Tuesday, 28 September 2021

(10.00 am)

Presentation by Counsel to the Inquiry on the Pharmaceutical Companies (continued)

SIR BRIAN LANGSTAFF: Yes, Mr Hill?

MR HILL: We are going to continue today, sir, with the presentation on the Hyland and Travenol products. When I finished on Friday, I was just about to move to Hemofil-M and it's perhaps worth reminding everybody what the product was. It was described by Dr Kingdon in his draft witness statement as being:

"A product produced as a result of the solvent detergent method, which had been licensed from a New York blood centre by Hyland Travenol. He described it as a freeze-dried high purity concentrate in which lipid enveloped viruses were dissolved using the NYBC process, prior to fractionation. The process was adopted in order to inactivate non-A, non-B hepatitis in the plasma pools."

That is the reason why that method was used. If we could have on screen, please, Soumik, SHPL0000409_072 -- let me try again SHPL0000409_072.

SIR BRIAN LANGSTAFF: 409, did you say?

MR HILL: Yes, sir, SHPL0000409.

SIR BRIAN LANGSTAFF: I think the 0 in the 409 got

missing.

MR HILL: Sir, it appears that there seems to be a technical glitch and we can't bring the actual document up, but I think I can describe it to you without presenting it on the screen. It is a memorandum, an --

SIR BRIAN LANGSTAFF: Just pause for a moment. Is it a technical glitch which affects only this document or is it a more general one?

MR HILL: We checked for documents this morning and they all seemed to be present. We think this document is corrupted.

SIR BRIAN LANGSTAFF: Right.

MR HILL: Can I just try the next document that we're going to go to and see whether or not this is a more widespread problem. Let's try SHPL0000293_141.

SIR BRIAN LANGSTAFF: Right, we'll just take a break.

MR HILL: Thank you, sir.

(10.03 am)

(A short break)

(10.08 pm)

SIR BRIAN LANGSTAFF: Right, let's start again.

MR HILL: Can we have on screen, please, Soumik SHPL0000409_072, please. This is an internal Travenol Laboratories document dated 28 August 1987 and it

concerns the crossover between Hemofil-T and Hemofil-M. It says the following with reference to a previous memo:

"Hyland believe that FDA licence could be issued by the end [November] 1987."

We understand that to be a reference to an FDA licence for Hemofil-M.

"Hopefully, UK customers will commence usage on a 'named-patient' basis ..."

SIR BRIAN LANGSTAFF: I'm missing something, am I? Where does it say --

MR HILL: There's a problem with the referencing again. Soumik, can we have SHPL0000409_072.

Yes, sorry, I brought up the wrong document there. So 20 October 1987, an internal Travenol document, Travenol Laboratories, the UK company, with a reference to a memorandum of 12 October:

"Hyland believe that FDA licence could be issued by the end [of November] 1987.

"Hopefully UK customers will commence usage on a 'named-patient' basis once 'M' has FDA approval, premium price makes this very limited.

"Hemofil-T (Heat-treated) [that is the product we were looking at on Friday] not accepted by market place -- poor solubility and record on viral safety.

"'Armour' (major competitor is Monoclonal productions) do not have FDA licence either ..."

But the marginalia shows that that licence was granted after the memo had been typed.

"In view of the above, we must submit our licence application without delay once data collated ..."

We can see there, sir, again, there is going to be reliance placed on the named-patient basis, at least until a licence is obtained.

On 7 December 1987 -- Thank you, Soumik, that can be taken off the screen.

On 7th December 1987 --

SIR BRIAN LANGSTAFF: Can you just help: do we know any more about the record on viral safety referred to there, poor record on viral safety?

MR HILL: I understand that to be a reference to the transmission of non-A, non-B hepatitis, which by 1987 was recognised that Hemofil-T was still transmitting non-A, non-B hepatitis.

SIR BRIAN LANGSTAFF: Being a poor record which was not accepting -- the marketplace not accepting it would mean that other products, by rival competitors, were better, presumably?

MR HILL: Presumably, yes. The market please seems to

have reacted not just to the lack of the good record on viral safety but also the solubility of the product.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: But certainly by 1987, there was an acceptance that VIIIY, the NHS product, for example, was --

SIR BRIAN LANGSTAFF: I follow that that's so in the UK. Is this memo just talking about the UK? It talks about FDA approval.

MR HILL: It does but it is an internal Travenol Laboratories Limited -- so the UK company -- memorandum. The reference to the FDA, I understand, in this context, to be useful to them in order to market the product in the UK, by pointing to the fact that the FDA have licensed it.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: On 7 December 1987, Hyland and Travenol Limited applied for a clinical trial exemption for Hemofil-M in conjunction with Dr Savidge at St Thomas' Hospital. That was granted on 20 January 1988 for a period of three years, that's SHPL0000496_191, but, of course, just a few months that memorandum that we've just been looking at.

The application for the full product licence was made on 12 June 1989, so some 18 months after that

memorandum. The reference is SHPL0000496_149. The application was initially refused on regulatory grounds as it was considered to be a high technology product under European law and consequently subject to a separate licensing regime which the product then went through. The licence was eventually awarded in 1994.

I'm not going to go through all of the detail in respect of that. I will give the references to the original application, which is SHPL0000496_149, and then SHPL0000293_182 and SHPL0000468_464, those are the main documents which show what happened to that application.

Of relevance to the Inquiry is the fact that the product wasstill available in this period between 1989 and 1994 when the licensing process was going through its motions. It was still available on a named-patient basis.

A DHSS note dated 14 November 1989 said that Baxter were supplying approximately 2 million international units of their unlicensed product to the UK each year. We understand that to be a reference to Hemofil-M. The reference for that is DHSC0003412_077.

Soumik, could we have on screen, please, SHPL0000293_141. Page 2 of that document, please.

This is a document from 21 May 1990 from Patrick Rafferty, who was medical director with Baxter, to Ron Feakes at Thetford. It's an internal memo. By this stage the company's name has changed from Travenol Limited to Baxter Healthcare Limited.

What Dr Rafferty says in the memorandum is this:

"In my capacity as Medical Director in order to understand more fully the clinical management of haemophilia patients and the potential role for highly purified in the centre of their haemostasis, I have met with most of the Haemophilia Centre Directors over the past few months.

"Following these meetings I have received a number of enquiries relating to the effects of monoclonally purified Factor VIII:C on the levels of Hepatitis C antibodies in patients ... If this relationship exists, and if monoclonally purified Factor VIII:C is confirmed as being effective in significantly reducing or eliminating the levels of Hepatitis C antibody in these patients, then as Medical Director I have a moral obligation to bring this to the attention of the clinical experts who were responsible for the management of Haemophilia patients.

"My understanding is that the Baxter

monoclonally purified Factor VIII:C, Hemofil M, is currently not yet licensed in the UK -- perhaps you could advise on of the most ethical approach for me to take in this regard, whilst meeting appropriate regulatory requirements."

We have a response to that memorandum.

SIR BRIAN LANGSTAFF: Just one question, on this. It doesn't say what the relationship between the level of the hepatitis C antibodies and the progression of cirrhosis is, whether it means that more antibodies the less cirrhosis, or the less antibodies the less cirrhosis.

MR HILL: No, he doesn't. What I take from this memo is the view of Dr Rafferty is that Hemofil-M is an effective product to use to limit the risk of hepatitis cirrhosis, and the way that Dr Rafferty expresses himself is that he feels then that he has a moral obligation to share that information with the haemophilia clinicians.

SIR BRIAN LANGSTAFF: Why is he then raising that? Plainly, as a commercial sales point, it would seem sensible to highlight it, but the constraint might be, might it, that that would then fall foul of the advertising prohibition on a named-patient basis?

MR HILL: Exactly so, sir. That is what is said in the

reply to Dr Rafferty's letter.

SIR BRIAN LANGSTAFF: I see. So where does that leave his moral obligation? To break the law? Or what?

MR HILL: Sir, that is a question for Dr Rafferty.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: If we could have onscreen -- if we look at the reply we will sees the position that was taken by Mr Feakes in response. It's SHPL0000293_142. The date is 1 June 1990. And it's a response to the memorandum we've just looked at of 21 May 1990.

What Mr Feakes says is this:

"The area of personal representations and unlicensed products is one where great care must be taken in order to avoid breaking both the acceptable Codes of Conduct (eg that of the ABPI) and of the law itself. The Department of Health has, in the past, prosecuted companies for advertising unlicensed products.

"Part VI of the 1968 Medicines Act (on Promotion of Sales and Medicinal Products) clearly indicates that only licensed products can be promoted and that the spoken word by Company Representatives constitutes a form of promotion. Moreover, the legislation under which we import Hemofil M (SI1984-673) states the importer:

"'Will not add any time issue or cause another person to issue any advertisement or make any representation in respect of that medical product and that he will sell or supply that medicinal product only in response to a bona fide unsolicited order.'

"Thus your actions must be very carefully calculated such that you cannot be accused of promoting Hemofil M. This is doubly important as Baxter received a formal complaint from the DOH [Department of Health] in early 1988 concerning our stand at the ISBT meeting held at Wembley late 1987 (promotion of Gammagard). Further transgressions could be very serious indeed.

"To give you a frame-work in which to operate you must abide by the following rules:

"(i) The provision of factual scientific information in response to a request from a physician does not in itself constitute promotion. Therefore you hoot not offer such information until requested.

"(ii) You should not approach individual physicians with claims of safety for an unlicensed product. Such information must be made available through the Scientific press, by application of data and substantiation by peer review.

"(iii) You should not set out to derogate

other, licensed, products.

"(iv) Discussing the therapeutic value of Hemofil M with a physician is only acceptable if it is the physician and not you who initiates the conversation.

"Although this does limit you quite substantially, you should applied by these guidelines otherwise we could, at the very least, antagonise the Department of Health. This might in turn be detrimental to our Product Licence Application.

"Going on to the availability of Hemofil M. When asked it is quite acceptable for you to inform the physician:

"(i) we hold small stocks in the UK.

"(ii) the product is available on a named patient prescription basis.

"(iii) the cost of the product.

"(iv) contact names in marketing (for further information) and regulatory (for prescription release details).

That is Mr Feakes' response to the conundrum that has been presented.

SIR BRIAN LANGSTAFF: Can we just go back to the first page of this letter.

Just looking at the legislation:

"Will not at any time issue or cause another person to issue any advertisement or make any representation ..."

So what this might mean is, is it, that he couldn't tell the DHSS, for instance, of the claims he was making for the suitability of Hemofil-M with a view to them letting the profession know, because that would be affecting causing another person to make a representation?

MR HILL: That would certainly be an interpretation that would be open to a --

SIR BRIAN LANGSTAFF: Well, it would be straight within the language that's quoted there, at any rate.

MR HILL: Yes, but there is a ... what Mr Feakes says adds one of the solutions to this is to publish your information.

SIR BRIAN LANGSTAFF: In a scientific journal.

MR HILL: In a scientific journal. Sharing pre-publication information with the DHSS I don't think would fall foul of this, unless there was an intention for the DHSS to then go on to inform and make an advertisement or a representation to various clinicians.

SIR BRIAN LANGSTAFF: It's difficult to think of what other reason there would be.

MR HILL: There may be reason to begin the discussions which lead to a product licence, for example, discussing how the licence is best approached, what form of licensing should -- what format the application should take, whether it should be a (overspeaking) -- licence and so forth.
SIR BRIAN LANGSTAFF: Yes, I see that might be a possibility.
MR HILL: But certainly it wouldn't be open to the company to try to work their way around the prohibition by using the official channel.
SIR BRIAN LANGSTAFF: Thank you.
MR HILL: I don't intend to say anything further on Hemofil-M. Turning to Proplex, this was the freeze-dried concentrate that contained Factors II, VIII and X, as well as Factor IX. I don't intend to go through the licensing story for this product. I note only the following: that interest in the product in the UK can be traced back to at least August 1974. That's OXUH0000630. Dr Biggs there appears to have obtained some emergency use on a named-patient basis.
SIR BRIAN LANGSTAFF: Do you have that reference again?
MR HILL: OXUH0000630.
SIR BRIAN LANGSTAFF: 630, thank you.

MR HILL: In March 1975 a temporary licence was granted to import the product. That is MHRA00033317_093.
The application for a product licence was made on 21 May 1975. MHRA0033317_095. The licence application was considered by the CSM Subcommittee on Biologicals in November 1975. So this is a month before the World in Action film.
The medical assessor at that time commented that Proplex would appear to have been adequately manufactured but is subject to possible contamination with hepatitis virus. But the medical assessor recommended that subject to approval of quality control, licence be granted.
The sub committee concluded that a product licence be granted subject to several conditions, and it's perhaps worth looking at that document, MHRA003317_079 -- MHRA0033317_079. We can see November 1975, Subcommittee on Biologicals, a month before the World in Action film, well, the previous month, we don't know how many weeks exactly:
"On the evidence before them, the Sub-Committee on Biologicals recommend the grant of a product licence for this preparation ...
"Provided that:
"Information is provided on:

"(i) The number of donations from which plasma is pooled for the manufacture of prothrombin complex.
"(ii) The reasons for, and rate of, rejections of donors and donations, centre by centre."
There are events and further provisos that I won't take you through.
If we could have on screen now, please, Soumik, MHRA0033317_077. This is a response from Travenol Limited to a letter that has been sent by the Licensing Authority on 29 January 1976 -- we don't have that letter, this is the response to it -- addressed to Dr Andrews, the Senior Medical Officer at the Department of Health and Social Security. It provides further information that has been requested as part of the licensing process. It says:
"1(a)i. The size of plasma pools used for the manufacture of each lot of Factor IX Complex can vary up to approximately 6000 litres.
"1(a)ii. The reasons for rejection of a donor or a donation are outlined in the product licence application, Part 3, section A. Donors are most commonly rejected due to serum protein electrophoresis unacceptability or for being positive for Hepatitis B surface antigen or for the RPR test. Rejection for either the first or last reason given above would

normally only be for a limited period of time."
You can see in the marginalia on the right-hand side is written "no rate of rejections", that information was requested by the DHSS but hasn't been provided in this letter. We don't know, sir, whether that was provided subsequently or not. We haven't seen any information that it was but that does not mean that it was not.
Proplex was granted a licence, on 15 October 1976, SHPL0000232_001. The timing is interesting, sir, in that the original consideration by the CSM(B), before the World in Action documentaries were broadcast, the letter that was sent in January was sent afterwards.
SIR BRIAN LANGSTAFF: But was the information that was requested ever actually provided, so far as we know?
MR HILL: We haven't seen any information that it was, but we have rather incomplete documentation from that period, so we can't say that there wasn't another letter that was followed up. Certainly somebody seems to have submitted that no information has been provided on a rate of projections but we don't know whose writing that is.
SIR BRIAN LANGSTAFF: Yes.
MR HILL: The 1978 haemophilia centre annual returns show

that they compiled information from 103 centres. Of the 2.2 million units used by Haemophilia Centres to treat haemophilia A patients with antibodies during 1978, only 149,000 of those were Proplex, and that compares with 1.9 million units of FEIBA.

So we can see that although Proplex is used, it is far less popular than FEIBA for inhibitor patients. It is not clear from the information in the returns how much was used for Factor IX patients.

I won't, sir, go through the subsequent history of the renewal applications and considerations. We can return to that if necessary. The picture is not always clear as to when or indeed whether renewal applications were considered, but nor is it clear the extent to which Proplex remained on the UK market during the 1980s.

That's to complete what I have to say about the licensing of Travenol products. I'm going to turn now to the communication of risk associated with those products. We've seen some indication of this in the documents that we've looked at, but this is to try to fill out the narrative a little.

If we go back to Hemofil and the original version of Hemofil, which was the non-heat treated Hemofil, as we have heard, the product licence

application was made in November 1972. A label was sent with that application, which contained the words "Warning, the risk of transmitting hepatitis is present". The package leaflet was also contained in the application and can we have this on the screen, please, Soumik. It's SHPL0000275_013.

We can see this is part of the application and it is the draft package leafletting, if we can go over to the next page, please, Soumik -- two pages on, to the fifth page of the document overall.

Under the heading "Cautions" it says:

"This concentrate [this is the second paragraph down] is prepared from large pools of fresh human plasma. Such plasma may contain the causative agents of viral hepatitis. There is no known laboratory test to demonstrate either the presence or the absence of such agents, and the concentrate has not been subjected to any treatment known to diminish the risk of transmission of hepatitis since such treatments greatly increase the loss of AHF activity during preparation. The concentrate should, therefore, be used when its expected effect is needed in spite of the unknown hepatitis risk associated with its use. Special consideration should be given to the use of the concentrate in newborns and infants where a higher

morbidity and mortality may be associated with hepatitis."

You may recall, sir, from Friday, the comment made by Dr Thomas, the medical assessor at the time, that during the -- in the product application there was no attempt made to disguise the risk of hepatitis associated with it.

SIR BRIAN LANGSTAFF: Just looking at that for a moment, the fifth line down, starting at the end of the fourth line down in the second paragraph, "and the concentrate has not been subjected to any treatment known to diminish the risk of transmission of hepatitis since such treatments greatly increase the loss of AHF activity during preparation", which is an interesting phrase because it suggests: (a) that the company has considered treating the product, (b) that it is not saying it can't be done. It is saying it's uneconomic or it lessens the amount of Factor VIII you get at of the product, not that you get none.

MR HILL: Yes.

SIR BRIAN LANGSTAFF: So it could, on that interpretation, on the words themselves, mean they could produce a safer product, does it, only it's just not worth the candle?

MR HILL: I am reluctant to try to interpret what was meant from the warning label without the --

SIR BRIAN LANGSTAFF: The reason I raise this is whether there's any other document that you know of that sheds any light on that?

MR HILL: Not that I'm aware of but it is something we can continue to look into. I'm not sure what methods of viral inactivation were being used or being thought about by the company as of 1972.

SIR BRIAN LANGSTAFF: Whatever they were, that sentence is at least open to that interpretation. Is it better open to another one or not?

MR HILL: It is open to that interpretation, yes.

SIR BRIAN LANGSTAFF: Yes. Thank you.

MR HILL: The licence was granted in February 1973, as we heard on Friday. The package -- a package leaflet dated from 1979 contains a broadly similar warning but with some further information about screening tests. It may help to have a quick look to that. SHPL0001055_023, please, Soumik. This is, as I say, dating from 1979 and we can see the "Warnings" section:

"This concentrate is prepared from large pools of fresh human plasma. Such plasma may contain the causative agent of viral hepatitis. However, each

unit of the plasma used in the manufacture of this product has been found to be nonreactive for hepatitis B surface antigen ... by radioimmunoassay. The concentrate has not been subjected to any treatment known to diminish the risk of hepatitis transmission since such treatments greatly increase the loss of AHF activity during preparation. The concentrate should, therefore, be used when the need for its expected effect outweighs the hepatitis risk associated with its use.

"This lot, after reconstitution as for use, has been found non-reactive for hepatitis B surface antigen ... using a solid phase radioimmunoassay technique licensed by the US Bureau of Biologics. The significance of a nonreactive test result with concentrated antihaemophilic factor has not been established. Therefore, the product should continue to be considered to carry a risk in respect to hepatitis."

Turning to Hemofil, I should add, sir, that we have less information about the data sheets for Hemofil than we do for the Immuno products that we looked at last week. That's just the nature of the type of sources that we have to work with.

Turning to heat-treated Hemofil, we heard on

Friday that, at the time that the original application for heat-treated Hemofil was considered by the Committee On Safety of Medicines Subcommittee on Biologics, it was "strongly deprecated" that leaflets had been sent to doctors which the committee considered to be promotional leaflets making unjustified claims. I won't go back to those.

A further application was made on 30 November 1984. The proposed bottle label contained the words "Warning, the risk of transmitting hepatitis is present". The carton label contained the following, SHPL0000283_005, please, Soumik. It's page 24 of that document.

In the section headed "Warning", a little further down the page:

"Plasma from which this product was derived was found to be nonreactive for hepatitis B surface antigen (HBsAG) when tested with licensed third generation reagents. In addition, the process used in the manufacture of this product includes a heating step designed minimise the risk of transmission of hepatitis. However, no procedure has been shown to be totally effective in removing hepatitis infectivity from Antihaemophilic Factor (human)."

The proposed direction sheet contained

a similarly-phrased warning. It's at page 30 of the same document, I won't go to it, but it also included the comment "Although these testing and heating steps reduce the risk of hepatitis transmission the possibility of such transmission should be considered in the use of the product".

The data sheet had a similar warning. That's at page 40 of the same document. The direction sheet contained a summary of the understanding at that time of the chimpanzee trials, to which we referred on Friday, that's at page 29.

