made it difficult for the rest of the industry by using such 'extreme' temperatures for so long a duration and thus established precedent. I could only respond that we had arrived at the time and temperature following extensive development work, and that our process was satisfactory for our product. I sense that Hyland is seeking to increase the severity of their inactivation step, the FDA is concerned about the limitations of both the Alpha dry heat and NY Blood inactivation processes. The FDA

will meet internally during the interim to review the special situations.

"We agreed to review this internally and meet again with him on June 17 to finalize our actions and the timetable. It is clear that Meyer intends to solve this problem quickly, with or without our cooperation."

That's where we will leave that document, sir.

SIR BRIAN LANGSTAFF: Well, just if we take away the highlighting and go back to the top of that page, the last in sentence, in the first paragraph:

"Everyone had a reason and Hyland mentioned an 18 million unit AHF inventory that would have to be reworked to heat-treat product."

Is the implication from that that Hyland, at least, and possibly some of the others, had in stock non-heat-treated products, which, despite the comparative lack of safety, as it was thought, they wanted to sell and intended to sell?

MR HILL: I think that is -- well, it's certainly an inference that can be drawn and perhaps might be the only inference from that sentence. I would also point to the reference to the international situation being reviewed extensively, and that is taken with Dr Meyer's comments that nobody in the world should be

exposed to HTLV-III.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: It seems to be the same issue that we looked at in the memorandum before is arising, that in countries which have not yet adopted a requirement for heat-treated products, non-heat-treated products might still be sold, too.

SIR BRIAN LANGSTAFF: So the position was that, so long as -- at least the implication is that the position is that, so long as countries in the worlds which did not themselves take a regulatory position which prevented the use of non-heat-treated products, could be sold and would accept non-heat-treated product?

MR HILL: That is certainly what I take from this document, yes, sir.

SIR BRIAN LANGSTAFF: Yes. That would be a matter for them, and their legislatures or organisations or their executive, whatever the particular situation in a particular country was.

MR HILL: And indeed for the doctors in those countries as to whether or not they (a) wanted to use that product and (b) had any choice in using that product.

SIR BRIAN LANGSTAFF: They may not have had clinical freedom in the same way as doctors in the UK did.

MR HILL: Indeed, and they may not have had access to the

more expensive heat-treated products.

SIR BRIAN LANGSTAFF: Yes. Yes, thank you.

MR HILL: The situation at the end of that meeting is that there is going to be another meeting on 17 June. We don't have the minutes of that meeting, though we do have other documents which demonstrate that it took place. But even before 17 June we see some of the fractionators pre-empting matters and taking their own steps.

On 3 June 1985, Hyland announced that it was discontinuing production of non-heat-treated Hemofil and Proplex and that it would recover any used units and replace them with heat-treated products. The public statement commented that this was being despite there being no clear scientific evidence that either of the products was involved in the transmission of AIDS. That's at paragraph 238.

I note that Dr Kingdon, in his 1990 statement, had said that Hyland had stopped the sale of all non-heat-treated Factor VIII concentrates in the USA on 31 January 1985.

That might take us back to the point that you have just made, sir, that these were still being produced as of June 1985, presumably for sale elsewhere; not necessarily Britain, I should add.

SIR BRIAN LANGSTAFF: No.

MR HILL: The Inquiry also has a document from Dr Rodell of Armour. He wrote on 12 July that Armour was "no longer manufacturing or distributing untreated Antihemophilic Factor (Human) for domestic utilization". So no longer making or selling unheated products in the US.

He said that the company was still continuing to export unheated products to German. That was, and I quote, "for heat treatment at that site".

That was being done because that was a more efficient way of providing that product to markets that were supplied out of Germany.

There is no reference in Dr Rodell's letter to Armour withdrawing or replacing the non-heat-treated products.

If we could have on screen, please, CGRA0000396.

This is a Cutter document which tells us something of Cutter's response. If we could have page 2 of this, please. You can see it's entitled "Coagulation Update 28 June 1985". What it says is this:

"Non Heat Action

"Effective 21 June 1985 all non-heat-treated KOATE and KONYNE were discontinued for sale in the

United States. A letter was sent to all customers who purchased these products in 1984 and 1985, announcing action and recommending return of any existing product. Internationally, a telex and bulletin were sent to all distributors and all affiliates announcing similar action. We are not requesting return of existing inventories of non-heat [treated] products internationally due to difficulties in customs licences, etc.

"No estimation of the volume of returns to Clayton available to date."

"The NHF and WHF [that's the National Hemophilia Foundation and World Federation of Haemophilia] -- have complimented Cutter for the action. The phone calls received from Customers all have been very positive, none have been negative. Most common remark is that of appreciation and admiration for the responsibility shown by Cutter. Additional comments have been on the completeness of the announcement package as compared with Hyland's letter."

If we go on, please. This is describing the situation of Cutter's competitors. This is Cutter's understanding of the situation:

"Competitively, Hyland announced similar action on 11 June 1985 but did not remove non-heat treated

Proplex and Autoplex."

Now I pause there to say, sir, that that's not entirely consistent with the letter which we have and which I refer to at paragraph 238 of the written presentation, which does suggest that Proplex has been replaced. It may be that Hyland's position on it changed or it may be that Cutter have misunderstood the situation there.

On 19 June -- sorry, returning to the document:

"On 19 June 85, Hyland recalled four lots of Proplex due to an AIDS donor in the plasma pool. Armour is reportedly not withdrawing any non-heat treated products. Alpha has reportedly sold all existing non-heat treated Profilnine to the [New York Blood Center] leaving them with no existing inventory and no plans to make an announcement."

I think we can take that document off the screen now.

Counsel to the Inquiry haven't been able to identify any documents from Alpha itself setting out its position and actions at that time, but that Cutter note that we have just looked at would seem to imply that all of Alpha's Factor VIII product, Profilate, was being heat-treated at that time, so that may be why there is no specific announcement.

It appears that these steps that were taken by the fractionators were sufficient to avoid the imposition of a further regulatory requirements. In his --

SIR BRIAN LANGSTAFF: Further?

MR HILL: Or -- and, indeed, any regulatory requirements in this --

SIR BRIAN LANGSTAFF: Because the earlier March plasma -- that wasn't a regulation it was a recommendation.

MR HILL: It was a recommendation, yes. And even, I think, "recommendation" can sometimes have a technical meaning and I don't think it even had that with the FDA; it was a public statement, as it were.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: So these steps avoid the imposition of any regulatory requirements.

Dr Kingdon said that he didn't recall any general product recall, and the Krever Report recorded that it was not until 1989 that the FDA record the recall and destruction of all non-heat-treated factor products.

In his Tragic History, Dr Evatt wrote that by the beginning of 1985 little non-heat-treated Factor VIII was being used anywhere.

If we could bring up, please, CVHB0000042, and

page 7 of it. If we could go down to the section just above "Acknowledgements", and expand the final paragraph.

There is a short explanation of some of the meetings that we have discussed earlier. What Dr Evatt goes on to say is this, and I quote from about halfway through that final paragraph:

"The world's hemophilia community quickly adopted the MASAC [that's National Hemophilia Foundation] recommendation, so that by the beginning of 1985 little non-heated clotting FVIII was used anywhere. The AIDS epidemic in the hemophilic patients thus suddenly ceased. Subsequent studies of birth cohorts demonstrated that no hemophilic patients, born in the USA in 1985 and later, were [identified] with" --

SIR BRIAN LANGSTAFF: It's "infected".

MR HILL: I'm sorry, sir?

SIR BRIAN LANGSTAFF: "... no hemophilic patients, born in the USA in 1985 and later, were infected ..."

MR HILL: "... were infected with LAV, later to be renamed HIV."

So 1985 onwards no person with haemophilia in the United States was found to be infected, if they were born in 1985 or afterwards.

"Tragically, during the period 1981 to 1984, more than 50% of the population of hemophiliac patients in the [United States] had already become infected and these individuals continued to present clinical symptoms of AIDS during the next decade and many would die."

It's on that note that Dr Evatt concludes his Tragic History.

I would add to that that, while the epidemic of AIDS cases may have been brought to an end by the use of heat-treated products, there were still a number of seroconversions that were associated with the use of heat-treated products.

In a review article from 1995, which we looked at in September and October, Professor Pier Mannucci referred to 18 well-documented cases of HIV transmission through concentrates that were subject to dry heat treatment. Many of these were patients who used batches of Factor VIII HT that had been subjected to heat treatment but which contained plasma that had been obtained before the HTLV-III screening test was introduced. Armour withdrew such products from the UK market following consultation with the DHSS in September 1986. My understanding is that those products weren't withdrawn from other markets.

The Inquiry will hear further evidence on this matter and I won't go into it in any further detail now.

It's also important to note that, while heat treatment, and particularly heat treatment in combination with the HIV screening test, was effective in inactivating HIV in these products, the heat-treated -- first generation of heat-treated products did not, in general, prevent hepatitis infections.

By the mid-1980s, most such infections were of non-A, non-B hepatitis, but there were still cases in which heat-treated products were implicated in infections of hepatitis B. The evidence of Dr Vivian Mitchell from the Leicester haemophilia centre and letter that he wrote to The Lancet in the 1980s are evidence of such infections. You heard about those at an earlier stage in the Inquiry.

That is where I will leave the story of heat treatment but, of course, the Inquiry will be hearing further evidence from domestic fractionators, and about domestic fractionators, and heat treatment plays an important part in that the story as well, of course.

I should also flag that at the end of this

presentation I will also briefly speak about what's often referred to as the "Prince controversy" about Dr Alfred Prince and his work on Armour's heat-treated product, and we'll come on to that a little later.

For now, I'd like to turn to the screening test for HTLV-III.

I stress that this part of the presentation is about the situation in the United States, the Inquiry will hear further evidence about the United Kingdom position in due course.

We discussed earlier, sir, Secretary Heckler and her announcement of the isolation of HTLV-III on 23 April 1984 and her prediction that a test would be available within six months. That was to prove optimistic.

In June of 1984, the United States authorities announced that five firms had been invited to develop and distribute HTLV-III antibody tests. They were doing so in cooperation with the US federal authorities, who were providing them with the assets. The first application for a licence for a test was made in December 1984.

The fractionation companies, of course, were aware that this was going on and, in September 1984, a conference call took place between representatives

of the main companies, at which a common position was sought on issues including informed consent, the information to be provided to the rejected donors, and the ever contentious matter of the recall of previously fractionated products where plasma from a donor had tested to be HTLV-III positive.

Dr Hink provided a memorandum of the call, which he succinctly summed up by saying "There was a lot of talk ... which led to nothing conclusive". So that's September 1984.

By 15 February 1984, an industry position had emerged, and we can see that position being set out by Robert Reilly of the American Blood Resources Association in a letter to Dr Petricciani. If we could have on screen, please, BAYP0005650.

If we go down to the third paragraph, please, starting "With the advent", what Dr Reilly wrote is this:

"With the advent of anti-HTLV-III testing, the manufacturers of blood derivative products are faced with a dilemma similar to that which arose with HBsAg [hepatitis B surface antigen] testing, ie:

"1. What steps should be taken when a donor who is given plasma in the past is determined to be positive to a test for anti-HTLV-III?

"2. Further, what should be done with such a donor's plasma still stored at the plasma center and/or at the plasma product manufacturer's location?

"3. What should be the disposition of 'in-process' plasma products containing such units of plasma?

"There are several facts that have emerged which are pertinent to a discussion of the above. First, it is estimated that approximately .05% to 1.0% of the normal donors will react positively to the anti-HTLV-III test. Second, at the very minimum, pools of plasma used in plasma fractionation include at least 1,000 donations of plasma which would mean that it is reasonable to assume that currently all lots of product produced contain plasma with anti-HTLV-III. Third, the risk of transmitting the AIDS virus through plasma products is not nearly non-existent with the exception of non-heat-treated coagulation products."

Go over the page:

"Therefore, our proposal for the handling of the items listed above is as follows:

"1. Intact units of plasma collected from donors subsequently found to be anti-HTLV-III reactive in storage either at the plasma center or the

manufacturer's location and which are not yet 'in-process' would be segregated and disposed of as would any other plasma found to be anti-HTLV-III reactive, ie destroyed or used for other purposes as may be approved by the FDA.

"2. For 'in-process' products containing anti-HTLV-III reactive plasma, no action should be taken. The basis for this proposal is that it becomes obvious that if we were faced with the alternative, that is the removal of these lots of products from the market, there would be either a total lack of availability of these life saving products or, at the very least, a very acute shortage of them.

"There is a second dilemma still currently facing fractionation manufacturers and that is the disposition of lots of coagulation factors manufactured using a heat treatment process which has been shown to inactivate known amounts of viral contaminants and which has been made from a plasma pool which contains a donation or donations from a confirmed AIDS patient. Then is a case we propose that the manufacturer should take no action if he has data showing inactivation of the HTLV-III virus by this heat treatment process."

That is the position of the fractionation

companies put forwards, and if we just go down we can see that the letter is copied to Penny Carr at Alpha, Steve Holst at Hyland, Steve Ojala at Cutter and Michael Rodell at Revlon/Armour.