The amendment to licensing Hemofil-T was granted on 27 February 1985. The particulars of the licence included a warning in the same terms as those contained in the proposed direction sheet and data sheet, that's MHRA0000087, page 14 of that document.

We also have a carton with the expiry date June 1988, which shows the same wording as the sample carton that was included in the application. That's SHPL0001013_004. You'll note, sir, that in those warnings, there is no reference to HIV, LAV, HTLV-III, although, as we heard, Dr Kingdon's view was that Hemofil-T did inactivate HIV.

Hemofil-M, as we've just heard, not licensed until 1994 but available on a named-patient basis

seemingly from 1987. I'm not going to take you through the labels that it contained, but we can -- for the transcript, the warnings contained in the original application are at SHPL0000375_082, and in the subsequent revised application, SHPL0000396_003.

Proplex, the application for the product licence was in May 1975, as we've heard. I won't take you to the documents, but the proposed direction sheet and data sheet contain a similar warning to the contemporary warnings for Hemofil at that time, the reference is MHRA0033317_098.

I will, if I may, sir, take you to a data sheet from February 1983, from Proplex, SHPL0000963_002. If we look in the central column, at the bottom we can see it's revised in February 1983 and this has been printed by the US company, Travenol Laboratories Inc, and printed in the US, as it states there.

If we can go to the next page of the document, please, Soumik. Under the heading "Warnings", the second paragraph, again:

"This product is prepared from large pools from human plasma. Such plasma may contain the causative agent of viral hepatitis. Although each unit of source plasma used in the preparation of this product has been found to be nonreactive for hepatitis B

surface antigen ... by licensed third generation reagents, the concentrate has not been subjected to any treatment known to diminish the risk of transmission of hepatitis. The product should, therefore, be administered only when its expected effect outweighs the hepatitis risk associated with its use."

If we go down a couple of paragraphs lower, under "Precautions", just above the subheading "Laboratory tests", you see a further warning which is the last paragraph there:

"Special caution should be taken in the use of this concentrate in newborns, where a higher morbidity and mortality may be associated with hepatitis, and in individuals with pre-existing liver disease."

Again, terms similar to those we have looked at from the 1970s for Hemofil in a document from February 1983. It's not clear, on the face of this document, whether or not it was a document that was used with UK product but that is what the American company was printing at that time. A version of the leaflet was revised in October 1984. The reference is SHPL0001049_034. The same warning was issued and, again, there is no reference to AIDS, HTLV-III, LAV, HIV. That is from October 1984. Once more, it's not

clear from the face of that document whether or not it was used in the United Kingdom.

That is all I intend to say on the communication of risk in respect of the Travenol products that we have been looking at. I will turn now to the question of donors.

In terms of donor pool sizes, we've heard evidence already on this, and I won't go back to it, but will just remind you, sir, that Dr Thomas's summary of the -- the summary of the report produced following the inspection of the Hyland blood banks, which we looked at on Friday, said that donor pools contained plasma from as many as 6,000 donors. That figure was confirmed in a letter from Travenol Limited, dated 22 June 1976, about Proplex Factor IX, which we looked at earlier today in the licensing section. The reference is MHRA003317_077, and the reference for Dr Thomas is DHSC0105593 --

SIR BRIAN LANGSTAFF: Dr Thomas was talking about 6,000 donors, did you say? What you showed me earlier talked about donations.

MR HILL: Yes, there is that distinction between donations. Whether or not it was an intended --

SIR BRIAN LANGSTAFF: In fact, litres, I think it was, wasn't it? 6,000 litres was what you mentioned?

MR HILL: Yes.

SIR BRIAN LANGSTAFF: That's, what, MRHA232001, I think, or SPHL232001. If it's 6,000 litres, that's about, what, 9,000, 10,000 donations, isn't it?

MR HILL: Depending on the level of --

SIR BRIAN LANGSTAFF: Assuming that a donation of plasma is about 600-odd millilitres.

MR HILL: Yes. It's not always clear in the documents whether references to donors are intended to specifically mean donors or whether it is intended to mean litres of plasma or donations. There's a lack of precision sometimes.

SIR BRIAN LANGSTAFF: Well, it does matter.

MR HILL: It does.

SIR BRIAN LANGSTAFF: Because it you take, on one view, the -- any risk per donation is one and a half times as much if you use different measure.

MR HILL: Yes. What we know from Dr Kingdon, in his witness statement that we looked at on Friday, is that he referred to plasma pools of up to 15,000 donations.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: He was very specifically talking about donations there. So whether or not 6,000 donors or 6,000 donations was meant in circa 1975, by the time of Dr Kingdon's statement in 1990, there appears to have

been a rise in the pool size up to 15,000 donations.

SIR BRIAN LANGSTAFF: Unless there is other evidence to help interpret, one just has to take the words as they come and interpret them on that basis, I think --

MR HILL: Yes, sir.

SIR BRIAN LANGSTAFF: -- hasn't one?

MR HILL: Yes. But I think the evidence does show that there was a growth in the size of the donor pools used by Travenol.

Turning to --

SIR BRIAN LANGSTAFF: So the growth that you would identify would be, what, 6,000 up to --

MR HILL: Yes.

SIR BRIAN LANGSTAFF: -- 6,000 litres or donors, depending on which, up to 15,000 donations?

MR HILL: Yes. We don't have any further detail as to when, why and with what justification.

SIR BRIAN LANGSTAFF: Or whether by steps, et cetera?

MR HILL: Exactly. We can seek to try to find out more but I'm not how much we will be able to find out on that.

SIR BRIAN LANGSTAFF: No.

MR HILL: Turning to the procedures that were used for the donors, we heard from Dr Kingdon's statement, his evidence about how things were done, the statement was

dated 1990, and it was sometimes unclear which period he was talking about in that statement and, out of fairness to Dr Kingdon, it's important to note that he joined the company in 1981, so some of what we're going to look at now took place before his time and he wouldn't necessarily have known about it. If we could have on screen, please, Soumik, SHPL0000279_012.

This is a document which is part of what is called the "Donor Centre Technical Guide". It's published by Hyland Division of Travenol Inc, so the American company. We can see that the manual is dated in the top left-hand corner box "March 25, 1975". I note that is before World in Action documentaries were broadcast. That doesn't tell us when the documentaries themselves were actually filmed. We don't know which part of 1975 --

SIR BRIAN LANGSTAFF: This is a revision issued on 30 April 1976?

MR HILL: This is, the original manual was dated 25 March 1975. This is the second revision to it and it's 30 April 1976, which is after World in Action documentary. It says:

"Donor requirements -- check list

"Purpose

"To establish the instruction regarding

adequate permanent donor records."

We can see the types of information that were required in that record, including the donor's name, permanent donor number, date of donation, bleeding number, vital signs and then the result of the syphilis test to be included.

"The donor record form is to be reviewed by the attending physician at least once every four months to determine continuing suitability of the donor."

I won't go through the rest of the document but we can see what the instruction says there.

If we could go, please, to SPHL0000279_029. This is an information sheet about establishing the instructions and the use and proper documentation of Source plasma (human) labelling, the original document from 15 December 1975, this the third revision dated 29 October 1976. It sets out what should be contained on the label of the plasma that should be affixed to every plasma container, and that includes the donor name, the donor number, the bleeding date, and so forth.

On the next page, we can see that the procedures are put in place for each label to be accompanied by 16 smaller labels that:

"... can be used identification of plasma

a guideline check list of requirements to be followed in determining suitability of a donor to qualify for whole blood or plasmapheresis donation.

"Scope

"Provisions of this instruction apply to all Hyland plasma centers."

We can see then a list of instructions. We don't have all of these documents but you can see the types of area that the different instructions cover: the fingernail dye examination and fixation, which I understand to be a method to try to prevent people donating too frequently; the weight, temperature, blood pressure, hepatitis B surface antigen tests; serological tests and physical examination. As I say, we don't have all of the documents that were part of that guide at that time, but we do have some documents which formed part of the guide over the succeeding years.

If we could have SHPL0000279_031, please, Soumik, the original variant of this instruction was 30 March 1976, this is the fifth revision dated 11 May 1976 and, again, we can see it's part of the donor technical guide:

"Purpose

"To establish the instruction for maintaining

segments for testing, donors' bleeding bags, documentation donor records, summation reports, VACUTAINER tubes used for special programs, samples for laboratory testing and donor center logs."

Soumik, could we please have SHPL0000279_018. This instruction is about establishing the proper documentation of the whole blood and plasma processing log. The issue date is 18 January 1977. It is the second revision of the document that dates from 6 October 1976. We can see the instructions given about the information that should be recorded, again including the bleeding number of the patient.

I won't go through the large number of other, similar documents, but we can see from them that there was a technical guide which contained such instructions. Obviously what the documents don't tell us is how those instructions were then implemented on the ground.

Then, jumping forward to October 1983, if we could have on screen, please, BAXT0000011_002.

This is a document which is entitled "Hyland Division of Travenol Laboratories Limited, File RA 1002 - October 1983, Source Plasma (Human)", and it is produced by Travenol Laboratories Limited, so the UK company rather than the US company.

If we could turn over to the next page, please, Soumik. The contents are set out there. There are four sections to it. The first section is about product description, donor definition and facility requirements.

The second section is for donor centre technical guide, table of contents, and that is a reference, as I understand it, to the same guide that we have just been looking at, but this is the version which is now in place in 1983.

Part three is the establishment licences and lists of approved plasma collection centres.

Part four is some of the regulations from the US.

So it appears to be a document that the UK company has produced to inform itself or others of the way in which the American company goes about collecting its blood plasma and whole blood.

If we could turn to page 5 of that document, please, Soumik. I'm not going to go through all of this, it is quite lengthy, but just certain features that can be picked out from it. 2c:

"Each unit of SOURCE PLASMA (HUMAN) shall be nonreactive for hepatitis B surface antigen when tested by a suitable test system of third generation

sensitivity.

"f. A label shall be affixed to each unit of source plasma delineating the following information ..."

It gives the information that should be on the label, including the donor number.

If we go over to the next page, please, Soumik.

This is the section about the suitability and safety of donors. And it says:

"The suitability of a donor shall be determined by a qualified licensed physician or by persons under his supervision and trained in determining donor suitability."

We can see, then, it goes on to describe the "Method of Selecting [the] Donor": "Informed Consent" and the "Medical Examination", which says this:

"Each donor shall be examined by a qualified licensed physician on the day of the first donation, or not more than one week prior to the first donation, and shall be certified to be in good health by the examining physician. Medical examinations shall be performed at subsequent intervals of no longer than 1 year."

It then goes on to list the qualifications of the donor, there is an age qualification, a weight

qualification, a qualification for blood haemoglobin.

A requirement -- if we go on to the next page, please, Soumik -- of hepatitis B surface antigen freedom.

If we go down to (n):

"Freedom from any disease, other than malaria, transmissible by blood transfusion, insofar as can be determined by history and examination indicated in this section."

"(o) Freedom of the arms and forearms from skin punctures or scars indicative of addiction to self-injected narcotics."

And:

"(p) Freedom from a history of viral hepatitis."

The "General" section states:

"Any donor who, in the opinion of the interviewer, appears to be under the influence of any drug, alcohol, or for any reason does not appear to be providing reliable answers to medical history questions, shall not be considered a suitable donor."

Then "Continued Donor Suitability":

"The accumulated laboratory data and collection records of the donor shall be reviewed by a licensed qualified physician every four months to determine and [carefully] certify whether or not the donor may

continue on the plasmapheresis program."

So that is the section about the suitability and safety of donors, and you may find interesting, sir, the distinction made between when a licensed physician has to be involved and when somebody operating under the supervision of that licensed physician is involved. Supervision is not, so far as I'm aware, defined in this document.

If we could go, please, to page 10 of the document.

"Donor Identification System", it says:

"A donor identification numbering system shall be established that positively identifies each donor and relates such donor directly to his blood and his plasma as well as to his accumulated records and laboratory data. Such systems shall include either a photograph of each donor which shall be used on each visit to confirm the donor's identified, or some other method that provides equal or greater assurance of positively identifying the donor."

I won't go to it, but at page 15, there is a further detail on the donor records that are required.

Page 18, please, Soumik. I'm not going to go through this, but we can see there that it is

a summary of the FDA licensing procedures that are in place as of 1983. We then see on page 19 -- please, Soumik -- the table of contents from the donor centre technical guide. So the iteration of a document that we've been looking at previously.

If we could go on to page 20, please, Soumik.

I won't go through all of these but we can see a large number of instruction sheets which form the guide. It goes on for some six pages.

Then, please, Soumik if we could go to page 29.

This is the list of centres that are used by Hyland. And it says that:

"Plasma used to manufacture Hyland Blood Products is collected only at Plasma Collection Centres licensed by the United States Food and Drug Agency.

"The centres and their locations are as follows ..."

It refers to the Hyland Therapeutics Division in Glendale, California, and Travenol Laboratories Inc in Deerfield, Illinois, and then a list of locations, all of which appear to be in the United States.

If we go over to the next page, please, Soumik.

As I say, all of these appear to be in the United States. There is one reference about a third

of the way down to Cherry Street Plasma Center, Inc. There is no additional information provided as to which city that is in or which state that is in, but all of the others on the list are in American cities in American states.

I don't know if there is any significance to the lack of information about the Cherry Street Plasma Center.

As we saw from the contents page, the document also contains extracts from the US Code of Federal Regulations concerning food and drugs, but I'm not going to go to those.

We can take that off the screen, thank you, Soumik.

That is the documentation that I wish to show you about the internal processes, at least as written, by Hyland and Travenol at the time of the 1970s and 1980s.

I would like to turn now to the issue of the use of plasma from prisons.

Could we have on screen, please, Soumik, CGRA0000291.

Some of this material, sir, is -- are documents that we will come back to in November when we're dealing with the way in which the pharmaceutical

companies responded to the risk of AIDS. My focus today is on how plasma was being collected before circa 1983, when the risk of AIDS becomes increasingly apparent. So we will turn back to this material at a later stage for a different purpose.

This document is dated 20 October 1983. It is an internal memorandum within Travenol and it is sent from WR Srigley to D Castaldi about a telecom with Dr Donohue. And Dr Donohue is Dr Dennis Donohue of the FDA's division of blood and blood products, and it is around this time that he is speaking to pharmaceutical companies about the risk of AIDS and what they are doing about it.

What is attached is stated to be:

"... 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."

"If you have any additional questions regarding the conversation, I would be happy to discuss it in detail with you."

So it appears to be of the text of a policy that

was explained orally to Dr Donohue about what Travenol were doing in respect of plasma from prisons.

If we go to page 2, you'll see the document is headed "Proposed Text for Conversation with Donohue", but we can see from the memorandum that this is the text that appears to actually have been used in the conversation.

What it says is this:

"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."

That is what the company -- now I remind you, sir, it's the American company -- is telling the FDA in response to Dr Donohue's overtures about this issue.

My submission, it's clear from this statement that Hyland and Travenol had previously manufactured coagulation factors from plasma obtained from prisoners. The statement doesn't define which concentrates were produced this way, but there's no suggestion that prison plasma was intentionally excluded from any particular products or that it was not used in particular markets such as the United Kingdom.

The date of that document is 20 October 1983.

SIR BRIAN LANGSTAFF: On 24 March '83, which would be some seven months earlier, the FDA had recommended to pharmaceutical companies they shouldn't make any more product from those donors thought to be in a high risk group.

MR HILL: That's correct, sir.

SIR BRIAN LANGSTAFF: It doesn't say whether prisoners in the United States penal institutions were thought to be members of a high risk group, but it's implicit in this document that, at least by October, they were

thought to be a riskier group from which to take plasma. But it looks as though between March and October they went on doing it.

MR HILL: Yes, sir, I think that is the only inference that can be drawn from the document: the reference to the fact that the discontinuation hasn't taken place as of 20 October but is due to take place in that week.

SIR BRIAN LANGSTAFF: They say in terms that they've got some in the pipeline, they're making product from it, and they're going to market it.

MR HILL: Yes. It is still ongoing at that time.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: The March FDA recommendations are something that we will come back to.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: There is evidence that in the 1970s, objections were raised to the practice of using prison plasma. Edward Shanbrom was a doctor who worked for Hyland as medical director and director of research between approximately 1965 and 1975.

On 30 October 2002 he gave a deposition as part of some litigation in the United States, and I'd like to turn to that now, please, Soumik.

It's CGRA0000495.

You can see the first page there shows what this document is: the deposition of Edward Shanbrom MD, 30 October 2002.

I won't go to it, but internal page 10 of that transcript contains the potted history of his CV that I have just given you.

If we could -- please, Soumik -- turn to page 7 of our electronic document. This is page 43 internal of the transcript. I will just read through the questions and answers that were given in this deposition:

"Question: ... do you recall specifically whether or not Hyland had a plasma collection operation [within] the Angola prison in Louisiana?

"Answer: Yes.

"Question: Did you become aware whether or not Hyland had a plasma collection arrangement with the Cook County jail system?

"Answer: No.

"Question: Other than Angola Prison, were you aware of any other prison facilities for which Baxter, aka Hyland, was procuring plasma directly or indirectly?

"Answer: I don't think so.

"Question: Did you ever express any objection to people at Baxter about the use of prison plasma?

"Answer: Yes.

"Question: Did you express them to the president?

"Answer: Yes.

"Question: And what was the nature of your objections?

"Answer: That hepatitis was present at the prison.

"Question: Was it, to your belief, more rampant within prison population than it was within the general population?

"Answer: No, just at Angola.

"Question: Just Angola. Have you ever that occasion to learn anything about the incidence level of hepatitis in prisons other than at Angola Prison?

"Answer: No.

"Question: But did you happen to believe that at Angola it was particularly high?

"Answer: Yes.

"Question: What was the -- if you can recall, the name of the president at Baxter at that time when you expressed these objections?

"Answer: I think it was both Fred Marquart and his successor shortly -- their president, Norm Achen.

"Question: What were their reactions to your objections?

"Answer: I was fired.

"Question: Okay. So would it be fair to say in that part of the -- of the collection of things that led to your termination, involved your objections about using prison plasma from Angola Prison?

"Answer: I'd like to think so, but I don't really know.

"Question: Would you say that your objections were strongly expressed?

"Answer: Very strongly.

"Question: And did you urge that Baxter cease using plasma collected from Angola Prison?

"Answer: Yes."

It's important to note, sir, that the Inquiry's copy of this deposition is incomplete and it doesn't include any cross-examination of the witness. This is what we would call his evidence-in-chief.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: I'm conscious of the time, sir. I have probably about five minutes more on prison plasma. I don't know if you would like me to continue or take a break now?

SIR BRIAN LANGSTAFF: Well, let's finish prisons before we take a break, a jail break.

MR HILL: If we could have, please, Soumik, CGI0000290, please.

This is a letter written on 3 June 1987, from Carl E Brooks, president of -- well, it's stated -- it's on the -- the heading is "Hyland Therapeutics Division Travenol Laboratories, Inc". I'm not sure if Carl E Brooks was president just of the Hyland division or whether he was president of Baxter overall, but certainly a senior executive within the relevant company.

It's sent to Charles J Carman, the chairman of the AIDS Task Force of the National Haemophilia Foundation, and it is in response to a television documentary which had recently been shown, the 20/20 programme. And you can see in the first paragraph that Mr Brooks is saying that he's pleased that NHF recognises that the programme was "highly biased and distorted".

I'd like to pick up the letter, please, from the third paragraph, which says this:

"We feel that Hyland/Travenol has at all times been responsible in its actions on behalf of the people who live with haemophilia. You and the NHF must recognise that the whole treatment community shares in the responsibility for some of the situations that exist today. By demanding the lowest possible price for coagulation factors, you contribute

to the need for plasmapheresis establishment owners and operators to operate in less desirable areas, prisons and locations where plasma is available at low costs."

This section is highlighted in the text.

"The NHF, we believe, has a clear responsibility to support organisations that act in the best interest of the patient population even when it may result in slightly higher costs. There has been a strong tendency over the past couple of years to support those organisations that offer the lowest cost, rather than support those who invest in improving the safety and efficacy of today's, as well as tomorrow's, products for the treatment of haemophilia."

Over to the next page, please.

"Hyland continues to be committed to leadership in haemophilia therapy worldwide. We manufactured the first AHF concentrate and provided the first heat-treated AHF. Hyland developed the first product for treatment of inhibitor patients. Hyland has invested heavily in rDNA Factor VIII research and development and was the first to begin human clinical trials of that material. We were the first manufacturer to provide a quality home care for treatment of patients with haemophilia in this

country. We were the first manufacturer to screen all plasma in compliance with the German BGA requirements in 1985 and 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. Soon, we hope to market a new high purity, viral safe AHF purified from plasma using monoclonal antibody affinity purification technique and improved viral inactivation technology. Hyland/Travenol decided prison locations were not the best for collecting source plasma several years ago and decided to cancel contracts with all prison sources. Certainly, based on information available today, no one can argue that prisons are locations where there are more than the usual population of what we now agree are 'high risk groups'. Further, over the past four or five years, we have either sold or closed down Hyland owned centres that are in these less desirable areas and have cancelled contracts with independent centres located in these areas or insisted on their relocation."