So the proposal seems to be that if there is a unit of plasma which is found to be positive for HIV antibody, and which hasn't been used in any products and isn't being processed, then it would be destroyed. But if the HIV positive donor is found and the plasma from that donor is already being processed or is already in a product, so long as that product is heat-treated, there is no need to withdraw or recall or prevent it being distributed. That is the proposition that the companies were putting forward. That's on 15 February 1985.

On 22 February 1985, a public meeting took place on this issue -- sorry, forgive me. On 22 February, it wasn't specifically on this issue, it was a public meeting about HTLV-III screening. There is a memorandum which I summarise at paragraph 254 of the written presentation, and that comes from Dr Ojala. He refers to this as being, and I quote him:

"... almost a press conference rather than a scientific meeting, and I believe this approach was intentional."

He goes on to explain that what he meant by that was that he thought that this was the FDA and the CDC using a public meeting to show their confidence in the HTLV-III screening tests that they had helped to produce. Dr Ojala said that that was necessary because of the negativity that had been shown towards the test by a number of representatives of the blood banking industry and what he refers to as special interest groups, which is presumably a reference to gay rights organisations.

So there is a test which has been produced by the FDA and the CDC and the companies involved, there is hostility to that test from the blood bankers and from gay rights organisations, but according to Dr Ojala, Bob Reilly spoke of the plasma industry, "he did not say very much specific other than we thought prompt approval of the test was a good idea". So, again, we see a distinction between the approach of the fractionators and the blood banking industry.

At the request of the fractionators, a meeting took place with the FDA on 26 February 1984. That was to discuss the specific issues that had been raised in Bob Reilly's letter, the question of product recall. It was preceded by an industry-only meeting, as was common and, according to a Cutter memorandum, there

was "no enthusiasm or desire" among their competitors to contest the HTLV-III screening test.

They did say, however, that they didn't want industry to be burdened, as it was put, by the confirmatory test, the Western blot test, which would be used to confirm that a donor was HIV positive. The quotation contained in the memorandum indicates that industry would simply tell a donor that they were being excluded and, so far as they were concerned, that was the end of the matter for them. The quotation is, and I quote:

"... industry cannot afford to deal with running confirmation tests."

So presumably donors would be left to go and seek confirmation on their own.

The meeting also discussed the imposition of ALT testing for the German market. That is something that I'm going to come back to in a second. We can see from the memorandum that Dr Rodell suggested that the industry might want to put forward a proposal to the FDA about ALT testing, in order to avoid regulatory action being taken. We'll come on to see what that discussion led to.

The reference to the memorandum to which I'm taking this from is BAYP0005664. That's a reference

which I've omitted from the written presentation and will seek to rectify that.

So the meeting took place with the FDA on 26 February 1984. I won't take you to any further note of it, because, in essence, the fractionators set out the position as per Dr Reilly's letter, and Dr Petricciani listened but didn't commit the FDA to any response on it.

Following that arranged meeting, an informal meeting took place, and I am going to take you to this, please, it's CGRA0000312. This is a memorandum written by Dr Carr of Alpha. The memorandum is dated 1 March 1985, but it refers to the meeting with the FDA on 26 February 1985. Reading from the top, this is what Dr Carr wrote:

"I had requested a meeting with Dr Petricciani after the Fractionation Industry meeting to include only the four commercial manufacturers. Present were: Bob Reilly [that's of the trade body], Mike Rodell [Armour], Steve Holst [Hyland], and myself. Steve Ojala [Cutter] had to catch a plane.

"We had all agreed that we would introduce the subject by asking the status of the study we" --

I'm sorry, I should have said that the subject heading is "Meeting with FDA on Prison Source Plasma.

"We had all agreed that we would introduce the subject by asking the status of the study we had heard FDA was performing on prison plasma and Bob Reilly did so. Dr Petricciani went briefly into the background of why they decided to institute such testing. He became aware that they were receiving more applications for Source Plasma establishments in prisons. They had had problems in the past with the shipment of [hepatitis B surface antigen] reactive units from prison sources and falsification of records. With the concern over AIDS and concern over the conduct of any kind of studies or activities associated with prisoners, they felt that if there were more and more prison sources of plasma that they were in a very uncomfortable position over how FDA could justify these with no scientific data, particularly in the socio/political atmosphere. If challenged, he believes they must have a scientific basis for allowing this to continue, otherwise this could be a political bombshell."

I pause there, sir, to note -- and this brings us back to the discussion we were having before -- that there is a continuation of the plasmapheresis stations within prisons in the United States in this period. It may be that the plasma being obtained is

not being used in coagulation products, but it is still being obtained, and the FDA are now undertaking a study to see whether or not there is a difference between prison plasma and other plasma.

SIR BRIAN LANGSTAFF: The implication, as I see it from the second paragraph there, is that there is not only a continuation, there is an expansion --

MR HILL: Yes.

SIR BRIAN LANGSTAFF: -- because that's the force of the word "more".

MR HILL: Yes. Yes.

SIR BRIAN LANGSTAFF: So whoever is collecting the plasma is marketing it somewhere --

MR HILL: Yes.

SIR BRIAN LANGSTAFF: -- or using it for some manufacturing purpose itself.

MR HILL: Yes.

The memorandum from Dr Carr then goes on to describe the parameters of the study and the way that the FDA are approaching it. There is a short paragraph, three paragraphs down, which says, and I quote:

"If prison plasma can't be differentiated from non-prison plasma, they would then consider relaxing the guidelines."

It's not entirely clear what the guidelines referred to are there, but it may be an inference that that is a reference to the guidelines from March 1983 about the way in which fractionators should avoid high-risk areas.

SIR BRIAN LANGSTAFF: Yes, but the high-risk areas there didn't include prisons, did they?

MR HILL: I don't know if prisons were specifically mentioned, but there is -- what is referred to in this and other documents is a gentleman's agreement that prison plasma wasn't going to be used.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: So it may be that the reference to guidelines is intended to capture that agreement. But there is certainly no regulatory action which has been taken about prison plasma. You'll recall from the letter or the memorandum from Hyland, there was a conversation with Dr Donohue about what Hyland's position was going to be, and Dr Donohue was offered a written statement from Hyland, and he said that that was not something that he would --

SIR BRIAN LANGSTAFF: Yes.

MR HILL: The memorandum then goes on to talk about the potential target date for the studies and then, at the bottom of that page, if we pick it up again, and

I quote:

"When asked as to what their reaction would be if a manufacturer wanted to do such a study, he stated that they would consider it good complementary information."

Turning over the page:

"I informed him that since we had made these [arrangements] two years ago ..."