SIR BRIAN LANGSTAFF: Just pause there for a moment. What does that -- how do you interpret the second from last sentence?

"Certainly, based on information available today,

no one can argue that prisons are locations where there are more than the usual population of what we now agree are 'high risk groups'."

What's it saying?

MR HILL: As I understand it, he is saying that the prison population mirrors the general population in terms of potentially high-risk donors. I don't know if that is a reference to levels of hepatitis C or, as it would then have been known, non-A, non-B hepatitis, or if it is a reference to levels of AIDS or HIV in the prison population. But it seems to be an argument that there is no particular risk that associates with a population of prison donors as compared to a population of donors drawn from the general public.

SIR BRIAN LANGSTAFF: And it seems to lead on to the description, "we have either closed or sold Hyland owned centres that are in these less desirable areas", "these" being a reflection back to prisons with no more than the usual population of high risk groups? I don't quite understand what's being said.

MR HILL: I don't know if a reference to these "less desirable areas" is a reference to prisons or is a reference to the point that was being made on the previous page, which is that the desire for low cost haemophilia product has led to manufacturers obtaining

plasma from "less desirable areas". My initial reading of it was that it's a reference to that earlier point that was being made, rather than to the prison group. He's saying that we've done both, as it were.

SIR BRIAN LANGSTAFF: What do you mean, the point where the author blames the customer for the lack of safety of the product --

MR HILL: Yes.

SIR BRIAN LANGSTAFF: -- because he wants it cheap?

MR HILL: Yes. Yes, so the reference on the first page is to the need for plasmapheresis establishments, as the author saw fit, to be operated in "less desirable areas". So I took that reference of the second page to be a comment that those plasmapheresis centres had been closed down, as well as the ones in prisons.

SIR BRIAN LANGSTAFF: Then you were going to turn to the last paragraph?

MR HILL: Yes, the last paragraph says:

"I trust, Charles, that just as Hyland led the way in vacating prisons and will conform with your request to move our collection sites for plasma to more desirable locations, as well as refuse to use 'brokered plasma' where quality of collection cannot be adequately assured, that we will have the support

of the NHF, the treaters and the patients, even if it does cause Hyland's costs to increase somewhat. I also trust that you will appropriately deal with those manufacturers who fail to comply through refusal to purchase or use their products and services."

That is the letter of --

SIR BRIAN LANGSTAFF: It seems to imply, there, that it is yet to move its collection sites to what it describes as "more desirable locations" and it is -- until the NHF got on the case, it was using brokered plasma, buying plasma from plasma brokers.

MR HILL: Yes.

SIR BRIAN LANGSTAFF: Is there any reference in the Travenol Limited -- what's the date of this? 3 June '87.

MR HILL: Yes.

SIR BRIAN LANGSTAFF: The document that we saw earlier from Travenol Limited setting out the identity of the places from which plasma was collected, does it mention anything about buying from brokers?

MR HILL: I don't think that it does. I will go back and check that, and I will check Dr Kingdon's statement. The phrasing of the letter is that it seems to be a response to something that has been asked of Travenol by the National Haemophilia Foundation. The

refusal to use brokered plasma doesn't necessarily imply an acceptance that brokered plasma was used in the past. It's saying that --

SIR BRIAN LANGSTAFF: Well, does it not? I mean, it's:

"... just as Hyland led the way in vacating prisons [leading the way] will conform with your request to move our collection sites ... as well as refuse to use 'brokered plasma' ..."

MR HILL: I don't read that as being an acceptance of --

SIR BRIAN LANGSTAFF: Of past use -- just saying that we are agreeing to refuse to use. But it hasn't said, as it might have otherwise said, "We don't ever use it".

MR HILL: It hasn't in this letter, no. I will check, though, with Dr --

SIR BRIAN LANGSTAFF: I take your point. It doesn't say in terms "We have been using it, we're now going to stop", but it perhaps would have been more in tone with the rest of the letter if it had said, "We led the way in not using it at all".

MR HILL: Yes. It doesn't say that. But again, this letter clearly demonstrates that prison plasma had been used by Hyland Travenol in the past.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: That, sir, is all I was going to say about the use of prison plasma at this stage. It's, as I say,

something we will come back to in November.

SIR BRIAN LANGSTAFF: We will take a break then, until five to 12.

(11.29 am)

(A short break)

(11.55 am)

SIR BRIAN LANGSTAFF: Yes.

MR HILL: Sir, on the question of whether Hyland used plasma brokers, that's an area that we're going to conduct some further research into and we will get back to you on that question, either in the coming week or so, or in November it might be helpful just to go to what Dr Kingdon said at CBLA0000011_005, and it's page 5 of that document, please, Soumik. This comes with the same caveat as previously stated: that this statement dates from 1990, and it's not clear whether the situation being described is that as of 1990 or for how much before that time. Paragraph 12, please, Soumik. What Dr Kingdon said was:

"The industrial manufacturers fractionate plasma collected from plasmapheresis centres around the United States. Hyland processes plasma collected from plasmapheresis centres owned and operated by Hyland throughout the United States and in addition, a number of independent contractors collect and process plasma

under contract in compliance with standards set by Hyland. Hyland also custom fractionates all fresh frozen plasma collected by the American Red Cross under a plasma fractionation contract. Under that contract, all American Red Cross plasma is fractionated in accordance with the process created by Hyland although it is subsequently marketed and sold under a different name. This arrangement has been in effect since July 1985. Prior to this American Red Cross plasma was fractionated under contracts with a number of commercial manufacturers. Although the final product was sold as American Red Cross concentrate the product varied depending on which manufacturer was used to manufacture any particular batch."

I take from that, that American Red Cross plasma was not used in Hemofil, because that was a product that was marketed under Hyland's own name, so it doesn't seem to be --

SIR BRIAN LANGSTAFF: Well, the American Red Cross plasma would have been plasma collected from voluntary donors, I think --

MR HILL: Yes.

SIR BRIAN LANGSTAFF: -- and for the purposes of the Red Cross, which my current understanding, subject to

further evidence, was one of the sources of blood and blood plasma for the American market, the other being blood banks, community blood banks, as well as the commercial fractionators. It doesn't help, really, with the question of contractors, and it doesn't help with the question of brokers, at least at a time previous to the date which this was referring to, which was the 1990s, was it?

MR HILL: The statement dates from 1990 --

SIR BRIAN LANGSTAFF: It appears to be describing what is, ie at 1990, as to what was, as opposed to which it doesn't really say very much, except in respect of the American Red Cross arrangements. Have I misunderstood it?

MR HILL: No, I think that's correct. The tense used is "Hyland processes", present tense:

"... plasma collected from plasmapheresis centres owned and operated by Hyland throughout the United States and in addition, a number of additional contractors collect and process plasma under contract in compliance with standards set by Hyland."

So as of 1990, there are Hyland-owned plants and plants that operate to Hyland's standards, and no reference to a third category of plasma brokers. Whether that was the case at earlier points in time is

not and by this statement, but Dr Kingdon wouldn't necessarily have been addressing that question in his statement. We have to do further research on it. That is -- I read that section, really, to remind us of the position that pertained as of 1990, but we don't know that that had been the position.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: The Red Cross plasma is, it seems to me, something of a red herring for this Inquiry in its terms of reference.

SIR BRIAN LANGSTAFF: Well, it may have mattered for the particular case for which he prepared this statement.

MR HILL: Yes. Yes, but it doesn't seem to be something that was used in products that were sold in the UK.

SIR BRIAN LANGSTAFF: No, not so far as we are aware.

MR HILL: Quite. I'd like to turn now, sir, to the question of the use of plasma from outside the United States. Could we have on screen, please, Soumik, PJON0000054_001. This is a document dated 2 February 1979, it is a report of a production visit to two plants, the Lessines plant in Belgium, which, as we've heard, was a Hyland fractionation centre, and a Swiss Red Cross plant as well, which I needn't trouble you with. It's Lessines that is of interest to us.

The report is produced by C Chard. At that stage, Dr Chard was the scientific services manager for Travenol Limited, the UK-based company. He subsequently became the scientific and regulatory affairs manager for Travenol Limited.

Another name that is mentioned in the top left-hand corner is G Hardy. Dr Hardy had been Dr Chard's predecessor as scientific services manager for Travenol Limited. I'm not entirely sure what Dr Hardy's position was as of February 1979, but he clearly was still involved to some extent in the company. The report is distributed to a number of people, including AW Barrell who was the manager director of Travenol Limited, and it was marked to be confidential.

Before we go through the report, I will just flag up one point. There is reference made to Buminate, which is an albumin product that Travenol produced, so it is not a Factor VIII concentrate, and I just flag that for when we're going through. The first page of the introduction to the report from Dr Chard is as follows:

"The full report of my visit to Lessines and the Swiss Red Cross is attached.

"The following are key points arising from the

report:

"The Lessines Hyland facility does not meet UK requirements for aseptic processing.

"If Lessines is inspected imports of Hyland products to the UK will probably not be allowed to continue, ie Buminate 5% and 20% from Lessines are at risk.

"There is no possibility of importing Lessines manufactured Hemofil made under present conditions.

"Our UK licence suggests that plasma originates in the US. In fact plasma originates from other sources outside the US, eg Lesotho and Belize -- this information should be submitted to the DHSS or plasma from these sources should not be used for UK products."

If we could turn now to page 3 of the full report. Paragraph 5, it contains a little more information about the plasma sourcing. Dr Chard wrote that:

"The UK licence files refer to US produced plasma. In fact plasma is received also from Lesotho and Belize, plasma from Lesotho was readily visible in the plasma freezer. As this plasma is routinely used for UK product it is important that either we inform the UK DHSS or discontinue using this plasma."

Then paragraph 7 "Conclusion":

"If Lessines is inspected (this is a possibility if a variation to source, Buminate 5% from Swiss Red Cross, is submitted) it is highly likely that the import of all Lessines manufactured Hyland product will be stopped until the areas are upgraded. This is a high risk area for the company and was avoided by the inspectors during their visit only because they were not aware we imported Hyland products from Lessines. There is little possibility of a UK inspector allowing Lessines to manufacture Hemofil for the UK market."

Those are the sections of the report that I wish to highlight, sir. I think it's worth making the point that it appears from the report that the products that were being produced in Lessines and imported to the United Kingdom were albumin products, Buminate products, not Hemofil. There was clearly some suggestion within the company that Lessines might be used to produce Hemofil and that may or may not be the reason why Dr Chard was sent out to inspect Lessines, but you will have seen his conclusion that there was little possibility of a UK inspector allowing Lessines to manufacture Hemofil for the UK market.

We don't know, sir, what steps, if any, were taken in respect of Dr Chard's comments that the DHSS should be informed about the source of --

SIR BRIAN LANGSTAFF: Well, just look at the last sentence on that page, if we can just go back to it, Soumik.

That suggests that you're right: that at that stage Hemofil was not being made in Lessines for the UK market, because otherwise it wouldn't necessarily be framed quite as it is.

MR HILL: There is other evidence which I haven't troubled you with that Lessines was used to label the bottles of Hemofil that were shipped over from the United States, but they had been -- the product itself had been manufactured in the United States, so it was purely an external process that was going on at Lessines at that time.

SIR BRIAN LANGSTAFF: Yes, so it was sort of a bottling plant, in effect, was it, or ...

MR HILL: Yes. Placing the labels that were required for the UK product onto it --

SIR BRIAN LANGSTAFF: I see.

MR HILL: -- at Lessines.

We do have a further document, SPHL0000276_036, which indicates that thought was being given in the company as of 1981, so two years after Dr Chard's

report, to the possibility of using Lessines to manufacture Hemofil.

Could we have on screen, please, Soumik, SHPL0000276_036.

This is an internal memorandum, again. We can see it is from Dr Chard to a number of other individuals within Travenol. For reference, it's -- from a head of notepaper -- from Travenol Laboratories Limited, so the UK company.

It says this:

"The planned inspection of Lessines by DHSS Medicines Inspectors for approval to source Hemofil from Lessines was postponed until September at Lessines's request.

"We have now officially received confirmation that the Hemofil variation will not be approved until an inspection has been carried out."

One further document to bring to your attention --

SIR BRIAN LANGSTAFF: Just before we go there, may just ask, the reference to Dr Chard's report shows that it comes from Peter Jones or is relating to Peter Jones.

MR HILL: Yes.

SIR BRIAN LANGSTAFF: Do we know how it came into his possession?

MR HILL: I don't know that, sir. We can try to find out.

SIR BRIAN LANGSTAFF: Certainly, he makes reference to Lesotho and Belize in a report which I think you may have shown us yesterday.

MR HILL: Yes. Yes, he does.

There is also a reference to Belize in the meeting of February 1984, to which we've made reference before. This is a meeting at NIBSC of officials from the UK, officials from the US and fractionators, documents to which we will return in some detail at a later stage, but for now if we could have PRSE --

SIR BRIAN LANGSTAFF: If we go back -- just on the same vein, if we go back to the list of places from which plasma comes, which Travenol Ltd in Thetford set out, there's no suggestion of any of those centres being situated in Belize or Lesotho?

MR HILL: No, the only one that isn't expressly stated to be in the United States is the Cherry Street --

SIR BRIAN LANGSTAFF: Where you just don't know?

MR HILL: We don't know.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: If we could have onscreen, please, PRSE0003071, and page 5 of that document.

The thing that I should add, sir, about the Travenol Ltd list of all the centres is that that

dates from 1983. You'll recall from Dr Kingdon's statement that the use of overseas plasma had ceased circa 1978 and was no longer being used by the mid-1980s.

SIR BRIAN LANGSTAFF: That wouldn't fit with the date of this visit to Lessines, would it?

MR HILL: It does and doesn't, in the sense that it's a 1979 document but the reference is to plasma from Lesotho being found in the freezer.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: And my understanding is that plasma which is said to be significantly out of date can be used for albumin production in the way it can't be used for production of other materials. So while that plasma was, according to Dr Chard, present in Belgium in 1979, it's not clear when that plasma was collected.

SIR BRIAN LANGSTAFF: No, but then that might be so of most fresh frozen plasma unless there's a date on it.

MR HILL: Yes, Dr Chard doesn't say anything about the date on which it was collected.

There is a document we will come to in a second which refers to a Lesotho plant and when it was closed, which I think was 1976. So if that is correct, then the plasma must have been taken as of 1976 and was still in the deep freeze in Lessines in

1979. I cannot comment on how likely that is.

The document we have onscreen, this is from February 1984. As I say, it's this meeting between various fractionators and officials.

At the bottom of page 5, we have a contribution from Dr Ashworth of Cutter. And he described collection procedures at plasmapheresis centres used by the four main US companies. It seems overwhelmingly likely that Hyland/Travenol would have been included within those four major companies.

"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."

Unfortunately the document doesn't say anything more about what that centre in Belize is. It's also notable that we are dealing with a description of what was being done at that time, February 1984, rather than a historic overview of how plasma had been collected in the past.

One final point of note about that last document is that that was a statement that was made in the presence of UK officials and US officials. So there

was no effort to hide the centre in Belize. It is referred to expressly.

Soumik, please can we have SHPL0000735_006.

A document that we will return to at a later stage about the response to the risk of AIDS but here used just to help us understand the way in which plasma was collected historically.

It is dated 23 August -- I think that's 1985, yes -- 1985. It is an internal Hyland memorandum from the American company, Travenol Laboratories Inc.

In terms of "Plasma Sourcing", it states:

"We have committed that we will not use plasma from high risk sources such as:

"prisons or

"geographic areas which are considered to be high risk, ie San Francisco, Hollywood and New York City.

"We do not obtain plasma from third world countries.

"Lesotho, [South] Africa was closed in 1976 (our only African plasma centre).

"The Mexico City plant (which used Mexican sourced plasma) was closed in 1981.

"Puerto Rico was closed in 1980."

No reference is made here to Belize. It's also

important to note that the fact that plasma had previously been obtained from what were described in this document as "third world countries" doesn't necessarily indicate that that plasma was used in Hemofil or any product that was on the UK market. We simply don't know.

SIR BRIAN LANGSTAFF: What's the document addressing generally, under "Plasma Sourcing"?

MR HILL: It is entitled "Outline of Product Safety Work".

SIR BRIAN LANGSTAFF: Yes.

MR HILL: I read this document to be part of a wider response as of 23rd of -- 1986, a stocktaking of where they are on the safety methods that are being used at that time, in respect of plasma collection and plasma use.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: The point there, that this is where I have got the date of 1976 for closure of Lesotho from. But we can see, by comparing that document to Dr Chard's report, that if Lesotho was closed in 1976, there was still frozen plasma in Lessines in 1979.

I'm going to turn now to the question of the effort to recruit donors from gay populations, or areas in which there was a high level of gay donors.

In September 1982, Dr Michael Rodell, ** who

was then the vice president of regulatory affairs and quality control at Travenol, and later moves to Armour, wrote to Harry M Meyer, the director of the National Centre for Drugs and Biologics at the FDA, and this was about the use of plasma, but was obtained from the homosexual community.

The reference is CGRA0000246, please, Soumik.

Again, I understand this to be part of the process by which the FDA was seeking to inform itself and seeking to influence the behaviour of the pharmaceutical companies as of September 1982 in response to the increasing knowledge of the risk of AIDS, and we'll see a reference to Dr Donohue again, who we referred to earlier.

What Dr Rodell said in this letter is:

"During a recent telephone conversation, Dr Dennis Donohue expressed concern existing within the Office of Biologics, regarding the use of Source Plasma (Human) obtained through specific recruiting efforts aimed at the homosexual community. Dr Donohue requested assurance that such plasma would not be in the manufacture of Antihemophilic Factor (Human) until the situation regarding Acquired Immune Deficiency Syndrome (AIDS) was more clearly defined.

"Hyland Therapeutics Division, Travenol

Laboratories Inc is not engaged in any recruitment programmes targeting the homosexual community for plasma that may be used in the production of Antihemophilic Factor (Human). Consequently we are able to offer such assurance to you.

"We do wish to point out, however, that there may be recruiting efforts of this type by organisations collecting Whole Blood (Human), as part of ongoing donor recruitment programs. Since quantities of Recovered Plasma to be used in fractionation do result from such activities, and fractionators would be unaware of the origin of the plasma, the probability for inclusion of this plasma in routine manufacture does exist."

A couple of points to pick up from this document, sir. The first is that the concern about directly seeking to recruit gay donors comes from the context of the fact that gay donors were found to have a high level of hepatitis B antigen in their blood, which was useful in providing vaccination products against hepatitis B, therefore that plasma was of use for that specific purpose.

Dr Donohue's concerns, as I read them from this letter, are that donors who were selected for that purpose were also having their plasma used for the

general production of Factor VIII materials, despite the fact that it would be rich in hepatitis B antigen.

Obviously, by September 1982, gay donors were considered to be high risk because of the emergence of AIDS.

A point to pick up from the final sentence --

SIR BRIAN LANGSTAFF: What is interesting about that is I well understand why obtaining plasma from those communities thought to have a greater prevalence of hepatitis B in order to produce a vaccine suitable for use against hepatitis B might, if the same plasma or a surplus plasma were then used for other purposes, give rise in that plasma of a greater risk of hepatitis B.

But the risk which Dr Donohue is talking about here in September 1982, 15 September '82, is the risk of AIDS.

MR HILL: Yes, that's the specific context of this letter.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: Although, as we will go on to see, there is certainly some criticism that this practice was ever engaged in.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: We will come on to the reason as to why.

There appears to have been some internal

discussion within fractionators around this time, in fact slightly before it, about this issue, and we can see that from an internal memorandum from Cutter, another company, a rival of Hyland Travenol. It is at BAUM0000008_1, please, Soumik. We will come on to deal with Cutter in due course this week, so I won't go into the names.

BAUM0000008 -- sorry, not underscore, just page 1 of the document. My mistake, thank you.

I won't go into those names, Cutter is a firm that we will deal with in due course. The opening line gives the context:

"Dr Donohue of FDA-BoB has asked you (Cutter) to voluntarily exclude plasma collected from known homosexuals from pools used in the production of Koate and presumably Konyne."