SIR BRIAN LANGSTAFF: It's "agreements".

MR HILL: Sorry, "agreements":

"I informed him that since we had made these agreements two years ago, much more had been learned, and with a shortage of plasma now and more expected with the advent of HTLV-III testing, industry management was questioning why the differentiation from other donor sources. I stated this for his information simply to prepare the way for any further enquiries we wish to make on our own.

"Note that Armour apparently has absolutely no interest in this subject but was willing to be present. Steve Holst obviously believes Hyland does have an interest but was really nonparticipatory since he is so new to his job. Although Bob Reilly was willing to participate in discussions on this, he obviously considers this as stated, a potential

bombshell and does not want to press further since it does not represent the majority of his constituency."

His constituency, I should add, is the American Blood Resources Association, so plasma manufacturers and plasmapheresis centres. Returning to the document:

"If we wished to press further it would be my recommendation that we try to do so with Hyland and Cutter."

End quotes.

If we look at the marginalia on the document, written is the question:

"Do we want to pursue?"

In answer to that question, sent to Pete De Hart and signed by Vaughan, it says:

"Pete,

"How much material do we get currently ..."

SIR BRIAN LANGSTAFF: "... (prison plasma)?"

MR HILL: "(prison plasma)", thank you. My written note is somewhere else.

"Could this represent an opportunity to ..."

SIR BRIAN LANGSTAFF: "... source substantial increased amounts?"

MR HILL: Thank you.

"If yes, we probably do want to pursue."

The reference there to getting "currently" might suggest that Alpha is one of the companies which is obtaining plasma from prisons, albeit they have entered into this "gentleman's agreement" not to fractionate it --

SIR BRIAN LANGSTAFF: Well, an agreement, let's call it.

MR HILL: An agreement.

SIR BRIAN LANGSTAFF: Whether it was between gentlemen, we'll wait to see with the rest of the evidence.

MR HILL: There were quotation marks there because it's a phrase which is used in one of the other documents.

So that is a memorandum from 1 March 1985, referring back to that meeting on 26 February, which was about both HTLV-III testing, and then, as a consequence of HTLV-III testing and heat treatment, the possibility of revisiting the issue of prison plasma with the FDA.

On 2 March 1985, the Department of Health and Human Services announced that the first HTLV-III antibody test kit that had been manufactured by Abbott had been licensed by the FDA.

In his 1990 draft witness statement, Dr Kingdon stated his opinion that the seven months that it took between the approval of the companies to begin working on this project and the licensing of this test kit

was, and I quote him, "in scientific terms ... a remarkably short period".

Dr Ojala, in a memorandum, refers to the CDC and the FDA considering that they have made, and I quote, "Herculean efforts" in order to get the test licensed so quickly.

Armour and Hyland began testing donors that month. However, according to Dr Kingdon's 1990 draft statement, there were insufficient test kits available to satisfy US demand until June of 1985.

The Krever Report says that HTLV-III testing became available in all centres by July 1985, and it had been available in the vast majority of centres by May 1985.

So just to give those dates in order again: March 1985, the FDA licence is granted; by May 1985, according to Krever, the testing is being done the vast majority of centres; and in either June or July 1985 there is full capacity for the US market.

A point to note now and come back to in the future is that Dr Kingdon expressed his view in his draft witness statement that, and I quote:

"Until there were sufficient kits available to meet US demand it is unlikely that any of the test kit manufacturers would have been willing to export their

tests abroad."

End quote. I'll leave that there, it's no doubt a matter to which we will turn in due course.

SIR BRIAN LANGSTAFF: The tests were developed before being licensed, presumably.

MR HILL: Yes.

SIR BRIAN LANGSTAFF: Do we know when they were actually developed, and therefore being in use, at least for a testing point of view, in other jurisdictions?

MR HILL: I don't know that on the top of my head, but we can look into that. From memory, there is a helpful table in the Institute of Medicine report, I think, which provides a contrast between different jurisdictions and who is doing what when.

There is always a difficulty in comparing like with like in tabular form, but that's something that I can have a look at in the break and then we can also do further work on trying to understand --

SIR BRIAN LANGSTAFF: From what you showed me earlier, there was an LAV test.

MR HILL: Yes.

SIR BRIAN LANGSTAFF: And LAV -- which was exactly -- my understanding is it was exactly the same basic virus that Montagnier identified, as did Gallo.

MR HILL: Yes.

SIR BRIAN LANGSTAFF: So that was available in August.

MR HILL: August 1984, yes. The CDC had worked to develop that with the Paris team. They were using it -- presenting results from it in the August, in order to do their laboratory work on viral inactivation through heat treatment. In the UK, we also have the development of some form of testing in 1984, from --

SIR BRIAN LANGSTAFF: Yes, I --

MR HILL: I won't try to remember the dates off the top of my head.

SIR BRIAN LANGSTAFF: That may also be August at the earliest.

MR HILL: Yes.

SIR BRIAN LANGSTAFF: But we may well hear from Dr Tedder in due course.

MR HILL: Sir, these are tests which can be done on individual samples.

SIR BRIAN LANGSTAFF: Of course.

MR HILL: But --

SIR BRIAN LANGSTAFF: But if they needed to be used as screening tests, there has to be sufficient quantity to enable the testing to be done.

MR HILL: Just so. And the licensing of the test is the licensing not just of a final test but of a process that leads to it, so it has to be a process of

industrial scale in order to be able to roll the tests out across the country. That is what was licensed in March 1985.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: On 12 April 1985 there is a fractionators meeting ahead of a Blood Products Advisory Panel meeting, so another one of these industry-only meetings. If we could have on screen, please, CGRA0000261.

This meeting sees the debate moving on to a related topic, which is the introduction of ALT testing, that's so a form of liver function test. That was to be instigated in response to the requirements of the German regulators, that any plasma with ALT levels at more than twice the normal level should be excluded from plasma pools for factor products. The German regulator had put that requirement in place. The American firms who wished to sell in Germany therefore had to as the here to it if they were going to be able to licence their products there.

It's apparent from the discussion that it was estimated that around 20 per cent of US plasma would be tested in this way, so that's about 20 per cent of US plasma would be used in products that were

available for the German market.

The issue for the fractionators -- the issues, sorry, for the fractionators were, first, what was to be done with plasma that was, to use the word in quotation marks, "positive" for being twice the normal ALT level. That plasma couldn't be used for a German product, so what do you do with it? But, second, how best to avoid the unwelcome, as the fractionators saw it, introduction of ALT testing for all of US plasma.

With that introduction, we look at the document, which is again another memorandum from Dr Ojala of Cutter, and an internal Cutter memorandum reporting on the meeting. The first paragraph -- there is a list of attendees and then the first paragraph says:

"Penny Carr (Alpha), Steve Holst (Hyland) and I met in the Osaka room at Alpha Headquarters from 9 to 12 on April 12, 1985. We followed this meeting with a 2 hour conference call to Bob Reilly ... and Mike Rodell ... to confirm our plans for testing in the upcoming Blood and Blood Products Advisory Panel meeting. The following are salient conclusions.

"ALT Testing:

"The Ojala script for an industry position was accepted with enthusiasm from Alpha and some reluctance from the others. Gerety [that's

a reference to Dr Gerety of the FDA] (or someone) will express concern to the Advisory panel that use of ALT positive plasma in domestic products will change the character of those products. Our formal presentation will state that we are simply hand selecting (via ALT screening) special plasma for a particular customer (the German market) and that all remaining plasma remains licensed source plasma which may be utilized in other products. The ALT test is not required by the FDA, nor do we want it to become so. We will state that any plasma 2 times normal will not be used for the particular customer."

That's the German market.

"We will further offer that any plasma with 5 times the upper limit of normal will not be used in domestic product and the donor will be deferred until the ALT levels fall back to normal. We will use the argument that 5 times normal may indicate a donor health problem. This may not please all of you, but it was the only way to achieve industry consensus. Further, plasma in the over 2, but less than 5 range will be used randomly in production so as not to concentrate this plasma in any particular lots. All coagulation products will be heat-treated for an extra margin of safety. We will endeavour to call German

plasma 'special' or some other term to nullify the idea that greater than 2 times normal plasma is 'positive' or other negative connotations.

"In practice, Armour will discard all 2X cryo and Hyland will discard all 2X plasma from coagulation products and Fraction II products. We estimate that approximately 20% of total US plasma will be screened, but will vary between manufacturers. Armour requirements are modest, and Hyland will screen all plasma for the interim to 'fill the pipeline'. Alpha will screen only A and B plasma from select centers. Hyland's conservative position is due to Armour's decision (ie, they want to be perceived as conservative in any subsequent litigation) and because they had two patients develop Non A/Non B in a clinical trial of their IVIG in Seattle. Holst thinks it is because of procedures at the clinical site ..."

That's a reference to why he thinks there are positive results there.

"... but Penny thinks it is because of starting with 2 [plus] 3 paste for the Hyland product. The FDA has summoned Hyland to Washington for a 'summit conference' on the Seattle incident. This is delaying their [intravenous immunoglobulin] approval, until

resolved.
"In summary, the minimum industry is:
"1) less than 2 X Normal -- German product
"2) 2 X normal -- 5 X Normal -- Random distribution in domestic product
"3) greater than 5 X Normal -- discards plasma, defer donor.
"This hasn't been approved by FDA, and Hyland and Armour will react more conservatively. I suggest this item be reviewed at the next BC [that's the internal Cutter committee]. Bob Reilly also mentioned that we will need to make some provisions in our business arrangements with our contract centers to preclude them from dumping 'high ALT' plasma on us.
"Prison Plasma:
"This subject [elicits] even more diverse viewpoints. Cutter and Alpha believe that science has [progressed] to the point that we can screen this plasma through testing (HTLV-III E, etc) and we now heat treat the products. Hyland says they have no current prison plasma sources (!) and Armour states that they will never have any. Reilly is perpetually gloomy on the entire subject, and feels we are destined to fail. Nevertheless, we agreed to hang together for a try with the FDA. We will propose to

begin using prison plasma cryo and abandon our 'Gentleman's agreement' unless the FDA takes issue and threatens regulatory action. We will further agree to do whatever testing the FDA deems necessary to answer any academic concerns. Sam Anderson will contact the NHF to [ensure] there are no major obstacles there, and I recommend Jack Ryan do likewise. It will not serve our purposes to effect change with the FDA and offend our customers. The argument for using prison plasma is the additional testing (HTLV-III) and heat treatment which provides product safety. Penny, Mike and I will try to discuss with this Dr Petricciani in Atlanta this week on a preliminary basis."
If we could go over to the next page, please. Just one final extract from this minute:
"FDA Letter (attached):
"No-one likes the FDA response to our meeting in February to review the position on recall. We will lobby for a change to 3 or 6 months for unpooled units (not 3 years), but in any event, the letter has not been officially sent to the manufacturers. NY Blood is doing retrospective testing on all plasma samples, and we agreed it was a bad idea. (They will inform transfusion victims of the results.)"
There is a little bit to unpack there, with

three distinct topics.
On the ALT testing our understanding of the idea being put forward is that 20 per cent of US plasma, approximately, was going to be tested for ALT. Where plasma was found to have ALT levels that are less than twice the normal limit, however "normal" was defined, that plasma would be used in products that would be sold to the German market.
Where plasma was above twice the normal limit, but below five times the normal limit, that plasma would then be placed in a general pool with the untested plasma, and that would be used to make products that would be available for the American market, and presumably other international markets that didn't have same regulatory requirements as the German market.
That is why it's a reference to it being randomly distributed across the plasma pool, rather than that plasma alone being used to make products, which would inevitably have a higher ALT level.
SIR BRIAN LANGSTAFF: Can you just help me with this: the assumption may well be that the German requirement is imposed to protect German consumers of blood products from the risk that high ALT level blood is infected with a virus which will transmit hepatitis.

MR HILL: Yes.
SIR BRIAN LANGSTAFF: So it's quite possible, if they're right, that that blood has a hepatitis virus in it. If blood with hepatitis virus in it is mixed in a pool with other donations, it was the medical understanding since the early 50s that it will take only one or two donations to infect the whole pool.
MR HILL: That is certainly my understanding of the risk assessment.
SIR BRIAN LANGSTAFF: So the proposal to mix high ALT blood through all of the pools would render all the pools, potentially, more hazardous than they might have been.
MR HILL: Potentially, yes.
SIR BRIAN LANGSTAFF: Yes. Thank you.
MR HILL: The plasma that was more than five times the normal limit would be discarded, but the reason for that being discarded would be given as donor health, and not a suggestion that the plasma was unsafe, but a concern for the donor.
Sorry, the other point I should make about that is that the German requirement for ALT testing may well have been about hepatitis. There were also some suggestions that ALT testing could be a surrogate marker for HIV. I'm afraid I don't know the reason

why the German authorities put in place this request, whether it was hepatitis or AIDS, or both.

SIR BRIAN LANGSTAFF: Well, you may want to check this, but I think it may be in his judgment in the *A v NBA* case that Mr Justice Burton may have identified that in Germany ALT testing of blood for transfusion, so not the same as plasma for plasma products, was introduced in the '70s, but that may need to be checked.