If we go down to the next paragraph, please. I'm only interested, for present purposes, in what this tells us about Hyland. It tells us that:

"Hyland (Mike Rodell) has had a policy that any plasma collected from a donor having a history of hepatitis (the disease, HBsAG positive, or in close association with others having the disease) are excluded from use in the manufacture of AHF. Currently Hyland collects plasma from homosexuals for

anti-HBs, but does not use it in their fractionation, it is sold to Alpha. Mike has told Donohue that he thinks Hyland excludes homosexual plasma from AHF but he wanted to check their procedures before making a solid voluntary commitment. My guess is that Hyland will make the commitment."

So, as I say, that precedes the previous document that we have just looked at, and Hyland go on to make the commitment.

SIR BRIAN LANGSTAFF: Precedes? This is 30 September.

MR HILL: 30 August.

SIR BRIAN LANGSTAFF: Oh, August. Beg your pardon, my fault. Thanks.

MR HILL: The reference, though, when taken together, is that while Hyland can say that it doesn't make factor concentrates using blood collected from donors who are recruited because they're gay, there is a reference to it being sold to Alpha, and it's not clear what Alpha then does with the product, from this document.

If we could go, please, to CGRA0000655.

This is a document dated 9 December 1982. It is again from Dr Rodell, Vice President of Regulatory Affairs and Quality Control at Hyland. It is sent to Charles J Carman, Chairman of the Board, and Dr Louis M Aledort, Medical Coordinator *(sic)* of the

National Haemophilia Foundation. It is responding to a letter of 2 November 1982 on various points.

I'm going to turn to the second page of the first paragraph. In this letter, Dr Rodell says, and I quote:

"Within the past several months, we have made a commitment to withhold from AHF manufacture any plasma obtained as a result of specific recruiting activities aimed at the gay community. You are no doubt aware of a significantly greater incidence of high titered anti-HBs plasma among homosexuals, likely due to close personal contacts with members of that community having clinical hepatitis B infections. Such plasma is of great need in the production of HBIG [hepatitis B immune globulin]; however, we no longer allow this plasma to enter those pools leading to AHF manufacture."

If we go down a couple of paragraphs, it says:

"I must point out that we, and other manufacturers, produce AHF derived from source material other than plasma donation. A significant amount of AHF is derived from Recovered Plasma, resulting from whole blood programs. Since manufacturers do not control the recruiting activities of collectors of whole blood, I cannot comment on the

characteristics of their donors, other than that they represent the general population."

The point from the first paragraph is the way in which the comments are phrased, firstly, that the commitment is made within the past several months and, second, from the final sentence, that the company no longer allows plasma collected from gay donors to enter pools leading to AHF manufacture. Again, the phrasing is interesting because it doesn't say that Travenol or Hyland produces the products from those donors, but there is reference to allowing the plasma to enter pools leading to AHF, anti-haemophilic fraction, manufacture.

SIR BRIAN LANGSTAFF: Just pause for a moment. It does seem to suggest, doesn't it, that Travenol Hyland is producing AHF derived from source material, other than plasma donations -- "we and other manufacturers", it says.

MR HILL: Sorry, sir, where is --

SIR BRIAN LANGSTAFF: The second-last paragraph:

"I must point out that we ... produce AHF derived from source material other than plasma donations."

MR HILL: Yes. So the first point is about the use of plasma from gay donors.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: The second point here is that, yes, in this letter, there is a reference to the fact that Hyland have been using plasma which is obtained from -- as the discarded product from whole blood donation collected by others --

SIR BRIAN LANGSTAFF: Yes.

MR HILL: -- and they use that.

SIR BRIAN LANGSTAFF: And they don't know where it came from --

MR HILL: They --

SIR BRIAN LANGSTAFF: -- because they don't control the characteristics of the donors.

MR HILL: "Since manufacturers do not control the recruiting activities of collectors of whole blood, I cannot comment on the characteristics of their donors other than that they represent the general population."

SIR BRIAN LANGSTAFF: I'm not sure how that actually follows. Because if he accepts they might be recruiting from the population, why would they represent the general population? He doesn't know, does he?

MR HILL: Other than in a broad sense --

SIR BRIAN LANGSTAFF: I mean, it's a phrase but it does seem to me that those two comments are slightly

contradictory. However --

MR HILL: Everybody is in the general population, if one defines the general population --

SIR BRIAN LANGSTAFF: Yes, but I think "representing the general population" would seem to be in the same proportions as the general population, that's the sense of it.

MR HILL: Yes.

SIR BRIAN LANGSTAFF: If you recruit specific people from within the general population, the result will not be representative of the general population. It will be unrepresentative.

MR HILL: Yes.

SIR BRIAN LANGSTAFF: It will be skewed.

MR HILL: Yes.

SIR BRIAN LANGSTAFF: That's why I'm not -- it seems to me to be an internally contradictory statement --

MR HILL: Yes.

SIR BRIAN LANGSTAFF: -- as it's written.

MR HILL: As it's written, yes. The only point I would make is that this is a letter which -- I am using it for the purpose of looking at the gay population --

SIR BRIAN LANGSTAFF: Yes.

MR HILL: -- and this is an extra bit, as it were, about a slightly different --

SIR BRIAN LANGSTAFF: I think what you showed me is that the letter is saying, "We don't use -- we don't target the gay population for the purposes of obtaining plasma which we use for AHF; we don't manufacture AHF from any plasma we get from that source; we can't speak to whether there may be some in other material which we do use, because we don't control its collection".

MR HILL: Yes, the other point is that, although Hyland have, within the past several months, made that commitment, in the past --

SIR BRIAN LANGSTAFF: Yes, in the past they were doing it.

MR HILL: Well, they were allowing plasma to enter pools from which concentrate was made.

SIR BRIAN LANGSTAFF: So they were doing it in the past.

MR HILL: They might not have been making --

SIR BRIAN LANGSTAFF: They were making no conscious effort to prevent it.

MR HILL: They weren't necessarily making the product. The previous document referred to the fact that the -- and it's a Cutter document providing hearsay evidence of what Hyland were doing. That said that currently Hyland collects plasma from homosexuals for anti-HBs (anti-surface antigen of hepatitis B), but does not -- (overspeaking) --

SIR BRIAN LANGSTAFF: If we go back to the first paragraph, what it seems to be saying is:

"Within the past several months, we have made a commitment to withhold from AHF manufacture any plasma obtained as a result of specific recruiting activities aimed at the gay community."

You're right, that doesn't say that we were doing it previously. But the last sentence:

"Such plasma is of great need in the production of HBIG; however, we no longer allow this plasma to enter those pools leading to AHF manufacture."

In other words, previously they were allowing it to enter the pools.

MR HILL: Yes, but the only issue is whether or not they were the ones who then went on to make that concentrate. It may have been that Hyland itself didn't make the concentrate but sold the plasma to Alpha, who then went on to make the concentrates.

SIR BRIAN LANGSTAFF: I see.

MR HILL: That is what the memorandum from Cutter would imply. But that, of course, is hearsay evidence about what Hyland were doing. The phrasing of this is interesting in that it doesn't say, if one looks at that last sentence, after the semicolon, it doesn't say, "however, we no longer allow this plasma to be

used by us to make a concentrate"; it refers to "we no longer allow this plasma to enter those pools leading to AHF manufacture".

SIR BRIAN LANGSTAFF: So this first paragraph is capable of covering both self-products and selling on to Alpha.

MR HILL: Yes, it could be either. It is only when you combine it with the previous document with Cutter that perhaps the wording used here takes on a particular resonance.

SIR BRIAN LANGSTAFF: It may or may not be that Cutter is describing what then happened with the excess plasma which Hyland weren't using -- Travenol weren't using for their own purposes.

MR HILL: Yes. The document of the 30 August 1982, the Cutter document, says:

"Currently Hyland collects plasma from homosexuals for anti-HBs but does not use it in their fractionation. It is sold to Alpha."

That's describing a situation as of August 1982.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: This memorandum or this letter, sorry, from December 198 --

SIR BRIAN LANGSTAFF: Later on, and so it may be saying, "We've stopped selling on to Alpha".

MR HILL: "Within the past several months, we have made a commitment to withhold from AHF manufacture", et cetera, et cetera.

SIR BRIAN LANGSTAFF: Yes, thank you. I've got there.

MR HILL: Another point to make about this letter is that it describes no longer allowing plasma to enter the pools leading to AHF concentrate. So that plasma is no longer going to go into those pools. It doesn't say what is happening to such plasma that is already in the pools.

You'll recall of course, sir, Dr Kingdon's evidence about how it could take six months to a year before a donation appeared in a factor concentrate, and one point when talking about AIDS testing -- sorry, HIV testing for the plasma donations, he refers to it being two years between the step being introduced and product still being on the shelf, because of the product's shelf life.

I mentioned earlier, sir, there was a criticism of the practice as a whole. If we look at CGRA0000404, this is a supplemental expert witness report from Dr Donald Francis MD DSc. This is part of US litigation and it should be borne in mind that this is an expert report on behalf of the plaintiffs in that litigation.

Dr Francis says, the first paragraph of this witness report:

"I am a physician specializing in epidemiology and virology. For over twenty years, I was employed by the United States Centers for Disease Control."

I wouldn't go through the rest of his career there.

If we could go, please, to the next page, paragraph 4. What Dr Francis says is this:

"Defendants" --

He is talking about the fact that he has learnt that defendants Cutter and Baxter collected plasma from urban homosexual men for hepatitis B immunoglobulin, HBIG, production and used that same plasma in the manufacture of Factor VIII and Factor IX concentrates. That is the factual premise upon which his comments are based. Of course, Dr Francis himself can't speak to whether that was done. That is the basis on which he makes these comments.

He says:

"Defendants could not have selected a higher risk population for transmission of AIDS than Hepatitis B positive urban homosexual men. These donors were infected with Hepatitis B in direct correlation to their number of sexual partners. Those

at highest risk of Hepatitis B were also at the highest risk for all other sexually transmitted diseases, including AIDS.

"By the mid-1970s, it was well known to defendants and the scientific community, that urban homosexual men had an exceptionally high prevalence of Hepatitis B. This population provided a source of plasma with high titers of Hepatitis B antibodies, which defendants used for the manufacture of HBIG, a product prescribed to create passive immunity to Hepatitis B. By the same time, it was also well known that a substantial proportion of this population engaged in a lifestyle of sexual promiscuity involving multiple partners, which caused widespread sexually transmitted diseases, including not only Hepatitis B, but also Hepatitis C (then unidentified and described as 'non-A non-B' or 'NANB' hepatitis) cytomegalovirus (CMV), and Epstein Barr disease. Thus, the same conduct that made urban homosexual men valuable HBIG plasma donors caused multiple other diseases that made this population inappropriate donors for any other blood or plasma product."

That was the view of Dr Francis. Of course, the litigation will have heard other evidence from other witnesses as well. That is all I'm going to say about

donors and Hyland Travenol at this point.

It leads to the final selection of documents. This is something of a smorgasbord of documents from various sources showing some of the communication that Hyland Travenol had with the United Kingdom and clinicians and Government at various times, so I'm afraid we will be hopping around a bit, but there are some documents which may be of interest within this selection.

If we could begin with, Soumik, with CBLA0005720.

We can see from the top of this document that it's a memorandum sent from Dr Bidwell to Dr Maycock, Dr Bidwell of the Protein Fractionation Laboratory in Oxford to Dr Maycock who, among the other hats that he wore, was the director of BPL at the time.

The date is 23 May 1975. The context, as I read the document, is the outbreak of hepatitis that has been reported by Dr Craske in respect of the use of factor concentrates, and in particular Hemofil.

We saw, in the World in Action documentary -- I'm not sure if we showed it on Friday but we've seen it before -- Dr Craske talking about the outbreak and the fact that it is linked to Hemofil, and at the time -- the documentary was broadcast in December, but

obviously Dr Craske was well aware of the outbreak before that -- there were 58 cases, Dr Craske said, of hepatitis in people with haemophilia.

And his Lancet article -- which is published in August 1975, so published after this memo was produced, but obviously Dr Craske was well aware of the situation before that -- The Lancet article is at PRSE0001794, and it refers to the outbreak taking place between April and June 1974. That is the context.

What Dr Bidwell says is that:

"Dr Rizza has just told me that Dr Josephson, who is the medical director of Travenol, is coming to the [United Kingdom] on Monday, 9th June. They are concerned about the reports of hepatitis associated with the Hyland product and if invited to do so I will join in the discussion in Dr Rizza's office. There is a meeting to be organised by Travenol on the 10th when others involved in the story of hepatitis associated with the Hyland product will be present. This will probably be held in London and Dr Rizza thinks he should go and hopefully we may find out any conclusions."

If we can now turn, please, to OXUH0001590_001.

We can see a note of that meeting which was

produced by Dr Cleghorn of the National Blood Transfusion Service. The note is marked to be confidential and it states this:

"On 10th June last I chaired an informal meeting at which we discussed the problem of hepatitis following the administration of AHG concentrates. A list of those attending is attached.

"Dr Craske presented the results of his epidemiological survey and there was further comment on the virological aspects by Drs Banatvala and Dane. It was clear that not only identifiable hepatitis B was involved but also presumptive A and/or other varieties.

"Dr Josephson on behalf of Travenol Laboratories stated that the incidence of hepatitis B was explained by manufacture of stock-piled plasma, the donors of which had been screened only by CEP. He suggested that it was unlikely that the problem was confined to the Hemofil and events subsequently have shown this to be true, at least in respect of Kryobulin."

"After considerable discussion, it was agreed that while we could expect a drop in the cases of hepatitis B as material screened by HA and RIA techniques came through, the problem of non-B hepatitis would remain."

The attendance list of the meeting -- if we could have this on screen, please, Soumik -- is NHBT0101337_008.

We can see those present included Dr Rogers, Dr Stern, Professor Ingram, Dr Peter Jones, Dr James, Dr Stableforth, Dr Craske, Dr Dane.

I pause there to note that that is the doctor whose correspondence we looked at last week about Immuno and hepatitis.

Dr Banatvala, Dr Josephson from Travenol, Dr Cleghorn, who made the note, Mr Pugh, from Travenol, and Mr Mee from Travenol. Those are both from Travenol Limited, the UK company.

Dr Johnson, we can see, is from Travenol International, the American company.

Mr De Vreker, again, from the International company, did not attend the meeting. Dr Rizza and Dr Bloom -- and you'll recall from the note made by Dr Bidwell that there may have been a separate meeting with Dr Rizza in Oxford.

SIR BRIAN LANGSTAFF: Could you just go back to the page before, please. And before.

MR HILL: The note is at OXUH --

SIR BRIAN LANGSTAFF: No, the page before this. Same document.

MR HILL: That is the first page of this document.

SIR BRIAN LANGSTAFF: Oh, so it will be, yes, OXUH0001590_001. Thank you.

I just want to understand what's being said in the second last paragraph there. Because I note that a Dr Dane has given an agreement --

MR HILL: I understand this --

SIR BRIAN LANGSTAFF: -- to a number of people in the pool.

MR HILL: I understand this to be a reference to, in fact what we have just been talking about, using pooled plasma with high hepatitis B antigen levels as a way of creating a product which can then be used as essentially a vaccine to try to prevent infection.

SIR BRIAN LANGSTAFF: I see.

MR HILL: So here, perhaps counterintuitively, the suggestion was originally that you need a pool of 30 such donors to be able to make an effective product. Dr Dane says he would rather have a pool which is nearer to 100 but people think that that was impracticable.

SIR BRIAN LANGSTAFF: I see.

MR HILL: So a slightly different issue.

SIR BRIAN LANGSTAFF: Thank you.

MR HILL: If we can turn, please, now, Soumik, to

SHPL0000276_141.

The next three documents are, in effect, a worked example of an adverse reaction being noted. We can see that the first document is from Professor Ingram at St Thomas' Hospital, dated 25 November 1975. It is sent to Dr Hardy, then the scientific services manager at Travenol Limited. Dr Hardy was one of the names that was copied into Dr Chard's report on the Lessines facility.

Professor Ingram is writing to Dr Hardy to inform him that a patient (the name is given) that has received a quality of Hemofil has developed jaundice.

The record of the Hemofil received is given.

It's noted that that patient has received other blood products between 5 August and 17 November, and then details are given of the jaundice which has been found.

SHPL0000276_138, please, Soumik.

4 December 1975. Dr Hardy writing to the DHSS, enclosing the correspondence between Professor Ingram and himself which refers to a case of jaundice which occurred while a patient was receiving Hemofil and other blood products. So we can see that that is being notified to the DHSS by the company.

If we could have SHPL0000276_140.

Dr Hardy, of course, referred to correspondence, not just a letter, from Professor Ingram -- correspondence -- and it's fair to say this implied his reply, as well, which is also dated 4 December 1975, which thanks Professor Ingram for the letter.

Notes that the patient did receive other blood products during the time in which the jaundice developed, and says that:

"With regard to the Hemofil batches quoted in your letter, I can tell you the batch number [he gives the number] is in fact the same batch [of concentrate] number [he gives the other number as well]."

There seems to be a mistake in labelling in that one had the US product label and the other had the UK product label.

"I can confirm that both the final product and all the plasma used in the manufacture of this Hemofil was tested by the radio-immuno assay technique for hepatitis B antigen, both by Hyland Laboratories and (in the case of the final product) by the Division of Biological Standards laboratories in Hampstead".

So if a product has been tested, I think it's implied in the letter, although not stated, that the results of those tests were negative because otherwise

the product would not have been used.

We can see that this case of hepatitis has been reported, both to the company and to the DHSS, but, as so often in these cases, the patient has been using multiple blood products, and the tests which have been conducted, on the donations and the final product, as of 1975 there is a question as to how sensitive those tests were.

Turning to a separate subject, and that is correspondence with the Government in and around 1979 about the possibility of Travenol becoming involved in fractionation within the United Kingdom, so not just importing the products but producing them commercially within the UK as well, an internal DHSS note records that in or around 1979 Travenol approached the then Parliamentary Under-Secretary of State of the DHSS, Eric Deakins, to discuss the possibility of setting up a fractionation plant in the United Kingdom.

Travenol were one of three commercial companies who are said in this note to have been interested in this. The others appear to have been Cutter and the Swedish company, Kabri. That's K-A-B-R-I.

The references are DSC0003743_131, and DHSC0002313_054.

A meeting of officials and Mr Deakins took place

to discuss the Travenol proposal on 29 January 1979. If we could have on screen, please, DHSC0002313_055.

We can see the date of the meeting is in the top line. Present are the Parliamentary Under-Secretary of State, Mr Brechin, Mr Dutton, Mr Harley, Mr Jones and Dr Waiter.

Dr Waiter I understand to have been the predecessor of Dr Walford in the position of the medical officer within the DHSS.

Mr Dutton is a name regularly seen on these papers at this time as well, also working within the same section of the DHSS, as was Mr Harley.

In paragraph 1 it says:

"It was established that Travenol's proposals would probably be to process blood plasma donated by volunteers in Britain and provide the NHS with its Factor 8 requirements at no cost. However, Travenol would doubtless then wish to extract albumin and other remaining components and sell them at considerable profit.

"2. Whilst the haemophilia lobby were very strongly pressing for increased production of Factor 8, there were a number of drawbacks to the proposal.

"2.1. It was felt that volunteer donors would

react strongly against any attempt to use donated blood commercially.

"2.2. It might lead to increased pressure to collect plasma only from donors [as opposed to plasma and blood], but this practice (which is common in the USA) was still very controversial and in some respects ethically questionable.

"2.3. Although factor 8 was the main component of interest to the NHS, there were some 20 derivatives from blood plasma and the extent of their use and cost in the NHS was not known. Enquiries were being made about the use of these products in the NHS, and a decision on the possibilities for collaboration could not effectively be made until the results were available.

"3. It was agreed that officials should meet Travenol's representatives to discuss their proposals in more depth. It was felt that the only real scope for co-operation at the moment would be if they processed the blood plasma collected by the NBTS, and were paid for doing so, but returned all the products to the NHS. This would probably lower their unit costs a little and afford them the prestige of supplying the NHS."

"[The Parliamentary Under-secretary] would wish

to be kept informed of the outcome of the meeting."

The date of the note is 1 February 1979.

Fair to say, sir, this is very much at an early stage in the discussions between Travenol and the DHSS.

Worth noting, though, that these discussions are taking place in January 1979. So that is at the tail end of the Callaghan Government rather than the Thatcher Government. Also before Dr Walford was in post. We picked up the story from when Dr Walford came to post.

The meeting between Travenol and DHSS officials took place on 19 March 1979. The reference for it is DHSC0000047. I won't take you to it, sir. It's fair to say that there were some exploratory discussions about the way in which Travenol could either work in partnership with BPL or manufacture a plant on its own, the question of whether Travenol would need to import plasma, and Travenol saying that it would, in order to make the prospect viable, and the need then to ensure that a distinction was drawn between NHS plasma and imported plasma.

Those were the types of issues that were discussed.

Mr Deakins was kept informed of that meeting in

a minute which was dated DHSC0002313_057. Mr Harley proposed that further work had to be done and further information gathered before any subsequent decisions were taken. And a somewhat non-committal letter was drafted in response to Travenol. And that is DHSC0002313_058.

July 1979 saw the election of the Thatcher Government, and Dr Vaughan became the Minister of State for Health. In an internal minute, he noted that Travenol were said to have "put a collaboration scheme to us, which was not pursued", that's what is written in the minute. That's DHSC0002313_010. And so we see Dr Vaughan showing an interest in the proposal that has been made and seeking to obtain further information about it.

The response of the civil servants to that, which is at DHSC0002313_012, is to place it within the wider context of a discussion that was then ongoing about the future of BPL -- the role, if any, of a commercial partner to BPL. And we can see that the issue then gets subsumed within that wider discussion.

We can see Mr Birrell (?), ** the managing director, writing to Dr Vaughan, on 13 February 1980, DHSC0000858, in which he seeks to encourage further engagement with the company. Again, it seems that

there was some debate about how that letter should be replied to, but some civil servants suggesting, in marginalia, that the reply should be made, and I quote "rather more non-committal". That is the same reference.

As we know, nothing ultimately came of commercial involvement within fractionation of the UK, and a relatively early decision was taken that, if there were to be any commercial involvement, it should be with a British company. Travenol, the international branch of Travenol, which would be the one who would be required to be involved, obviously did not meet that description. I note in passing, sir, that Mr Birrell ** in 1984 wrote a number of letters to Lord Glenarthur and to individuals within the DHSS, which we discussed during Lord Glenarthur's evidence.

Finally, from Mr Birrell, ** the reference -- sorry, I've misplaced that reference for the moment. Yes, the reference is DHSC0026448 and DHSC0032854. I don't ask for these documents to be brought up. But these are letters from Mr Birrell ** to the superintendent at the Medicines Inspectorate at the DHSS and to John MacGregor MP who appears to have been the local MP for Mr Birrell ** and/or Travenol

Limited. These were complaints that BPL was being held to a lesser standard than commercial firms. He complained about dual standards and contrasted the most rigorous standards required of commercial companies with the position of BPL. This is in the context of the Critical Medicines Inspectorate Report and, indeed, a critical 1981 World in Action documentary.

The final document in respect of Hyland and Travenol is HSOC0029671_046. This is a Haemophilia Society document of a meeting dated 12 February 1976 in which the Society have received confirmation from Travenol Laboratories that they will provide some help to the Society, but the committee were, and I quote, "very disappointed" to learn that it was far less than they had originally been led to believe. Travenol were paying for the printing and mailing of the programme and registration forms of the congress, the printing and mailing of the first issue of the new-style news bulletin and the provision of treatment materials to be used during the Society's congress.

It was agreed to accept those offers but, as I say, some disappointment expressed about the level of support that was being offered by Hyland Travenol at that time.

That, sir, concludes the presentation on Hyland Travenol. As I say, the presentation on Immuno is distinct because they were separate companies at the time, although they've been dealt with together in this section of the timetable. There are, of course, a number of loose ends which we've identified during the course of this presentation, which we will come back to in due course.

SIR BRIAN LANGSTAFF: Yes. Well, thank you very much. Well, we will take a break then, now, until two o'clock. Two o'clock.

(1.05 pm)

(The Luncheon Adjournment)

(2.00 pm)

MS RICHARDS: Sir, we turn this afternoon to Armour. The themes and issues that I'll be exploring in relation to Armour today and tomorrow, we'll start with a brief explanation of its corporate structure. I'll then look at the licensing history, insofar as relevant to the Inquiry's terms of reference, and some of the product details.

I'll then look at matters relating to donors, selections, screening and pool sizes. Then communication of risk by way of product inserts, data sheets and the like, and to some extent, explore

interactions between Armour and relevant third parties, such as haemophilia Centre Directors in the United Kingdom.

As Mr Hill explained last week, in early November, one of the hearings in early November, we will be exploring in more detail, and across the full range of pharmaceutical companies who imported factor concentrates into the UK, their knowledge of the risk and the way in which they chose to respond or not respond to risks in relation to both hepatitis and HIV. So although the documents that we look at will obviously touch on those issues, there will be a much more detailed examination of that in November.

In relation to Armour, one issue of particular significance is that of seroconversions from its heat-treated product, how it responded to that information, and the chain of events and decisions that resulted in the withdrawal of the heat-treated product from the UK market. Again, I will be touching on the handful of documents relating to that, but that will be the subject of a more detailed explanation and exploration at the November hearing.

It's also important to bear in mind that you will be hearing from a witness in relation to Armour, Mr Christopher Bishop, who worked for Armour in the

United Kingdom. He will be giving evidence to the Inquiry in early November. We will see his name come up in a number of documents that we look at today and tomorrow, a number of themes will need to be explored with him and you'll obviously wish to hear his evidence before drawing any conclusions in relation to the Armour material.

The focus of the material that we look at this afternoon and tomorrow in relation to Armour will be contemporaneous documents, so documents from the 1970s and 1980s, there are a number of secondary sources, books, journalistic investigations, subsequent litigation, subsequent inquiries such as the Krever Inquiry Report, which you'll no doubt wish to consider and draw on in due course but I'll be focusing, for the purpose of today and tomorrow, on the documentation as it existed at the time.

As Mr Hill has already made clear, it's an incomplete picture. There's a lot of material that we do have but there's also unfortunately a lot that we don't have.

In that regard, we're very conscious that there are Core Participants who are highly knowledgeable in relation to the activities of pharmaceutical companies, whether from their own research and

investigations or involvement in litigation in the US or here, or both, who may well be able to identify documents that I don't refer to, and we very much welcome any suggestions of any further material that we should consider.

So starting with the corporate structure, Armour is an American -- or was an American pharmaceutical company founded in 1951 in Kankakee, Illinois in the States. It prepared, amongst other products, factor concentrates in the United States which were distributed to the United Kingdom through a United Kingdom company called Armour Pharmaceutical Company Limited. It changed its name a number of times and so I'll look at that shortly.

The information that we have in relation to Armour's corporate history is largely drawn from a witness statement of a Ms Samantha Silver, the reference -- we don't need to put it up at the moment, Soumik, but the reference is WITN3422001. Ms Silver is a partner in Kennedys Law, instructed by Armour in relation to the Inquiry, and provided a statement to assist in setting out Armour's corporate history, and she confirms in her witness statement she's also reviewed relevant material at Companies House for the purpose of providing that witness evidence.

There is also a statement from a [Ms] Rajinder Bassi -- again, we don't need to pull it up now, but it's WITN6391001 -- a partner in a law firm called Kirkland & Ellis International, who represent Revlon Inc in their current incarnation, and [Ms] Bassi provided [her] statement largely in response to the written statement that the Inquiry received from Jason Evans.

Just looking first of all at Armour on an international plain, since its foundation in 1951, Armour has been owned by several different parent companies. In 1970, we understand it was purchased by Greyhound and then Greyhound in 1977 sold Armour to Revlon. And then, in 1986, the William H Rorer Group -- R-O-R-E-R -- purchased Armour from Revlon.

So far, so straightforward. The position is inevitably a little more complicated than that. Ms Bassi's statement suggests that a company called Pantry Pride acquired 90 per cent of Revlon's shares in November 1985 and that, shortly afterwards, because Pantry Pride was not interested in non-cosmetic companies, Armour, together with a couple of associated organisations which I'll turn to, Plasma Alliance and Meloy Laboratories, were sold, she says, to the Rorer Group in January 1986, and you will

recall Ms Bassi making the point, she says that the current Revlon was incorporated in April 1992 and has in order operated in the pharmaceutical or healthcare centre.

Picking up the timeline, in any event, for Rorer's purchase of Armour in January 1986 the next relevant event was in -- I'm not quite sure of the date -- 1990, a French pharmaceutical company, Rhône-Poulenc acquired and merged with Rorer and the name was changed to Rhône-Poulenc Rorer. There was then in the mid-1990s a joint venture between Armour and Behringwerke, the German company, and a joint venture called Centeon was set up, and that took over, we understand, the role of supplying factor concentrates to the United Kingdom.

Ms Silver's statement sets out the subsequent corporate history of the parent companies of Armour and Behringwerke, subsequent mergers and the like, but I don't think I need to go into those. For anyone who is interested in following through to the present day, the statements are available.

I then turn to the particular position of Armour in the United Kingdom. Armour Pharmaceutical Company Limited was incorporated in the UK in 1959. In 1982, Ms Silver's statement suggests that Armour

Pharmaceutical Company Limited changed its name to Revlon Health Care Limited, and that then in 1986 when Rorer purchased Armour, Revlon Health Care Limited changed its name to Rorer Health Care Holdings. She says that that particular limited company was dissolved in 2010.

We'll see, as we look through the documents from the 1980s, that sometimes the documents reference Armour Pharmaceutical Company Limited and sometimes they reference Revlon, sometimes the Rorer name appears, and sometimes more than one of those names appear on the same document.

I should also draw attention to the fact that, again, according to Ms Silver's statement, at the same time that Armour Pharmaceutical Company Limited changed its name to Revlon Health Care Limited, a new company, also called Armour Pharmaceutical Company Limited, was formed, and thereafter underwent several name changes as the parent companies changed.

If we just look at a handful of documents it does appear that Armour Pharmaceutical Company Limited remained the relevant operative subsidiary in terms of the supply of blood products in the UK in the course of the 1980s.

So if we just look at ARMO0000094, please,

Soumik.

We see here a document from 1982, Armour Pharmaceutical Company Limited.

If we then go to ARMO0000145. I'm sorry, we don't need to look at the text of the document, I'm just seeing how the company name appears over the years.

We can see this is now May of 1984. We've still got Armour Pharmaceutical Company Limited.

If we then go to ARMO0000157, this is a product licence -- we'll be looking at the licensing history in due course, but this June of 1985 and it's granted to Armour Pharmaceutical Company Limited.

Then, lastly, if we go to DHSC0002432_033, this happens to be a letter from Mr Bishop to the Parliamentary Under-Secretary of State in December of 1990. It's still Armour Pharmaceutical Company Limited.

Just, then, in terms of other organisations within the overall group, Meloy Laboratories Inc, M-E-L-O-Y Laboratories, Inc, became part of the Armour/Revlon Health Care Group's research and development division in the 1970s, and we'll see a handful of references to those as we look through some of the documents.

Then probably of the greatest direct relevance, Plasma Alliance, which was a plasma collection organisation, was owned by Armour. So 1975 for something called Blood Plasma Services was purchased by Armour, and then Armour acquired further plasmapheresis centres in the States, which were then rationalised into this one subsidiary, Plasma Alliance.

Again, we'll look at some of the document as we go through the themes. As at 1980 it would appear that Plasma Alliance operated 22 plasma centres to collect, test and ship plasma to Armour's headquarters in Kankakee, that plasma being derived from paid donors. We'll look at the information we have in relation to donors in due course.

Just in terms, then, of where the documents that the Inquiry has have come from -- and again, we're grateful to Ms Silver for the statement she provides and the explanation she provides in relation to that -- it would appear that, to the extent that Armour documentation survives, it survives because it was preserved for the purposes of litigation, either in the States or in the UK, and that's Ms Silver's understanding. She sets out her understanding in the statement that, during the entire period that

Factor VIII was sold, records were kept in hard copy form and archived in Illinois and Pennsylvania and then, rather later, in New Jersey.

Armour's shipping records pre-dating 1980 were, she understands, that's Ms Silver understands, destroyed in the normal course of business, save to the extent that they've been retained for the purposes of litigation. Ms Silver's not aware of what Armour's retention and destruction policies were.

So it's not clear how Armour archived documents generally, only that the documents we have we largely seem to have because they have been kept for the purposes of responding to litigation.

We'll see as we look at the documents a number of names, as we consider Armour in more detail. Obviously Mr Bishop, who I've already mentioned. Some of the names that we'll see crop up will be: SG Brooks, who was head of regulatory affairs for part of the relevant period for Armour Pharmaceutical Company Limited in the UK; WJ Tarbit, who worked in the registration department for Armour Pharmaceutical Company Limited; K Fitch, chairman and managing director of Armour Pharmaceutical Company Limited; Mr Bishop I've already mentioned; and then Michael Rodell in the States, vice president of

regulatory and technical affairs, Revlon Health Care Group; and then Mr Robert Christie, director of clinical science at Revlon Health Care UK, and Armour Pharmaceutical Company Limited.

Just to give a flavour of how we will sometimes see more than one company name appear on a document, rather unhelpfully, if we look at ARMO0000374, if we just look at the top of the page we can see this happens to be a document from April 1985. We've got Revlon Health Care (UK) Limited, Armour Pharmaceutical Company Limited and, indeed, a third company, Berk Pharmaceuticals Limited, on that single document.

Then if we go to AMRO0000151, this is August of 1984, we have Revlon Health Care (UK) Limited at the top of the page, and then, at the bottom of the page, Armour Pharmaceutical Company Limited.

So it's not always easy to understand what the precise relationships are, but in any event they were plainly closely associated companies at the most material time for the purposes of the Inquiry's investigations.

So with that short and not necessarily particularly clear account in relation to corporate matters, I'm going to turn then to product licensing.

The product I'm principally concerned with is Factorate. For the benefit of the transcriber that's F-A-C-T-O-R-A-T-E. That was the concentrate produced for the treatment of haemophilia A by Armour in the States. In the period with which we're primarily concerned, Armour was not producing a Factor IX concentrate for supply to the United Kingdom. There is -- and I'll come on to it very briefly, there was a Factor IX product, Mononine, licensed in the UK in around 1993, but in the seventies and eighties it's Factorate that we're concerned with.

So if we go to ARMO0000001, please, Soumik.

We will see here details of the Factorate product, which was the first product for which Armour received a product licence in the United Kingdom. The product licence number, and we'll see it referenced as we go through the materials on a number of occasions, was 0231/0038.

This is the application made by Armour for a product licence in the UK in March 1975. The application is in two volumes. We don't need to open the other one but I'll just read the reference out for the transcript. It's ARMO0000002. And that second volume contains a number of clinical studies which were provided to the Licensing Authority. But it's

this document at ARMO0000001 that we find the most relevant information.

We get a sense of the range of information provided from the index, so section A of the material is entitled "Active Constituent".

If we go over the page, there's a section on "Finished Products", and we're going to come to particular parts of the application in a moment.

If we go to the bottom of the third page we can see the date in the bottom right-hand corner, March 1975, and the application is being submitted by Armour Pharmaceuticals Co. Ltd.

If we go to the next page, and we zoom into the top half to start with, this is the application form. The proposed licence holder is Armour Pharmaceutical Co Ltd, the role of the proposed licence holder is described as the "person who imports or procures its importation", and then, bottom of the screen, we can see that the name of the product is Factorate. And this was an application signed by the head of regulatory affairs, Mr Brooks.

If we go to the next page, we'll see the product particulars. We don't need to go through the detail of it but you'll see there in very broad outline terms: uses, recommended dose, contra-indications,

et cetera. We'll see what's said by way of warning shortly.

If we go to the next page we can see the heading "Supplementary Particulars" and the "Manufacture" explains that:

"Factorate is manufactured from fresh frozen human plasma which when tested is found to be negative for hepatitis B antigen activity."

So that's our first reference to testing in relation to hepatitis B, and that's the testing of the plasma.

Then we'll see, at paragraph (c) on that page:

"The Name & Address of Place of Manufacture Assembly."

That's Armour Pharmaceutical's manufacturing headquarters in Kankakee, Illinois, in the States.

If we turn to page 6, please -- sorry, if we turn to page 16, please, Soumik. There's an awful lot of detailed information in this so I'm just going to alight on certain points of particular relevance.

This is a section about the "Method of Manufacture, "Description of the Manufacturing Process". And then you'll see at stage 4:

"The final product is re-checked for hepatitis associated antigen."

So what's described is a process whereby the plasma is checked and then the final product is re-checked for hepatitis-associated antigen. That is, of course, a reference to hepatitis B.

If we go next to page 24, we can see that part of the material supplied to the UK Licensing Authority with the licence application is this document entitled, "Raw Material Specifications", drawn up in October 1973 by the manufacturer, so Armour in Kankakee in Illinois. And we will see, if we just look at the description in the first paragraph, it says:

"Plasma for Fractionation, Normal, (Human), is the liquid portion of whole blood ..." et cetera, et cetera.

Then pick it up in the fourth line:

"... drawn from adult humans by plasmapheresis who have not been immunised to produce specific antibodies ..."

Then if we skip down three lines:

"... and who, at the time the blood is drawn, are in condition physically to give blood, insofar as can be determined by personal history, by physical examination and by appropriate tests on the day the blood is collected."

Just pausing there, there are number of references, as we will see in the material, to essentially donor selection processes, and there is a little more detail in some of the later documents than we have here, but it is still not entirely clear precisely what was drawn out by way of personal history, what physical examinations were undertaken. It becomes a little clearer what tests were undertaken on the blood.

And you will see the qualifying words "insofar as can be determined". Then it continues:

"Donors with a history of viral hepatitis, or an event of exposure to hepatitis within the normal incubation period, shall be excluded."

If we go to the bottom of the page, we see a heading "Collection and Processing of Blood":

"Blood collection clinics supplying human plasma under these specifications and licensed by the US Department of Health, Education and Welfare, Food and Drug Administration, must comply with applicable requirements defined in the Code of Federal Regulations, Title 21, Part 600. Non-licensed clinics supplying human plasma under these specifications must also comply with these regulations ..."

So that might be thought to suggest that, at

this point, and this is a document from October 1973, Armour obtained its blood from both licensed and non-licensed clinics. This, I think, pre-dates its acquisition of the Plasma Alliance plasmapheresis centres.

SIR BRIAN LANGSTAFF: And there's no reference to them owning the clinics themselves?

MS RICHARDS: Not at this point in time or in this document, no. We know that by 1980 they certainly did, but the precise dates upon which they were acquired are not clear.

If we go to the top of the next page, the first paragraph explains that:

"Blood shall be drawn from acceptable donors by licensed physicians or by specially trained assistants under their direct supervision. Determination of the suitability of the donor is the responsibility of the licensed physicians and must be made by them or under their supervision."

Then if we go to the bottom of the page, we can see the heading "Records", and so this relates to records of donors:

"Adequate records detailing the medical history of the donor, all physical examinations given him, and appropriate release statements he signs must be

maintained. And, adequate systems identifying the blood, plasma, and serum, and correlating them with records supplied to Armour Pharmaceutical Company and records at the donor centre, must also be maintained.

"Records of all donors represented in the plasma supplied to Armour Pharmaceutical Company must be maintained for a period of at least six (6) months after the latest expiration date of the products prepared from the plasma. A period of twelve (12) years is recommended".

So something of a difference in terms of magnitude between the recommendation of 12 years and the requirement of six months.

Over the page, there is further requirements and stipulations in relation to records relating to shipments of plasma to Armour. So you'll see from the first paragraph they:

"... must be accompanied by records that include adequate donor identification ..." et cetera.

Then if we go to the next page, please, we move to a heading towards the bottom of the page entitled "Plasma" -- sorry, I should actually just draw attention, above that, to "Facilities Inspection", where it says:

"Bleeding and processing establishments, and all

processing equipment and records will be available for inspection, during regular business hours, by designated representatives of Armour Pharmaceutical Company."

That's an entitlement by Armour to inspect the establishments from whom it obtains plasma.

And then the next sentence also explains that inspection will be available by designated representatives of the Food and Drug Administration.

Then if we go to "Plasma Properties", we'll see it says, "Plasma for Fractionation", and then there are number of elements set out.

If we go over the page we see point 7 is:

"Shall be free of Hepatitis B antigen as tested on individual units by Radio-Immuno Assay."

If we then turn to page 31, this is a further section of the licence application headed "Quality Control Checks made at Each Stage in the Process". Stage 4, you'll see from the bottom there, is:

"The lyophilised material is examined according to the Finished Product Specification provided in Section 11. It is also checked for Hepatitis B associated antigen."

So that is presumably a reference to what we saw described as the re-checking of the finished product.

If we then go forward a number of pages, Soumik, to page 94, we can see here a section of the material with the licensing application headed "Hepatitis Associated Antibody".

And there is then, if we go to the top of the page, under the heading "Biological Principles of the Procedure", a description of the technique used to measure the hepatitis B antigen levels in the serum, using what's described there as a sandwich principle.

Then, two pages further on, please, Soumik, to page 96. Under the heading "General", if we pick it up a few lines down, it says this:

"Although the association of infectivity and a positive result for Hepatitis B Antigen is strong, it is recognised that presently available methods for Hepatitis B Antigen detection are not sensitive enough to detect all infectious units of blood or all possible cases of hepatitis."