MR HILL: I will have a look at that and, again, that may be possible to do that over the break, otherwise we can return to this topic.

SIR BRIAN LANGSTAFF: Well, in due course, it's not a matter of immediate importance, but it's something which I thought I'd better mention because it's something which I recollect from memory, I may be wrong. But you will want to check it out.

MR HILL: I will do so. What I would add, though, is that, even if a stated reason of AIDS was given for the test, ALT is about liver function.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: Inevitably, hepatitis is a relevant consideration when testing for ALT levels.

Sir, that's the ALT testing part of the discussion. The prison plasma discussion leads to

a suggestion that, despite some disparate views within the group, they are willing, all, to put forward a proposal to the FDA to see what the FDA will say in response to a proposal going back on the supposed gentleman's agreement on the use of prison plasma, and there are suggestions of making contact with the National Hemophilia Foundation. I will come back to that in a second.

The third issue is the FDA's response to the letter that had been sent in February, and the meeting that had taken place in February, about product recall. I'm afraid our documentation, or at least the documentation we've identified, is limited on this. So we have a rather opaque minute, and I'm wary about trying to decipher that. It appears that the FDA have come up with a counterproposal, which involves some kind of period of look back or of quarantine for products, and the industry is going to lobby for a change to three or six months, it says "not three years". I don't know if that is the period that the FDA had proposed or whether or not that had come from somewhere else. But I'm afraid, because of the limitations of the documentation, I can't assist much further on that point.

What we do know is that Jack Ryan, who was

referred to in this minute, did make contact about prison plasma with Dr Charles Carman and Dr Peter Levine of the National Hemophilia Foundation. On 1 May 1985 there was a conversation between the three men. From a Cutter document, it's recorded that Dr Levine responded to the proposal on a personal basis, a personnel basis that he thought reflected the views of the NHF. What he said was, and I quote:

"... he still feels that ... we are taking risks that are not justified. Specifically increased risks for hepatitis non-A non-B as well as hepatitis B."

Just referring back to the discussion that we have looked at, there is -- the justification for returning to prison plasma is framed in respect of both heat treatment and the introduction of HTLV-III testing. Heat treatment had been demonstrated by that period to be effective in respect of HIV, and HTLV-III testing was, of course, concerned with AIDS, but there is still a hepatitis risk which, as we know now, had not been addressed by either of those measures, or not -- certainly not fully addressed. Hepatitis viruses were not inactivated by most first generation heat-treated products.

Jack Ryan of Cutter informed Dr Levine and Dr Carman that Cutter would continue their dialogue

with the FDA, as they thought that the company's position was, and I quote "safe ... and justified".

Counsel to the Inquiry having identified any further documents in which the use of prison plasma was raised. We are unable to comment on what, if any, changes in practice were made. Similarly, it's not clear from the documents seen by counsel to the Inquiry what decisions were reached on ALT testing, although it does seem that it became more prevalent in the years that follow.

I'm afraid that the presentation rather ends here, because it is a presentation primarily about the response to AIDS, and some of these issues obviously continue into the '80s.

It's perhaps worth referring back to a document that we looked at in September from Dr Carl E Brook, who was the president of Hyland and who sent a letter to the National Hemophilia Foundation in 1987. You may recall, sir, it's a letter which sticks in the memory with Dr Brook criticising the National Hemophilia Foundation for seeking low-cost product which, on his argument, had pushed the fractionators to look for low-cost sources of plasma.

In that letter Dr Brook, defending Hyland's position, stated that the company had been, and

I quote:

"[The] first manufacturer to screen all plasma in compliance with German BGA requirements in 1985."

I pause there note to that this is the conservative position, as it was referred to by Dr Ojala, now being used a couple of years later in support of Hyland's position.

He also claimed that Hyland had behaved in a responsible fashion by not using material rejected for Germany's ALT requirements in any other market, as several other US manufacturers did. So that was Dr Brook's comments.

As I say, sir, we have reached the end of the chronological period covered by this presentation.

Just to summarise the position as of July 1985: all US fractionators, by that time, were producing heat-treated factor concentrates from plasma screened for HTLV-III antibodies. Donors were subjected to screening regimes that were intended to exclude high-risk donations, including from gay donors. This led to a high level of protection against transmission of HIV but not, in most cases, for these first generation heat-treated products against non-A, non-B hepatitis. The protection against AIDS afforded by these measures had led to the reversal of the previous

approach to withdrawing batches of factor concentrate that were known to be contributed to by donors who were later guide of AIDS so such products were not recalled if a product had been heat-treated. But some fractionators were considering going further and had opened a dialogue with the FDA with a view to reintroducing the fractionation of plasma from prison donors and coagulation products.

This was an issue that had split the pharmaceutical companies, not least because of the anticipated increased risk of hepatitis, but as we have seen from that last memorandum from Dr Ojala, even those companies that were not proposing to do this themselves were willing to -- as Dr Ojala put it -- hang together in an approach to the FDA.

The introduction of ALT testing in respect of plasma destined for the German market has posed a new set of problems for the fractionators. A consensus had been put forward for a probably that was intended to ward off mandatory testing of all US plasma for ALT levels. That proposal, if it were to be implemented, would have meant that products exported to German would be produced from plasma specifically selected as being relatively low in a marker for hepatitis, whereas domestic products would be drawn from plasma

that either had not been tested or was known to have higher ALT levels.

That, sir, is where the main part of the presentation ends. There is a short appendix about Dr Prince, and I note the time. I don't know if that is a something which I imagine would take about 20 minutes.

SIR BRIAN LANGSTAFF: Well, shall we go ahead and deal with it?

MR HILL: Very well, sir.

In December 1984 -- so we've gone back in time a little -- December 1984, Armour commissioned Dr Alfred Prince of The New York Blood Center to undertake studies on the efficacy of its heat treatment process for Factor VIII. The purpose was to see whether a measured quantity of HTLV-III would be inactivated by the heat processes that Armour were using. The proposed approach was to take a known amount of the virus and add it to the concentrate, so to spike the concentrate, before the concentrate was freeze-dried or lyophilized, and before it was then heated.

Following that process the product would be tested to see how much residual virus it contained. Virus reduction was measured by determining how many

logs of inactivation had been achieved so if a sample in which the amount of virus is reduced in size by 10 to the power of 4 millilitres is achieved, and it is said that there has been a four log reduction, or a four log kill. The industry standard at the time was a five log reduction.