Then it goes on to explain how false positive results may be obtained and gives two different -- a description of two different types of false positive results.

So that's the most salient parts of the licensing application, the first licensing application made in March 1975.

If we then look at how that licensing application was considered by the Licensing Authority and some of the further conditions that were contemplated, we start at DHSC0105603, please.

If we go to the second page, what we have here is a report from the medical assessor, Dr Andrews. It's a report dated 16 October 1975. We don't need to go to it now but the date is on page 8 or so of the document.

We can see that Dr Andrews here essentially summarises the application. So we've got the heading "Summary, Report and Recommendation", and Dr Andrews then sets out a number of matters relating to the application. If we go over to the fourth page, please, Soumik.

We can pick it up at the top of the page, under "Contra-indications and warnings", so again this is still Dr Andrews summary of the application:

"There are no known contra-indications to AHF but the risk of transmitting viral hepatitis is present since no completely reliable laboratory test is yet available for detecting the presence of hepatitis virus."

Then, towards the bottom of the page, there's a paragraph headed "Labelling", and we'll come on to

the question of product labels later, and then "Chemistry and Pharmacy", and under the heading "Methods of manufacture", the report says:

"Blood is drawn from acceptable donors by licensed physicians and the plasma obtained using plasmapheresis techniques must conform in all respect to the applicable requirements for source of plasma (human) defined in the USA Code of Federal Regulations. This applies to licensed and unlicensed clinics. A copy of these are not included in the submission. Adequate records detailing the medical history of the donor, all physical examinations given him and appropriate release statements are kept for a recommended period of 12 years."

Then if we go to the next page, we can see under the heading "Plasma properties", paragraph 7.2, again, Dr Andrews is summarising the application:

"The plasma is ...

"7. Is free of hepatitis B antigen as tested on individual units by Radio-Immuno Assay".

Then if we go to the next paragraph, 7.3, he describes there the four pages of preparation, and we see Stage 4, he summarises:

"The final product is tested for freedom from hepatitis associated antigen."

If we then go, I think it should be, two pages further on. Yes. So we get the date of the report from here, 16 October, and we can see the comment from Dr Andrews, having summarised the application material for the relevant sub committee. Dr Andrews then says this:

"It is not quite clear who is the supplier of the donated plasma ..."

Then, I'm afraid we can't read the next bit.

"... would appear that this could be a number of units (licensed and unlicensed) which work to FDA standards. It is also not clear whether the tests for hepatitis surface antigen is carried out on individual donations at the time of donation or during the routine examination of patients undergoing plasmapheresis. The company have been asked for information on this point together with a request for clarification of the place where quality control tests are carried out. It would appear that the manufacture of the product is satisfactory though the manufacturer has not as yet been inspected."

It's not clear who that's a reference to inspection by, whether it's by the FDA or equivalent or inspected by the UK Licensing Authority.

Then there's a reference to stability data and

shelf life.

"It is recommended that subject to approval of the quality control situation that a product licence be granted."

So that's Dr Andrews' recommendation.

If we then turn to DHSC0105604_002, we can pick up here the consideration of Armour's application by the Subcommittee on Biologicals at their meeting on 12 November 1975. If we go a little further down the agenda, we can see item 5 on the agenda is "Consideration of applications" and the fourth application is for Factorate, the product licence number there set out.

If we go over the page, we can see the minutes of the meeting, just draw attention to paragraph 2, "Confidentiality". Perhaps not so relevant for the purposes of considering the individual licensing applications but you may wish to bear in mind, sir, when you consider the Subcommittee on Biologicals' July 1983 decision on the question of whether imports from the States should be banned at that point in time, confidentiality was always regarded as highly important by the Committee on the Safety of Medicines and its subcommittee, and so those who were present at meetings were not supposed to discuss the content of

what had gone on at meetings.

You'll see here that reminder being given "Confidentiality":

"The Chairman reminded members that the material they received was of a highly confidential nature and should not be made available to outside contacts."

Then if we look at the bottom of the page, section 5 of the minutes, "Consideration of applications", and that refers to the applications being considered. The consideration of this application is in an appendix to the minutes at DHSC0105604_005. If we go closer we'll see then the recommendation:

"On the evidence before them the Sub-Committee on Biologicals recommend the grant of a product licence for this preparation for the purposes indicated in the application, provided that ..."

Then number of conditions were set out.

"1. Information is provided on:

"i. The number of donations from which plasma is pooled for the manufacture of the product.

"ii. The reasons for, and rate of, rejection of donors, or donations, centre by centre."

There were a number of other requirements set out at paragraphs 2 through to 5, including product

labelling and compliance with the batch release procedure but, for present purposes, it's the request for information about pool sizes and rejection of donors that's most relevant.

So that's the recommendation of the Subcommittee on Biologicals.

What happened next was that the Committee on Safety of Medicines considered the application in November 1975, date unclear. We don't have the Committee on Safety of Medicines' actual decision but they effectively, we'll see from another document in a moment, it would seem, approved it, subject to those conditions.

This is November 1975. What, of course, then happened was the broadcast of the World in Action documentaries, on 1 and 8 December 1975, and this led to an enhanced consideration being given to Armour's product licence application by the Licensing Authority with, as we shall see shortly, the involvement of the Minister of State for Health.

So if we pick it up at MHRA0004180, this is not specific to Armour's application but is a meeting which considers the World in Action documentary. So this is described as a note of a meeting of the Divisional Management Group held on 9 December 1975.

It's not entirely clear what the Divisional Management Group was, but it seems that it was a group within the Medicines Division of the Department of Health, certainly some of the names -- Dr Harris, Dr Holgate and others -- are familiar from that.

Just before we look at the discussion on the documentary, flag up paragraph 1.2, which is a reference to the minutes of a previous meeting, where it says:

"It was agreed that the first sentence [of the minutes of the previous meeting] should read 'Dr Holgate said that shortage of funds inhibited visits to manufacturers' premises abroad'."

So we'll obviously need to see if we've got the full set of minutes but you'll recall Dr Walford's evidence, she had a recollection of going on one inspection visit when she was at the Medicines Division but this would appear to suggest that the Licensing Authority was inhibited by lack of funds from conducting its own routine inspections to premises abroad.

In any event, if we go to the bottom of the third page of these minutes, very bottom paragraph, we see the heading "Blood Coagulation Factors for Haemophilia":

"Mr Tringham reported that a television 'World in Action' film had made criticisms of Travenol's production of 'Factor VIII' in the USA. The criticisms were in conformity with an inspection report carried out on behalf of the Division."

Again, that's obviously dealing with Travenol there rather than Armour.

"The Minister of State had been briefed [and the Minister of State at the relevant time was Dr David Owen] and was concerned about the supply of the Factor and about the hazards of using it."

If we go to the next page we see then Armour is referred to:

"A similar product manufactured by Armour had recently been cleared by the CSM [Committee on Safety of Medicines]; Supply Division were anxious that it should be licensed as it would be available at a lower price than the Travenol product. There was some doubt as to whether the collection of blood products for either product was satisfactory. Dr Holgate said that he doubted whether inspection of the American collecting centres would be useful. What was needed was to strengthen the requirements in the product licence, and to insist on returns from each collecting centre including the rate of rejection of donors or

donations."

Just pausing there, sir, you will no doubt have picked up the reference there to the Supply Division being keen to have product cheaper than the Travenol product, and the Medicines Division there expressing doubt as to whether the collection of blood products for either the Travenol product or the Armour product was satisfactory.

Then we pick it up in the next paragraph:

"The story of the television film was that Britain could be self-sufficient in Factors for haemophilia within a few years. The Department in 1972 had allocated £500,000 and had bought the equipment needed for production. However there were some difficulties. Neither of the production units had applied for product licences. The SHHD [the Scottish Home & Health Department] had written to the factory at Liberton and Medicines Division had reminded HS2 Division that though the Lister Institute of Preventative Medicine (Elstree) had a contract with the Department, this did not give them exemption from the requirement to hold a product licence. Mr Tringham emphasised that his concern was to regularise the situation, not to stop production. The haemophilia patients' group were protesting at the

delays in the commissioning plant. The Supply Division were concerned that in the meantime doctors might develop brand preferences for the imported products. Dr Holgate said that doctors would prefer the British products as being safer. Indeed, once a pure supply is available, doctors will want to use the product in situations in which the currently available Factors would be too great a risk."

So an insight there into the thinking of the DoH as at 1975.

If we then turn to how that played out in terms of the consideration of Armour's application for a product licence, we can see from DHSC0003742_077 a minute dated 16 January 1976 from Mr Tringham, in what's described as the Medicines Branch. It's headed "Factor VIII product licence applications" and it refers in the first paragraph to a meeting with Dr Owen. We haven't got any other record of that meeting that I'm presently aware of, and we may be able to find it or we may not have it. I don't know. But it says this:

"At the meeting with Dr Owen in connection with the Television programme about Factor VIII, he indicated that he would wish to see any further applications for product licences to authorise the

importation of Factor VIII."

Pausing there, you'll recall the evidence given by some of the politicians from whom you've heard in the 1980s was very much that ministers would not or should not become involved in the consideration of licensing applications. This, by contrast, is an example of Dr Owen, as Minister of State for Health in 1976 indeed becoming involved in matters relating to a licensing application.

So picking up the paragraph:

"Accordingly, we have prepared a submission about the application from Armour Pharmaceutical Co."

We'll look at that submission in a moment.

"I understand that Supply Division have received a 'very favourable' tender from the company for the supply of Factor VIII to haemophilia centres [presumably that means cheaper] but, of course, action on this depends upon the granting of a product licence.

"While the submission was being typed I received a telephone call from a representative of the company inquiring as to the outcome of their application. I told them that we should probably be writing to them in the near future. In the course of the conversation I was able to sound the company's representative about

their attitude to some of the matters covered in the submission, and I formed the impression that in practice they would be able to accept the conditions mentioned at the end of the submission; but of course this may depend upon the attitude of the American company."

So if we then turn to the submission itself, DHSC0003742_078. So "Factor VIII -- Application by Armour Pharmaceutical Co Limited":

"This submission concerns the application for a product licence under the Medicines Act 1968 by Armour Pharmaceutical Company Limited in respect of Factorate, their brand of the antihaemophilic factor (Factor VIII). The application was considered by the Committee On Safety of Medicines ... at their meeting in November 1975 ..."

So, sir, that's the evidence we have as to the committee's overall consideration:

"... they advised that a product licence should be granted subject to the acceptance by the company of certain conditions. No action has yet been taken on this advice.

"Summary of application.

"Armour Pharmaceutical Co Limited submitted a product licence application for Factorate on

2 April 1975. The application states that ..."

Then various matters are then set out, that the manufacturing takes place at the factory in Illinois, reference there to testing for hepatitis B antigen of the plasma, human plasma being supplied by blood collection centres licensed or unlicensed, but were required to comply with the Code of Federal Regulations.

Carry on down the page, subparagraph (d) refers to checking the donations for freedom from hepatitis associated antigen, and (e) refers to:

"Labelling will contain a warning to the effect that the product is prepared from pooled human plasma and that despite careful selection of donors it may contain causative agents of viral hepatitis."

So that's this ministerial submission summary of the application.

The committee's --

SIR BRIAN LANGSTAFF: He refers to non-licensed centres as being outside the USA.

MS RICHARDS: Ah, can we go back up to that?

SIR BRIAN LANGSTAFF: "... non-licensed clinics (that is to say clinics outside the USA)."

So that's his understanding of that phrase.

MS RICHARDS: Yes, it is. I don't think there's anything

in the material I've seen that suggests that his understanding is correct -- or, sorry, suggests whether his understanding is correct or not but we can check.

SIR BRIAN LANGSTAFF: Yes, I suppose the question would be whether any clinic is allowed to operate as a centre within the USA without being licensed. If it isn't, then non-licence would have to be outside the USA, I suppose.

MS RICHARDS: Yes, yes.

SIR BRIAN LANGSTAFF: So the question then might arise as to compliance with the Code of Federal Regulations is checked and monitored.

MS RICHARDS: Yes. I imagine we ought to be able to find out the answer to that, because you'll recall from the licence application material, the provisions of the Code of Federal Regulations that were said to apply to unlicensed clinics were set out. So provided we can get hold of the Code of Federal Regulations from 1975, we'll hopefully be able to find the answer to your point, sir.

So then picking it up at the bottom of the page, we can see:

"The [Committee on Safety of Medicines], on recommendation of their Sub-Committee of Biological

Products, advised that a product licence be granted subject to the following ..."

The first is about the method of assays and standard of calibration. Then (b) is:

"The following conditions being observed:

"(1) Information should be provided by the licence holder on

"(i) The number of donations from which plasma is pooled for the manufacture of each batch of product [so pools sizes].

"(ii) The reasons for and rate of rejection of donors or donations ..."

So those are essentially the conditions that the Subcommittee on Biologicals had recommended and this submission suggests that the Committee on Safety of Medicines reached the same view.

If we then go down the page to the next heading, "Licensed action", the submission continues:

"The normal action on receipt of advice by the Committee in these circumstances would be to invite the company to amend their application to incorporate the conditions proposed. If they agreed a licence would then be issued on this basis. If the applicant did not agree the conditions could not be enforced without first giving the company the opportunity of

appearing before or making written representations to the Committee.

"In view of the minister's interest action on the lines has not yet been taken and we have considered whether any other conditions would be appropriate."

Then if we go to the next paragraph and just zoom in:

"A representative of NIBSC has recently visited the fractionation plant but there has been no formal inspection by DHSS either of the plant or of the premises used for collection. In light of experience of inspection of other companies producing blood products in the USA it is not considered that time and money would be well spent in inspecting the clinics where blood is collected. Inspectors could be shown only the best and even the worse might be run highly efficiently on the day of visit. While an experienced inspector might deduce the truth there can be no certainty of this. It ..."

That might be --

SIR BRIAN LANGSTAFF: "Seems best".

MS RICHARDS: Yes.

"... seems best to assume that all blood products of this nature coming from the USA may be obtained

from plasma taken under the worst circumstances and any protective measures should be achieved by other means."

Top of the next page.

"The applicants are of high repute as manufacturers. Visits need only be made to the fractionation plant in order to verify the ability of the quality control staff to carry out the necessary tests and assays and, in cases of dubiety, to verify the records held at the centre and to ascertain that information supplied to the licensing authority in the UK is substantially correct.

"The applicant has been required, in accordance with section 19(3) of the Act to give an undertaking to permit the premises to be inspected by or on behalf of the licensing authority. If a licence is granted, inspection visits can therefore be undertaken at any time to Armour's premises.

"This undertaking does not however extend to the premises not belonging to Armour (in the USA or not) where the donations are taken. It might be prudent to secure a similar undertaking on the inspection of such premises.

"Both the manufacturing premises and the collection centres (wherever situated) are subject to

inspection by the FDA. There are however grounds for doubting whether the stringent provisions of US law are in fact fully enforced. In this connection Dr Theodore Cooper, US Assistant Secretary for Health, has written to the [Chief Medical Officer] about US procedures (ANNEX B) ..."

We will look at Annex B, it doesn't say anything about Armour but it's of interest generally.

"... it should be possible in the ensuing correspondence to obtain further information on this point."

Then the next heading in the submission is "Source of donations":

"It may be worth considering whether limitations should be placed on the sources from which blood is obtained.

"One possibility would be to authorise the marketing of the product only if it is derived from blood given by volunteers without payment. It is understood that over 50% of blood used in the USA is given voluntarily. It seems likely however that a restriction of this nature would affect the economics of the supply arrangements and would be unacceptable to the applicant. In any case it might be difficult to show that in fact blood from paid

donors is necessarily less safe than from unpaid donors."

So that's considered and, as it were, rejected, for the reasons given. Then it continues:

"An alternative approach would be to limit the sources geographically. The licence could relate to material obtained either at either --

"(1) licensed clinics in the USA.

"(2) Centres in other named countries, specifically approved by the UK licensing authority."

If we go over the page, top of the page:

"On this basis, approval would be given in respect of other countries if sufficient was known of the local conditions including enforcement arrangements to give some confidence in the product. The point is that in the USA each clinic must be specifically licensed ..."

So again, that's the Department's Licensing Authority's understanding.

"... and therefore presumably some check is carried out. For collecting centres outside the USA, all that is known is that they are open to the inspection by the Bureau of Biologics, but in view of the distances involved it is unlikely that all centres are inspected regularly, if at all.

"Such a condition could be combined with the condition envisaged in [paragraph] 9 as to the undertaking to allow inspection of donation centres, the approval under [paragraph] 13(2) being conditional on the giving of such an undertaking."

SIR BRIAN LANGSTAFF: It seems a little odd to say in one paragraph "they might be open for inspection but it probably doesn't happen", and then to say, "Well, perhaps we should ask for the same".

MS RICHARDS: Yes.

SIR BRIAN LANGSTAFF: But there we are.

MS RICHARDS: Yes, what the practical utility would be in terms of improving safety is --

SIR BRIAN LANGSTAFF: It may be better than not having the undertaking.

MS RICHARDS: But whether it actually increases the safety of the product --

SIR BRIAN LANGSTAFF: Is questionable.

MS RICHARDS: Yes.

Then paragraph 16:

"Here again, it is possible that the applicant would be unwilling to accept such a condition for commercial reasons but the limitation would appear to be practicable."

Then there's a heading "General conditions":

"There are at present regulations under the Therapeutic Substances Act ... about the manufacture of blood products. These were made many years ago, but were not of any practically effect until importation began -- because they were not regarded as legally binding on the Crown, the only effective supplier. They cover basic requirements, including the medical supervision of collection and checking the health of donors.

"In this respect they are more stringent than the US regulations but in general they are much less detailed and do not incorporate references to modern test requirements."

Then paragraph 18 explains that those regulations, the Therapeutic Substances Act regulations are, in any event, about to be superseded by new regulations:

"... and it seems desirable that the opportunity should be taken to give effect to more up to date and specific requirements on the general lines of the US regulations. In so far as the products are already subject to these regulations, this will make no practical difference but it will assist in dealing with products imported direct into the UK from countries other than the USA."

Then there's a heading of "Other sources of supply":

"Three other companies have product licences in respect of imported Factor VIII and two other applications under consideration. Brief particulars are given in ANNEX C."

Top of the next page:

"In addition Factor VIII is now available from the UK National Blood Transfusion Service. Until recently the Medicines Acts controls were not applied formally to NHS production. Arrangements for its application were promulgated in the Summer of 1975; these involved administrative measures in England and Wales and formal licensing in Scotland. In fact however at the present moment no formal action under the Medicines Act has been taken in respect of the preparation of Factor VIII. Although it is not suggested that anything is amiss in this connection, it must be borne in mind that some embarrassment might arise if an applicant were to ask whether the UK product had received the same scrutiny at his product.

"If any of the additional requirements mentioned in this submission are to be added to the Armour licence it would clearly be right to impose the same conditions in respect of other similar products. New

general requirements as contemplated in [paragraph] 18 would achieve this result. Alternatively, the companies can be asked to accept the conditions individually and if they did not action could be taken under section 28(3)(h) of the Medicines Act to vary the licences on the grounds that the standards are no satisfactory."

Then "Matters for decision":

"It seems necessary first to decide whether a visit of inspection should be carried out before determining the licence application. If, as suggested in [paragraph] 6, it is agreed that no visit should be made at this stage, decisions are sought as to whether the company should be asked, in addition to the conditions imposed by the CSM, to agree that --

"(a) Plasma should be obtained only from donor centres in the USA, or in other countries specified in respect of which the licensing authority is satisfied as to the arrangements ...

"(b) DHSS Inspectors may visit collecting centres ...

"The Minister of State is asked to agree that subject to the company accepting the conditions proposed by the CSM and conditions (a) & (b) above, if he considers them appropriate, a product licence

should be granted accordingly.

"Agreement is also sought to the proposition that, as outlined in [paragraph] 21, such conditions should be applied to other licence holders."

So that's the submission that was apparently sent to the Minister of State for Health, who would still have been Dr David Owen at that point in time.

If we then pick matters up, still in January 1976, we see a meeting takes place with the Minister, following his consideration of the submission, and that's at DHSC0003742_076. So we can see the date of the meeting is 21 January 1976. Present, number of names Dr Owen, Minister of State, and then we've got, amongst others, Dr Tringham and Dr Andrews -- presumably, although it's not an uncommon name, the Dr Andrews who had done the medical assessment for the Medicines Division -- and Dr Waiter, whose name we see on a lot of material from this time.

Paragraph 1:

"The meeting had been called at Dr Owen's request following his consideration of a submission about an application from Armour Pharmaceutical Company to supply Factor VIII to haemophilia centres."