It was anticipated that virus could be inactivated both by the freeze-drying process itself and by the subsequent heating of the product. Armour's heating technique involved dry heat at 60ºC for 30 hours. We looked at this earlier in the table. Hyland's equivalent product was dry heat 60 degrees for 72 to 74 hours, and Cutter's product was dry heat, 68 degrees for 72 hours.

Just as a point of comparison, the heat-treated product produced by BPL in the UK, 8Y was heated at 80ºC for 72 hours. I note in parenthesis here, sir, that although figures of 60 degrees and 10 hours were given for some of the other products, those were products which were not dry heated but were heated either in solution or in suspension, and so forth.

So Armour, 60ºC for 30 hours, is a less robust heat treatment than its rival dry heat competitors at the time.

Dr Prince provided the results of his first

study in January 1985. He wrote, and I quote:

"Disappointingly, we were unable to show the greater than 5 log kill as had been hoped. The most that can be concluded from the study is that the combined effect of lyophilisation and heating inactivated more than or equal to 2.5 to 3 logs."

Dr Prince's results were at odds with those that had previously been obtained by experiments conducted by the Centers for Disease Control. On 29 November 1984, Dr Evatt had written to Armour with the results of those studies, and Dr Evatt said that they indicated that heat treatment at 60 degrees for 24 hours, so less time than Armour used, had left no detectable virus in a sample of Factor VIII concentrate. His letter concluded, and I quote:

"Because LAV appeared to be extremely heat labile, we believe that the procedures presently used by the manufacturers for heat treatment of hepatitis virus would adequately inactivate the LAV virus."

That's Dr Evatt's view, as expressed in late November.

The CDC results were subsequently published in the Journal of Clinical Investigation in August 1985, the lead authors were Dr Evatt and Dr McDougal, who we heard about earlier.

In October 1985, they had joined with Dr John Petricciani of the FDA in writing a letter to The Lancet which advocated heat treatment on the basis that heating at 60ºC for 20 hours would result in a 20 log reduction.

SIR BRIAN LANGSTAFF: A 20 log?

MR HILL: A 20 log reduction. Now, Dr Prince would later criticise the assumptions that lay behind that article, but it was an article that was published in The Lancet in October 1985.

Going back in time to Dr Prince's initial studies, that's January 1985, so at this stage Armour have been informed of the CDC's experiments in November 1984, but it's obviously before that Lancet article is published later in the year.

At that point, January 1985, Armour was left with conflicting studies concerning the safety of their heat treatment process. In an internal company memorandum, on 11 February 1985, Dr Rodell identified for his colleagues at Armour limitations in Dr Prince's study. In particular, he identified the low quantity of active virus that was included in the sample that was used by Dr Prince.

Dr Rodell considered that the experiment should be considered preliminary in nature. He said that

Dr Prince's team had been provided with samples with a higher level of virus, which would be used in further experiments in the coming weeks. The company would also go on to commission further studies from other respected sources.

Dr Prince and his team did indeed conduct the further studies, and they reported them to Armour during the course of 1985. His findings were that heating at 60 degrees in the dry state had only, and I quote:

"... a modest process efficacy for inactivation of HTLV-III/LAV."

This, he said, was a finding that was in contrast to the results obtained by Dr McDougal of the CDC, and he said that this was, and I quote, "difficult to explain".

The implication of Dr Prince's results, though, was that Armour's established heat-treatment process main not be sufficiently robust to inactivate HTLV-III to the industry standard of 5 logs. Dr Prince wanted to publish his results and he sent a draft article to Armour. The company invoked a clause in their contract that required him to obtain Armour's permission for any publication. That permission was not forthcoming.

If we could have on screen, please, CGRA0000512. This is a memorandum from 8 November 1985, and is from Dr William Terry of Armour, and it is noted to be for the record. If we could expand the main text, please:

"Through the efforts of Bernie Loev we were able to determine that there is a contractual arrangement with Dr Prince which precludes him from publishing, without our approval, data from experiments supported by RHCG."

That's Revlon Health Care Group, the parent company of Armour.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: "Dr Prince submitted a manuscript to me entitled 'Safety of Blood Derivatives Pasteurized in the Dry State'. The data in this manuscript indicate that Generation I, Generation II and Factor IX are not rendered virus-free when they have been contaminated with HTLV-III and heated in the dry state at 60° for even as much as 72 hours."

I pause there to note that Generation I and Generation II are different types of Factor VIII:

"I told Dr Prince that while our foremost concern was the safety of patients receiving these products, these data taken in isolation could only be confusing to the scientific community, the treatment

community and the public and that we therefore were not prepared to give him permission to publish. I pointed out the discrepancies between both his test system and his test system results when compared with the data reported by McDougal and others. I have indicated that we certainly wished to continue working with him and hoped that we could do a more comprehensive study, utilizing his sensitive test system, but applying it to the heating conditions and the products of all the major suppliers.

"While Dr Prince was obviously disappointed and somewhat contentious, he accepted the fact that he would not be able to publish these data and the conversation ended on a reasonably cordial note."

In later litigation, Dr Prince said that he had been annoyed with Armour, and that he set out to repeat his experiments outside of his contract with the company, so that he could publish the results. He did so in a letter to The Lancet on 31 May 1986. In that letter he said that he found viral inactivation from heating at 60 degrees was, on its own, and I quote, "surprisingly modest".

He identified viral inactivation of between 0 and 1 log, when the sample was heated at 60 degrees for 10 hours, and between 2 and 4 logs, observed after

72 hours of heating. The freeze drying process on its own resulted in an additional 0.5 to 1 log of inactivation.

If we could have PRSE0002534, please. This is the letter to The Lancet, "The effect of heat treatment of lyophilised blood derivatives on infectivity of human immunodeficiency", and if we could turn to the second page, please. If we could just expand the final paragraph of the left-hand column, beginning "The finding". Dr Prince wrote this:

"The finding of only modest sterilisation process efficacy for HIV adds to the concern about the efficacy of this procedure. It should, however, be stressed that this finding does not mean that dry heat-treated products are unsafe with respect to the transmission of AIDS. Indeed three studies have reported absence of anti-HIV seroconversion in recipients of dry-heat treated [Factor VIII] preparations. Purification and processing steps before lyophilisation can remove or inactivate virus and lyophilisation alone under commercial conditions probably inactivates more virus than is observed with shell freezing. Furthermore some products are heated above 60°C. Nevertheless, these findings indicate the

need for caution in relying on the efficacy of dry-heat sterilisation. Long-term surveillance of recipients of such products for seroconversion to anti-HIV is still required."

If you could take that down, please.

The approach taken by Armour to Dr Prince's work has been the source of intense controversy for decades, not at least because, as we have heard, heat-treated Factorate came to be associated with a number of seroconversions. Dr Peter Jones gave evidence to the Lindsay Inquiry in Ireland about --

SIR BRIAN LANGSTAFF: Can I just mention for the sake of the [draft] transcript that they've rendered your "Factorate" as "Factor VIII", whereas what you meant it to be was the name of the product itself, Factorate.

MR HILL: Yes, Factorate Heat Treated, the Armour product, was associated, as we've heard, with 18 seroconversions by Professor Mannucci.

SIR BRIAN LANGSTAFF: I mention that so that when the [draft] transcript is perfected that can be picked up.

MR HILL: I'm grateful, sir, thank you.

Peter Jones gave evidence to the Lindsay Inquiry about a particularly contentious meeting of Armour executives and scientists that was held in

October 1985. In Dr Jones' opinion, and I quote, the record of that meeting, appeared to -- the company:

"... appeared to consider it ethical to continue to market unsafe product whilst attempting to manipulate the results of their laboratory tests in order to throw doubt on the safety of their competitor's products in the eyes of the FDA. They're doing this in order to protect their share of the market."

That was evidence given by Peter Jones to the Lindsay Inquiry.

Mr Justice Krever came to the following conclusion in his report. Can we have, please, KREV0000001, electronic page 529. It's the final paragraph above the subheading, beginning "Not only". The reference to the "bureau" here is to the Canadian regulator, the Bureau of Biologics. I quote:

"Not only did Armour not transmit Dr Prince's data to the bureau but it prohibited Dr Prince from publishing his research on the safety of its products. Armour reasoned that the publication of Dr Prince's research 'in isolation could only be confusing to the scientific community, the treatment community and the public.' Armour was also concerned about the negative impact that publication of Dr Prince's findings could

have on its competitive position. Armour's obligation was to convey safety-related information about its products to the bureau promptly. It could have addressed risk, if any, of confusion by including in a timely report to the bureau all the contradictory and inconsistent data it believed qualified Dr Prince's findings."

So that is the view of Mr Justice Krever in his report.

A criminal case was later brought in Canada against Armour, and against Dr Rodell personally, and against a number of other defendants as well. Part of the prosecution case was to allege that there had been a duty to disclose Dr Prince's studies.

The case was heard by Madam Justice Benotto. She acquitted the defendants, and she came to a different conclusion to Mr Justice Krever. In her view, Armour and Dr Rodell had been justified in their position, particularly in light of the other studies that the company had considered and commissioned.

If we could have MDUN0000020 _ 250.

This is paragraph 90 of Madam Justice Benotto's judgment in the criminal trial in Canada. I quote:

"This was a time of great uncertainty. In the face of this, and in light of the clearly articulated

studies of the CDC, supported by the FDA, it would have been unreasonable, if not irresponsible, for Armour to have thrust such confusing, incomplete and inconclusive information into the community."

Thank you, we can take that down.

SIR BRIAN LANGSTAFF: Did she say anything about the central thesis in Mr Justice Krever's comments, which was that there was a duty on Armour to report the studies, whatever they were, to the Bureau?

MR HILL: Off the top of my head I cannot remember if she specifically addresses that point. But what she does do is emphasise that she's coming to her conclusions not just on the criminal standard of proof, but she says that, in her view, having listened to one and a half years of evidence, the conduct of Dr Rodell was reasonable, responsible and professional, and Dr Rodell himself was, and I quote, "responsible and professional throughout, consistent with his well-deserved reputation for integrity".

SIR BRIAN LANGSTAFF: I follow that. But if the suggestion is correct in what Mr Justice Krever says that the obligation on Armour was to report to the bureau the studies which they had available to them, then they should have sent all of them to the Bureau.

MR HILL: Yes, I think it's fair --

SIR BRIAN LANGSTAFF: That would follow, I think, logically.

MR HILL: Yes. So, Mr Justice Krever's critique is about not providing it to the regulator.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: But Madam Justice Benotto, when considering --

SIR BRIAN LANGSTAFF: Is dealing with the conduct as opposed to -- the conduct apart from not sending it to the regulator, which they didn't do.

MR HILL: I think she is dealing generally with the allegation that was made by the prosecution that there was a duty to disclose this both to the regulator and to the --

SIR BRIAN LANGSTAFF: What was nature of the charge?

MR HILL: It was -- I don't have the exact Canadian statute to hand, but I can -- if you give me a second, I will try to find the ... *(Pause)*

Sir, the charges were of criminal negligence and common nuisance, and they were brought against Armour, Dr Rodell, the director of the Bureau of Biologics, the chief of the Blood Products Division and the national director of the Blood Products Service of the Canadian Red Cross.

The corporation is also charged with -- that's Armour -- with failing to report a deficiency under

the Food and Drug Act. Those accused were involved with the manufacturing, licensing and distribution of heat-treated Factorate, Factorate the product.

SIR BRIAN LANGSTAFF: So it was acquitted of a failure to report?

MR HILL: Well, the acquittal is of a charge of criminal negligence and common nuisance, and the part --

SIR BRIAN LANGSTAFF: I think we may need to have look at that in due course, but thank you for that.

MR HILL: I think it's fair to say that Madam Justice Benotto went -- deliberately stepped outside the legal test which she was required to apply in the criminal court in order to give her view that Dr Rodell had behaved reasonably and responsibly throughout, including in respect of the Prince allegations.

The presentation, sir, doesn't attempt to scale the mountain of evidence and opinion that have been formed in the wake of this controversy. Several of the protagonists have given extensive testimony, and indeed we've referred to the fact that the criminal trial, of which this was one part, lasted over a year and a half. Previous inquiries have considered and commented on this matter. There are references to some of the documents in some of the inquiries in the written presentation. The technical details involved

are complex. They deal with the sensitivity of assays, alleged arithmetic errors, the questionable assumptions that underpinned some of the work.

I'm not going to try to go into that level of detail now. This is merely a preliminary sketch, as it were, of this issue and this controversy which has been well documented elsewhere. Certainly counsel to the Inquiry do not make any comment on either Mr Justice Krever or Madam Justice Benotto's view of matters.

That, sir, concludes the presentation today, and includes this round of presentations on the pharmaceutical companies. As I said at the start of these presentations, they are the result of a great deal of work done by other members of your legal team, and Ms Richards and I are very grateful for the assistance that we've received from them.

SIR BRIAN LANGSTAFF: Well, thank you very much indeed.

That leaves us then with tomorrow we hear from Mr Bishop, do we?

MR HILL: We do, sir.

SIR BRIAN LANGSTAFF: So 10 o'clock tomorrow. 10 o'clock.

(3.40 pm)

(Adjourned until 10.00 am on Thursday, 4 November 2021)

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