Then we see some matters set out from the

discussion:

"i. The price being quoted by Armour Pharmaceuticals was 8p per unit which compared with 10p and 12p from other sources. If a licence was granted, no quantity would be specified and the Haemophilia Centres are free to go to anyone of the approved suppliers.

"ii. Even though this product was cheaper, it would not necessarily be favoured by doctors because of the fact that, as it had a lower solubility than Hemofil it could not be injected but would have to be infused, which represented in itself an additional overall cost. Solubility was one of the essential criteria that had to be satisfied if the medical profession were to generally adopt a Factor VIII product and Dr Owen said it was crucial that the supplies that we were to produce ourselves fulfilled this criteria. At present, the products coming from the Elstree Plant were not of a sufficient solubility and in this respect they were inferior to the Scottish product. Dr Owen asked that the Scottish Laboratory and Elstree should get together to discuss their processes and to share their technology and he asked for a progress report on this within 1 month."

Over the page:

"Dr Owen agreed that negotiations could start with Armour Pharmaceutical but he asked that it should be spelt out that the overall policy of the British Government was, in line with the WHO [World Health Organisation] recommendation, to aim for self-sufficiency."

So although this note doesn't make it entirely clear, it looks as though the Minister was endorsing the course identified in the submission.

So we see the Department actioning that by letter to Armour on 27 January 1976 at ARMO0000004. This a letter from the Licensing Authority within the Department to Mr Brooks, the head of regulatory affairs at Armour. It says:

"Before determining your application in respect of Factorate (Factor VIII) the licensing authority requires the following information ..."

Then there are a number of matters set out reflecting the various conditions identified by the Committee on Safety of Medicines and by the Department itself. The relevant ones, for present purposes, are at b:

"Confirmation that the following conditions will be observed.

"i. Information will be provided by the licence

holder on the number of donations from which plasma is pooled for the manufacture of each batch of the product, and the reasons for and the rate of rejection of donors or donations centre by centre."

So that's the condition that the subcommittee and the Committee on Safety of Medicines had identified.

Then if we go over the page, top of the next page:

"Confirmation that plasma will be obtained only from donor centres in the USA or in other countries specified in respect of which the licensing authority is satisfied as to the donation arrangements, being premises in respect of which you provided an undertaking that they may be inspected by or on behalf of the [UK] licensing authority."

So that is the condition that effectively emerges as a result of the minister's interest in the Armour application.

The response from Armour is at ARMO0000005. A letter dated 2 February 1976. If we go towards the bottom of the page -- they respond to the other conditions, which I needn't take up time with. At the bottom of the page:

"The number of donations is approximately 1,540

per batch to give a pooled plasma of approximately 1,000 litres."

So that's the information that's provided in relation to pool size.

Then, in terms of the information about rejection of donors, what's said is this:

"The rejection rate at blood collection centres is below 1% for accepted donors. The only data available concerns those rejected for blood pressure, temperature, and other illnesses on the day of the donation. No data is available on rejections caused by other medical examinations."

So that's the sum total of the information given in relation to rejection of donors.

SIR BRIAN LANGSTAFF: Centre by centre?

MS RICHARDS: Yes, the request is centre by centre, precisely.

Then if we go over the page -- thank you, Soumik, it's already there -- paragraph (f):

"We confirm that the plasma will be only from donor centres in the USA, and from USA sources."

Now, the first part of that sentence is obviously clear in linguistic terms: donor centres in the USA and from USA sources. I am afraid at the moment, sir, I don't understand what that means.

SIR BRIAN LANGSTAFF: Well, if it were donor centres in the USA, and from USA sources, meaning people who live in the USA, that would stand to reason. But I think it probably means -- as I would interpret it, but I accept it is not entirely clear -- other places within the USA where you can buy plasma or obtain plasma.

MS RICHARDS: That certainly would fall or be capable of falling within the language.

SIR BRIAN LANGSTAFF: Which could include, therefore, plasma imported into the USA from somewhere else, wherever.

MS RICHARDS: Yes, possibly. We'll see what's set out in the product licence in a moment but that's the correspondence that ensues.

Now whether -- that may well not be the sum total of the correspondence. We don't have, currently, a further exchange of correspondence, but it may be that it exists, and again, as Mr Hill indicated, there are a number of threads we need to try to follow through and see if we can find out more information.

SIR BRIAN LANGSTAFF: It could be other sources than donor centres which themselves are USA-centred, but it's not clear at all.

MS RICHARDS: When we go to the actual licence, the licence more closely reflects the language of the DHSS letter. So if we go to ARMO0000320, please.

If we go to page 7, Soumik. This is the actual licence granted in March 1976, so:

"Product licence No. 0231/0038 ... granted under and subject to the provisions of the Medicines Act ... to

"Armour Pharmaceutical Company Limited ..."

et cetera.

And we'll see it continues for a period of five years. If we just go down, we see the date, 25 March 1976, so a few weeks after the correspondence we looked at.

If we go over the page, we can see what I understand to be a schedule to the licence, "Particulars of the products to which the licence relates". Don't need to go through any of that.

Then if we go to the next page, part 2 of the schedule is "Further provisions subject to which the licence has been granted". If we look down to paragraph 6, we can see it says:

"Information shall be provided by the licence holder on the number of donations from which plasma is pooled for the manufacture of each batch of the

product, and the reasons for and the rate of rejection of donors or donation centre by centre."

So that replicates the language of the condition identified by the Committee on Safety of Medicines. But what's not clear is whether, in fact, that required Armour to do anything other than it had already done in that letter from February, which was to answer in very general terms the request for further information or whether there was any ongoing requirement beyond that. We've certainly not seen in the material that we've been able to examine any evidence of the further submission of data, pursuant to any kind of ongoing requirement.

Then if we look at paragraph 7 we see the condition that was outlined in the ministerial submission:

"Plasma shall be obtained only from donor centres in the United States of America or in other countries specified in respect of which the licensing authority is satisfied as to the donation arrangements being premises in respect of which the licence holder has provided an undertaking that they may be inspected by or on behalf of the United Kingdom licensing authority."

So that, again, replicates the language, but

doesn't make clear what in practice it meant, beyond the very skeletal information provided in Armour's February letter.

So obviously one of the matters that you'll wish to consider in due course, sir, will be the extent to which this enhanced consideration of Armour's application in fact resulted in any greater reassurance as to the safety of the product.

SIR BRIAN LANGSTAFF: Yes.

MS RICHARDS: So that's the licensing application, the original licensing application, and the grant of the licence in relation to Factor VIII in 1976.

SIR BRIAN LANGSTAFF: Just a matter of interest, have we any -- on that last point, have we any material which might suggest that the DHSS wrote to Armour saying, "Can you please let us know centre by centre what the rejection rate is and why"?

MS RICHARDS: Not that I have seen. That doesn't mean it doesn't exist. Again, it's possible it exists and we haven't found it, or it exists and we don't have it, or that it doesn't exist. So it's one of those further loose ends that we will want to try to reassurance ourselves as to, but there may be no matter.

SIR BRIAN LANGSTAFF: Well, I can understand why we might

not have a document which is held or one would expect to be held by Armour but if it was sent from the DHSS here in the mid-seventies, you'd expect at least a carbon copy of it.

MS RICHARDS: Yes, although we know there are some DHSS materials that have never been found, and that was apparent from the evidence we heard from Lord Glenarthur, Lord Clarke and Lord Fowler.

SIR BRIAN LANGSTAFF: Yes.

MS RICHARDS: It may well be that there is further material but currently we've not got it, or not found it.

If we then look within this same document reference, Soumik, to page 5, we'll see that over the following years -- this is at paragraph 10 -- there were a number of subsequent variations to the licence. You've got the dates there. The variations by letter.

We don't have a clear understanding, I'm afraid, of what those variations are. I've seen an example of one which is not of any great moment. I think it was about the methods of reconstitution. But in any event there were variations from time to time.

If we then go to the second page of this document we can see there a renewal of the product licence. So you'll recall the date of the grant was

25 March 1976. It's then renewed. Date of renewal is 25 March 1981. So five years on. The oddity is that, if you go further down, the renewal is dated 31 July 1984. And, I'm afraid, we don't understand at present why that is the case.

In any event, the schedule which appears to be attached to this product licence renewal is on the next page, and if we go one page further on, this is in the particulars of the products to which the licence relates. Paragraph 6, we'll see there reference to hepatitis:

"Factorate is prepared from human plasma, each donation of which has been found negative for Hepatitis B Surface Antigen (HBsAg) by the radioimmunoassay (RIA) method. In addition, this lot, after reconstitution has been tested and found negative by the RIA method. However, since no completely reliable laboratory test is yet available to detect all potentially infectious plasma donations, the risk of transmitting viral hepatitis is still present."

That's Armour's first product, Factorate.

I'm going to turn next to the second plasma product for which it sought and obtained a licence, which was High Potency Factorate in 1978, but perhaps,

given the time, we can come to that after the break.

SIR BRIAN LANGSTAFF: Let's take a break and come back at twenty to four. I hope that gives everyone enough time. Twenty to four.

(3.13 pm)

(A short break)

(3.40 pm)

MS RICHARDS: Could we have ARMO0000021.

We'll see this is November 1978, and this is Armour's application for a separate product licence for its High Potency Factorate:

"Please find enclosed six copies of Volume I and II of our Submission for a Product Licence for our new high potency form of Factor VIII, to be identified as High Potency Factorate."

Then the second paragraph:

"Reference to our previous submission [so that's the product application licence that we looked at before the break] will confirm that we examined this product for quality and safety in a similar manner that previously agreed."

That application for a product licence was successful, as we will see from ARMO0000036. This is the Licensing Authority's confirmation, 13 June 1979, that the authority had been given for the grant of

a product licence for High Potency Factorate, and we'll see the separate licence there 0231/0044.

If we go over the page, we can see the licence itself and the date of grant is 13 June 1979.

In terms of supplemental conditions or requirements, page 3 sets out what I think are largely the standard conditions of the product licence at the time. So paragraph 1 refers to compliance with various statutory requirements. Paragraph 2 is leaflets shall comply with the requirements of the Medicines (Leaflets) Regulations 1977, likewise labels shall comply with the medicines labels regulations 1976. Paragraph 3:

"The product shall not be recommended to be used for any purposes other than those specified in Part 1 of this Schedule as Uses."

4 is:

"The specification ... shall be in accordance with the information contained in the application ...

"5. The product shall be manufactured only in accordance with the method given in the application for this product licence."

No separate or additional conditions appear to have been imposed in relation to this particular product.

If we go to the application, which is at ARMO0000023. If we go to page 3, it's a similar form to that which we looked at before the break, so the name of the product is High Potency Factorate, if we go down the box to 7, "Details of [previous] applications", reference is made to the Factorate licence and then, at the very bottom of the page, we can see the date of the application, 20th November 1978.

If we go a further two pages on, please, we'll see there are some supplementary details in relation to "Product Literature":

"Labelling and Package Insert

"Details ... are as attached.

"Data Sheets

"It is intended to defer final drafting until the licence is granted."

I'll come on to some aspects relating to labelling and data sheets in due course, and if we just turn over the page, we can see the draft package insert that was included with the application. If we go to page 10, we can see that it was proposed that the warning should read as there set out:

"Factor VIII is prepared from human plasma, each donation of which has been found negative for

hepatitis B surface antigen ... by the radioimmunoassay ... method. In addition, each batch, after reconstitution as recommended on page 3, has been tested and found negative by the RIA method. However, since no completely reliable laboratory test is yet available to detect all potentially infectious plasma donations, the risk of transmitting viral hepatitis is still present."

Just pausing there, and we will see other references to hepatitis B in very similar form to the references in the 1975 application, the original application, for Factorate. We're now, of course, in late 1978, all the references we see are in the context of hepatitis B. There's the general reference there to viral hepatitis and that risk being still present. But there is nothing in the material submitted to the Licensing Authority that we have seen which addresses specifically any issues relating to non-A, non-B hepatitis, the existence of which, sir, you may think was well known and understood by late 1978.

SIR BRIAN LANGSTAFF: Well, yes, but the expression "viral hepatitis" is capable of covering both.

MS RICHARDS: It is undoubtedly capable of covering both. The question might arise as to how it might be

understood by those for whom the warnings are intended, in the context of a discussion about testing for hepatitis B, and no such test to detect all potentially infectious plasma donations, would that be understood by the reasonable reader or reasonable patient, if they ever saw this, as pointing out possible risks of transmission of non-A, non-B hepatitis?

Within the same document, we can see at page 12, at the bottom of the page, "Caution" at the bottom:

"The product is prepared from Pooled Human Plasma. Despite careful selection of donors and non-reactivity of the reconstituted solution for hepatitis B antigen by the radio-immuno assay procedure, freedom from causal agents of viral hepatitis cannot be assumed."

So the same terminology. Then the next page, last paragraph:

"High Potency Factorate is manufactured from human plasma donations collected at licensed establishments which are subject to the USA Federal Law."

So here, by this time, it is being said all collections are from licensed establishments.

"Each donation and each product lot has been

found negative for hepatitis B Surface Antigen by radio-immunoassay. Vials from the final dosage form are examined for quality and safety aspects agreed for the Armour product [that's a reference to the original Factorate] which was licensed for supply to hospitals on 25th March, 1976."

Top of the next page, in terms of manufacture:

"All plasma is collected in establishments licensed by the FDA, Bureau of Biologics, and transferred to Armour under conditions defined in Title 21 of the Code of Federal Regulations.

"Plasma and plasma records are inspected upon receipt at Armour Pharmaceutical Co, Kankakee, Illinois ... and if satisfactory, the plasma is approved for fractionation."

Then if we turn to page 27, bottom half of the page, we can see there the plasma properties are set out, and point 5 is:

"Free of Hepatitis B Surface Antigen as tested on individual units of plasma by Radioimmune Assay or other assay meeting requirements of Title 21 ..."

Over the page, page 28, the bottom half of the page, so paragraph 3, there are various requirements there in relation to information to be included with shipments of plasma to Armour, so from the collection

centres to Armour's manufacturing plant, and (f) is:

"A statement confirming that all units have been tested and found non-reactive for Hepatitis B Surface Antigen as defined in Title 21, Code of Federal Regulations ..."

If we go on to page 31, there's a draft data sheet, and we can see at the top the page, this is a draft data sheet for the plasma, to be submitted with each shipment of plasma sent to Armour in Kankakee. The bottom of the page, you'll see there "Hepatitis B Surface Antigen", so that's the data sheet requirement.

Then if we go to page 50, we can see this is part of the quality control materials submitted with the licence application, similar to what we saw in relation to the 1975 application, "Hepatitis Associated Antibody ... Biological Principles of the Procedure", and then there is a description of the radioimmunoassay technique that's used in similar terms to the terms we saw previously.

That's the application for the High Potency Factorate and, as we've seen, the licence was granted in June 1979. If we turn to ARMO0000046, we can see a follow-up letter from Armour to the Department of Health, 21 November 1979. The text of the letter

refers to a request that a copy of any data sheets be forwarded to the Department:

"It is our intention to make this product available early in 1980 and in connection with this we have now finalised the data sheet text."

If we go to page -- oh, sorry, I should just continue with the letter, last few lines:

"We would like to point out that because of the specialised nature and use of the product, it is not our intention to include the text of this data sheet in the ABPI Compendium."

We'll look at what was and was not within the ABPI Compendium tomorrow.

If we go to the third page, we can see the data sheet being sent to the Licensing Authority and if we go over two pages, it should be to page 5, we can see, under the heading "Warning", again, similar terminology to elsewhere in the documentation:

"Factor VIII is prepared from human plasma, each donation of which has been found negative for hepatitis B surface antigen ... by the [RIA] method. In addition, each batch, after reconstitution as recommended, has been tested and found negative by the RIA method. However, since no completely reliable laboratory test is yet available to detect all

potentially infectious plasma donations, the risk of transmitting viral hepatitis is still present."

Then it would appear, if we go to ARMO0000047, this is an application to vary the High Potency Factorate licence, the basis of the variation is not particularly material, but you'll see the date is February 1980 and if we look at the first paragraph, last sentence, it says:

"It had been our intention to launch the product in January this year, but to date the product has not been made commercially available."

So there was a period of delay before Armour was actually marketed in the UK, although, as we'll see shortly, it did subsequently become available and was used.

There's a product licence application also made for High Potency Factorate in Ireland by Armour. If we look at ARMO0000092, and if we go, first of all, to page 5, we can see at paragraph 12 the heading "Warning", again, in very similar, potentially identical, terms to the application that was made to the UK Licensing Authority.

What's interesting in relation to this application is some of the clinical studies material that was provided to accompany it. So if we go to

page 135, we'll see, as part of the material that was included within the Irish licence application, is a letter here from a Dr Lavine, February 1978, enclosing trial data in relation to the product. Then if we turn to page 143, we can see under the heading "Summary of the Trials Reported":

"The following information summarises the four separate evaluations of High Potency Factorate ..."

If we go towards the bottom of the page, we can see that there's a reference under the heading "Adverse Reactions" to one case of adverse reaction reported, thought by the clinician to be a case of short incubation non-A, non-B hepatitis.

Over the page, there is what is presumably some details of how that short incubation hepatitis was said to have manifested itself.

Then if we go to page 146, there is there a further description about a patient's -- it's about five lines down, in Study 1, at the top of the page, one patient developing hepatitis ten days after the infusion:

"... made a prompt and complete recovery and showed no evidence of liver damage on follow-up one month later."

Then towards to the bottom of that paragraph, it

says:

"No other adverse effects were observed in any of the ten patients."

It's a short and passing reference to non-A, non-B hepatitis in the Irish application that was being made in around the same time -- no, sorry a little later. The clinical trial data was available in the late 1970s, but it's a November 1981 application.

Then if we turn to ARMO0000116, this is a letter dated November 1982 to the Department's Medicines Division. The particular issue is a request for a shelf life extension for High Potency Factorate, but we can see by this that, by this time, clearly High Potency Factorate is being marketed within the United Kingdom. Third sentence:

"This material is required urgently to fulfil commitments to our customers ..."

So the precise date upon which High Potency Factorate became -- was being supplied within the UK is unclear but sometime between 1980 and 1982.

If we then turn to ARMO0000132, please. We'll see there, in February 1984, Armour wrote to the Medicines Division at the Department of Health and Social Security, you'll see there reference to the two

product licences that we've looked at, and then the text of the letter says:

"Further to today's telephone conversation, I confirm that the name Factorate shall be changed to Factorate Heat Treated and the name High Potency Factorate shall be changed to High Potency Factorate Heat Treated. Labelling will be amended accordingly."

I'll come back to the question of the heat-treated product shortly. If we just next look at ARMO0000145, this is a letter, May 1984, in relation to the High Potency Factorate, from Armour to the Medicines Division at the Department requiring a product licence after the expiry date of the existing licence.

If we go over the page, we can see the renewal application there set out. For reasons that are unclear, the change of name to Heat Treated Factorate is not there incorporated. So this appears to be an application for renewal of the non-heat-treated High Potency Factorate product licence.

If we go to ARMO0000153, we will see that it was indeed renewed on 13 June 1984. The product licence for the High Potency Factorate there renewed.

Before I look a little further at the question of the heat-treated product, I just want to show you

some documents which cast some light on the extent to which Armour occupied a significant market share within the United Kingdom. So if we go firstly to DHSC0003719_118, this is a table dated 21 December 1976, within the Department's Supply Division, addressed to Dr Waiter. It's sales figures for October, together with total figures for the contract year. We can see there that Armour occupy a fairly small part of the market at this point in time, because, of course, Factorate had only been licensed earlier in 1976. So we can see the total for the 12 months to the end of October 1976 for Armour was 897,308 units; Travenol and Immuno, which had both had licences for longer by that point in time, much larger amounts; and Abbott, a smaller amount, 383,624. So that's the position in the early days.

If we then go to PRSE0003437, we will see the position changes over the following years. This is a table showing quantities of Factor VIII concentrate used in UK haemophiliacs breakdown by manufacturer for the years 1980 and 1981. You'll see from that, that Armour are by far and away the largest supplier in terms of quantities. So 1980, 16,576,000 international units, and for 1981, 14,646 -- sorry, 14,646,000 units, and then the figures speak for

themselves: the next largest is, I think, Immuno's Kryobulin product and then Hyland's Hemofil.

The annual returns, I'm not going through details of annual returns, but we've looked at the annual returns for some of the bigger centres and some of the Reference Centres to see if there are any particular patterns discernible in terms of use of Armour products. The short answer is that it varies enormously from centre to centre.

We can take that down, thank you. Soumik. So I'm going to take a handful of examples without putting up any of the underlying documents, many of which, in terms of annual returns we've looked at in the course of evidence and presentation so far.

If we take Birmingham Children's Centre, Armour is first used to a modest extent in 1977. Its usage increases over the years that follow until, in 1980, it's around 1 million units of Armour used. By 1981, Armour was the only commercial concentrate in use at Birmingham Children's Hospital, with the figures being around 1.4 million in 1983 and around 1.6 million in 1984.

That, you'll recall, is the Centre of which Dr Hill was the director.

A rather different picture emerges in relation

to Belfast. Armour's first used in Belfast in 1980 to a relatively modest extent. Increased usage in 1982, it was the commercial concentrate used second only to Kryobulin in terms of volume, but -- and then a significant usage in 1984. We don't have the returns for Belfast for 1983.

Cardiff, by way of contrast, which of course is the centre at which Professor Bloom was the director, shows, for the most part, fairly limited usage over a number of years in the late 1970s of Armour and, until around 1982 when it's used to a greater extent but amongst a range of commercial concentrates there used, and then barely used at all in 1983 and 1984.

Interestingly, if we look at one of the other children's hospitals, so Glasgow Children's Hospital, it is apparent that Armour was the commercial product of choice for the then director, Dr Willoughby. It's very substantially used from 1978 through to 1982.

But the picture essentially varies very much from centre to centre, so there's no obvious pattern in terms of usage, other than as the overall figures show, it, if not dominated, the market, was a very significant player in the market by 1980.

SIR BRIAN LANGSTAFF: And the reason for that?

MS RICHARDS: There is no obvious reason that we can

detect, I'm afraid. There was the issue relating to price that we saw referred to earlier in the 1970s, in the departmental material we looked at before the break. The extent to which that price differential was maintained over the following years and the extent to which that, in turn, influenced individual Centre Directors is unclear.

Unfortunately, for many of the centres, we don't have the relevant director alive to ask.

SIR BRIAN LANGSTAFF: No, we do have, I suppose, a division, do we, in the -- one of those figures you showed me earlier, was it the 1976 table? That's probably --

MS RICHARDS: DHSC000 --

SIR BRIAN LANGSTAFF: 118.

MS RICHARDS: -- 719 --

SIR BRIAN LANGSTAFF: C719_118.

MS RICHARDS: That's the one.

SIR BRIAN LANGSTAFF: We've only got the price there, and Armour is obviously selling for a fair bit less than both Travenol and Immuno. It's easy to work it out because if one reads across to the figure on the right-hand side, having divided by 10, both Travenol and Immuno are charging more per unit than Armour is. Armour is charging less than 10p a unit.

MS RICHARDS: Yes, and we saw that being a feature that apparently attracted itself to the Department's Supply Division when the licence applications were being considered.

What I don't know, sir, is whether that -- (overspeaking) --

SIR BRIAN LANGSTAFF: Whether it was maintained.

MS RICHARDS: -- it was maintained.

SIR BRIAN LANGSTAFF: We don't have any other documents with values written on them?

MS RICHARDS: Not off the top of my head. We might do. We can certainly see if we can find out any more about that.

SIR BRIAN LANGSTAFF: Okay.

MS RICHARDS: There may be a range of reasons, of course, why directors choose particular products. We'll get a sense, I think, when we look at Bayer perhaps, of some of the marketing techniques that were used and it may be that Mr Bishop will be able to cast some light on the issue as well, in terms of his interactions with Haemophilia Centre Directors.

SIR BRIAN LANGSTAFF: So at the moment we don't know why it is that Armour began to conquer the market to the extent that -- in the figure you've shown me from 1980 or '81, it was very nearly half of all the commercial

concentrates used, and about three times as much as its nearest rivals. It may be price. That's the only factor that we can identify as a possible, and it's only a possible factor.

MS RICHARDS: Yes. And it's the reason why I went back to some of the annual returns for the reference centres or bigger centres to see if there was any discernible pattern. But there wasn't. So, as I say, one sees there are some directors for whom Armour was plainly the commercial concentrate of choice, and Dr Hill at Birmingham Children, Dr Willoughby at Glasgow Children are two examples of that. But when we look at some of the other big reference centres, Cardiff, Newcastle, there isn't an obvious pattern that emerges in terms of an overwhelming preference for Armour or, indeed, any particular concentrate, year after year.

SIR BRIAN LANGSTAFF: Yes. Thank you.

MS RICHARDS: If we then just pick the picture up in 1983, in terms of usage, DHSC0002229_055.

This is a minute -- I think we probably looked at it when Dr Walford gave her evidence, but for present purposes it's the table on the second page that is of interest.

It says:

"The following companies import coagulation

factor concentrates into the UK from the USA."

Then we've got the companies listed, and then annual sales. And you'll see the figures in relation to Factorate: 15 to 20 million international units, then the High Potency Factorate: 1-1.5 million international units. Alpha's Profilate is 5 million, Travenol's Hemofil is 8-9 million. Immuno's Kryobulin, there are the various different figures, we've got the red pack, 0.9 million, the blue, 4.1, and then the Prothromplex and the FEIBA. And then Miles' Koate, which we look at when we look at Bayer, 8 million.

So again, Armour, as at June 1983, which is the date of this document -- so the figures may, for example, go up -- I don't know whether they go up into '83 or whether they stop at '82, but Armour continued to dominate the market. But again, I'm afraid, that data doesn't explain the reason why.

Then to pick up the picture in relation to the licensing process for the heat-treated Factor VIII, if we go to SHPL00000067_028, this is a letter to Immuno but we know from another letter that it was sent in similar or identical form to Armour. So it's 26 November 1984 from M Duncan to -- this is to Immuno, but it says:

"Following our recent telephone conversation may I confirm that the licensing authority wishes to encourage all companies involved in the production of Factor VIII to use a dry heat treatment process in the course of manufacture.

"We are inviting each company to consider this proposal and, hopefully to make early (abridged) application for a new product licence."

Then if we go to ARMO0000156, we can see a letter from Armour, 4 January 1985:

"Application for Variations to ..."

Both product licences.

And then the letter begins with reference to the letter from ME Duncan dated November 26, so clearly a letter in identical form or similar form went to Armour.

"... we enclose applications" -- sorry, let me read the whole thing.

"With reference to the letter from Dr ME Duncan dated November 26, 1984, and the undersigned's [that"s Mr or Ms Collins, regulatory affairs manager for Armour] meeting with her on December 19th, 1984, we enclose applications (two copies of each file) to vary the above Product Licences. The variation relates to the inclusion of a heat treatment stage in

the processing of the products. Much of the information presented has already been assessed by the DHSS in relation to our CTX [clinical trial exemption] and PL applications relating to [non-A, non-B] hepatitis ...

"It is understood that such applications as these are being considered a priority by the licensing authority in view of the general situation relating to AIDS in the UK."

So that's the application for variation for heat treatment being submitted by Armour in January 1985. If we go to ARMO0000157, we can see the application for the variation. This is in relation to the High Potency Factorate, and the proposed variation, we'll see from the right-hand side, under the heading "Proposed":

"The method of manufacture will be as currently undertaken but with an additional step in respect of having heat treatment. The finished lyophilised vials from the current process will be subjected to a heat treatment in a water bath at an attained temperature of 60ºC +/- 1ºC for a period of 30 hours."

The significance of that particular heat treatment method as opposed to others will become apparent when we look in more detail at the issue of

seroconversion through the heat-treated concentrates in November.

The application for the variation for the heat-treated Factorate is ARMO0000164.

We can see it's dated January of 1985.

And if we go to page 5, we'll see there the heading "Reason for change/background statement":

"For some years work has been progressing at a number of centres particularly in the USA on the development of Factor 8 products with reduced risk of the transmission of hepatitis. Work at Armour Pharmaceutical Company, Kankakee, Illinois, resulted in the development of a heat treatment stage incorporated as the final part of the process in the current production of intermediate potency Factorate ... and High Potency Factorate. Initial studies revealed that heat treatment, a commonly accepted concept in the destruction of heat-labile viruses, was insufficient alone to prevent the transformation of Hepatitis B, although evidence existed to suggest that non-A non-B viruses might be removed by this process.

"The process was approved by the FDA for the US market and by the BGA for the German market. A Product Licence application was submitted 16 February 1984 for the High Potency Heat Treated

Factorate ... Earlier a CTX application was submitted for the intermediate purity product Factorate Heat Treated ... on 11th August, 1983 in order to undertake a definitive study at UK Haemophilia Centres over an extended period of time in previously untreated patients to determine if infectivity of the product had been eliminated."

Pausing there, we will look at some documents relating to that Armour study of its heat-treated material either this afternoon or tomorrow morning.

"Subsequent events indicated strongly that while the products were clinically effective, the heat treatment process employed did not achieve the desired objective in relation to [non-A, non-B] hepatitis, and the Product Licence application was withdrawn and the CTX surrendered in November 1984.

"During 1984 concern among UK physicians continued to grow over the AIDS situation."

Then reference is made to isolation of the causative virus and to the development of tests with the virus.

If we then pick it up in the next paragraph:

"The heat treatment process developed for Factorate and High Potency Factorate products in relation to NANB hepatitis looked as though it may be

sufficient to destroy the LAV HTLV III virus.
A programme of work to assess the situation in relation to a number of heat-treatment processes and products has been undertaken by the US Centre for Diseases Control (CDC) in conjunction with the FDA Bureau of Biologies (BOB). It would appear that the in vitro situation 60ºC for 4 minutes will inactivate the virus in certain conditions ..."

Then over the page, there's then further information about the proposed heat treatment process, which was 60 degrees centigrade for 30 hours. It's asserted that all the indications are that this process is effective in the destruction of the virus.

Then if we pick it up a few lines down in that first paragraph:

"There have been unprecedented number of 'named patient/requests and the situation with regard to such supply on the scale sought is totally unsatisfactory. It is clear that Haemophilia Centre Directors believe that a heat treated product, even though not proven over time to eliminate the AIDS risk virus is preferable to a non-heat-treated product."

Then the next paragraph explains that studies are continuing:

"However, we believe the products with the heat

treatment process as proposed are safe and effective. Furthermore we believe the heat treatment process proposed will render the existing products obsolete and thus apply for a variation to the existing Licences."

Then there is, again, a large amount of material which is provided. I don't think we need to look at most of it, but if we go to page 32, we can see some information about studies in humans of the heat-treated product.

"Heat treated Factorate proposed for introduction onto the UK market has been and is currently on the US and German markets. Hence there is already considerable exposure of patients to this product. Furthermore, the product is being used in the UK on a 'named-patient' basis and has been used in the abortive clinical study (CTX 0231/0070A). Additionally a half life study has been conducted in the UK by Dr Rizza, Consultant Haematologist at the Oxford Haemophilia Centre."

Then there is reference to a half-life study in the US that was conducted. Then if we go towards the bottom of the page, we can pick up the reference to Dr Rizza's study:

"The second study, as mentioned above, was

conducted by Dr C Rizza at Oxford Haemophilia Centre on the material used under the CTX 0231/0070A."

Then it goes on to set out a conclusion in relation to the half life of both heat-treated and conventional Factor VIII.

We'll come back to elements of the study, but if we then go to, I think it's page 166. No, I don't want to conflate the US and the Oxford studies.

I can pick up the Oxford study by reference to the CTX material and because that may be a reference to -- oh, no, this is the Oxford one, I think. Sorry.

"Revlon Health Care (UK) Limited supplied the investigator with sufficient supplies of the following to allow for completion of the study."

And there's reference to "Heat Treated Factorate" lots.

"Standard commercially available Factorate Lot Y73903 was taken from the stock at the Oxford Haemophilia Centre."

Then there's a reference to four patients being entered into the study. If we go to the next page you'll see, under the heading "Informed Consent", it's said:

"Written informed consent was obtained from all participating patients."

Then the results over the page, page 168, are there set out.

So that, I think, is really just an indication of one of the studies that was undertaken domestically in relation to heat-treated Factorate prior to it being licensed, the half-life study. There's a further study that we will come on to.

Before we do that, if we go to ARMO0000301. You'll see that this is a letter from Revlon Health Care/Armour Pharmaceutical Company Limited, 2 November 1983, to Dr Preston in Sheffield.

"... I confirm that we have now been granted our Clinical Trial Exemption Certificate by the [Department] and can proceed with trials to evaluate our Heat Treated Factorate to the protocol left with you for information."

Then there's a reference to the study underway at Oxford. So we have a study in Oxford and a study in Sheffield ongoing essentially from 1983 in relation to the heat-treated Factorate.

Then, if we go to ARMO0000121, this is the application, the CTX application. If we turn to page 3, we'll see there that it's an application under the clinical trials order 1981.

If we go over the page to page 4 we can see the

date of it, which is 18 August 1983.

If we go to page 5, we can see a section "Particulars of Medicinal Product and Trial" and, if we go over the page, we are told the full details of the proposed trial are that the investigator is Dr Rizza at Oxford, the duration of the trial is one year.

"number of patients involved:

"Approximately 25 depending upon availability of patients fulfilling inclusion criteria."

Then if we go to page 12, we can see the protocol for this study. It's dated May 1983, the date is in the bottom left-hand corner. And if we go to the next page, we get some background information about the trial:

"One of the primary concerns in the use of coagulation factors in the haemophiliac patient who has mild to moderate disease which requires infrequent treatment or in the newly diagnosed patient, is the knowledge that each exposure presents a risk of causing hepatitis."

Then under the heading "Objective", further down the page:

"It is the purpose of this study to use our especially prepared Factorate product exclusively for

an extended period of time in a number of previously untreated patients or in those who have received minimal treatment to determine if infectivity of the product has been eliminated."

So this was a proposed PUP study, effectively.

"Minimal treatment is defined as having received no Concentrate or cryoprecipitate during the preceding six (6) months and not having undergone major surgery [et cetera] and having no history of hepatitis, yellow jaundice, sub-clinical hepatitis or any abnormal liver function tests."

If we go over the page, we see the "Study Design":

"Selected study sites will be haemophilia centres run by recognised experts in haemophilia care, who have an adequate number of patients to assure the recruitment of at least five (5) untreated subjects each over a one (1) year study period. In addition, these centres will be asked to recruit an equal number of patients who have had infrequent treatment and are free of hepatitis markers."

Next paragraph:

"It will be essential for the centres recruited to have close control over their patients to ensure that those entered into the study have access to and

use only the trial Factorate. Any break in this rule will end the study for that subject at the time the non-study product is used. Patients will be entered into the study as they require Factorate HT [heat treated].

"The end point of the study will be the presence or absence of hepatitis as measured by hepatitis markers and liver chemistries taken serially over the one year period of study."

Top of the next page:

"All patients or their guardians will have the purpose of the study carefully explained and will sign an Informed Consent. They will understand and agree to the use of study Factorate exclusively for the one year period of the study. However, in the best interests of their patients, the physicians may prescribe any treatment considered necessary. If this includes Factor VIII other than the study material the patients will continue to be followed but not included in the analysis."

Then if we just go over to the next page and pick it up under "Study Design", towards the bottom of the page, this is the penultimate paragraph:

"The patients will be mild haemophiliacs and therefore not on home treatment. Any intercurrent

illness will be recorded with date and time of such illness."

Then at the bottom of the page:

"The patient records or duplicates will be segregated at the treating institution to ensure that the investigator or staff will be notified at any time the patient enters the institution either as an out-patient or in-patient."

At the top of the next page:

"In the absence of transfusion hepatitis patients will be followed for 1 year following treatment with heat treated Factorate."

Then it explains about undertaking of liver function tests and other tests, collection of blood, et cetera, et cetera.

"This study will continue for twelve months. A complete physical examination will be repeated at the twelve month visit.

"Those patients whose liver function tests remain elevated for one year after the attack of non-A, non-B hepatitis or become carriers of hepatitis B virus will be referred to the local liver clinic for investigation of chronic liver disease. Liver biopsy will only be carried out if clinically indicated."

Then one final reference is at page 21. Now this is not part of the protocol for the study that we've just been looking at. But this appears to be part of the same material that was submitted to the Licensing Authority in relation to the CTX application. So an application under the Medicines Exemption from Licences (Clinical Trials) Order 1981, Factorate heat-treated product. We can see the first paragraph talks about the time spent on trying to develop a Factor VIII with a reduced risk of transmission of hepatitis. Then if we go, however, to the penultimate paragraph, it says this:

"In addition, the recent upsurge in incidence of Acquired Immune Deficiency Syndrome ... has highlighted the problem of possible transmission of illness through blood products. The nature of the AIDS syndrome and lack of knowledge of the background aetiology are such that it is impossible to determine whether procedures such as heat treatment might afford protection. Nevertheless there is a growing body of opinion that heat treatment of material could maximise safety without detriment to the product or its clinical efficacy.

"The present study is proposed to assess the value of heat-treatment on transmission of non-A non-B

hepatitis. The discovery of common interests led to an approach to the UK Haemophilia Centre Directors Working Party on Hepatitis with resultant collaboration on the design of the study."

Top of the next page:

"The Haemophilia Centre Directors expressed a wish that the study be conducted with Factorate, rather than High Potency Factorate as, for economic reasons [that may be the answer, sir, to your question] this is the product most commonly used in the UK."

SIR BRIAN LANGSTAFF: Well, it may only be the difference between the people choosing the cheaper of those two, as opposed to Armour as against the rest.

MS RICHARDS: Yes, and the next paragraph:

"This situation has been discussed informally with DHSS professional staff and it was agreed that this present application could be supported with development data on the High Potency Factorate product [et cetera].

"We believe that this study, performed under the auspices of the country's leading haemophilia specialists, studying in depth a group of highly investigated patients is the definitive course to follow at this time in order to prove the efficacy of

heat-treated Factorate in prevention of transmission of non-A non-B hepatitis."

So the purpose of going to that in some detail is really to illuminate the protocol drawn up by Armour together with, it would appear, Haemophilia Centre Directors, Dr Rizza being identified as the investigator, and contemplated in 1983 with the knowledge of the risk of AIDS one sees referenced in the page we just looked at, the use of Heat Treated Factorate in patients with mild haemophilia.

SIR BRIAN LANGSTAFF: Yes, patients who had not previously needed treatment with any factor concentrate?

MS RICHARDS: Yes.

SIR BRIAN LANGSTAFF: So if they were to be enrolled in the study, assuming it -- well, I don't think one can assume it to be ethical, given what our ethicists have said about the need for therapeutic benefit for a patient. But if it were, they'd have to be told about the risk, potential risk of AIDS, as well as the potential risk of hepatitis, coming from the treatment they'd never had before.

MS RICHARDS: Yes. Yes, the ethical questions to which the protocol and the study give rise are multiple and fairly evident.

SIR BRIAN LANGSTAFF: Yes. Is there any material -- since

we're on that particular tack, is there any material that you spotted in the protocol which suggested there would have been treatment in any event with a non-heat treated Factor product?

MS RICHARDS: There was one passing sentence, is all I can recall, which if we go back to page 14 of the document we had up, ARMO0000121, and if we look at the second paragraph under "Study Design", it would be reading a lot into the use of one short sentence, it is the last sentence:

"Patients will be entered into the study as they require Factorate HT."

It could be said that the inference to draw from that is that they're only treated if they require the product. But I don't recall there being anything else which addresses that issue. I'll re-read it again overnight.

SIR BRIAN LANGSTAFF: That may be of some importance. I mean, that could indicate that, although one starts off with a recruitment of 20-odd patients who'd never been treated before, there will be an occasion or so when one of them needs to have an agent to stop bleeding, and assume that DDAVP won't work, if it is one of those cases, or cryoprecipitate is thought insufficient, that they might then have used whatever

Factor product was available.

MS RICHARDS: Yes. There are quite a lot of assumptions that one has to build into that one sentence, and it's perhaps instructive to note the date of this protocol is May 1983.

SIR BRIAN LANGSTAFF: Yes.

MS RICHARDS: One need only think of the consideration that was being given by the Haemophilia Reference Centre Directors at their special meeting in May 1983, resulting in that letter from June of 1983, which talked about the position of those who were previously untreated patients.

SIR BRIAN LANGSTAFF: Yes.

MS RICHARDS: That, sir, is probably an appropriate note on which to end for today.

SIR BRIAN LANGSTAFF: Yes. Yes, thank you.

MS RICHARDS: I should say it's possible that I may finish the Armour documents in the course of tomorrow because there is so much more of the Armour story that we're going to be telling in November. If I do, then we may go on to Bayer at some point in the course of tomorrow afternoon. Of course, you know that the time estimates from counsel are hopelessly unreliable, so it may not turn out to be the case, but it's a possibility we might start Bayer tomorrow afternoon

at some point.

SIR BRIAN LANGSTAFF: Yes, thank you.

(4.34 pm)

(The hearing adjourned until 10.00 am the following day)

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