Wednesday, 29 September 2021

(10.00 am)

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

MS RICHARDS: Sir, before I resume where I left off yesterday afternoon, there are a couple of issues from yesterday afternoon I just want to go back to.

The first relates to the January 1976 ministerial submission. So that was the submission made by the Medicines Division as Licensing Authority to the Minister of State for Health, Dr David Owen, in the context of the Armour application.

If we just go back to that, DHSC003742_078. Soumik, I might have missed out a zero there. I think it should be 0003742_078.

Just a moment, I'll check the reference, DHSC003742_078.

This was the submission, if we go to page 3, paragraph 10, just to pick up a point I meant to come back yesterday and didn't, paragraph 10 talks about the in principle availability of inspection by the FDA, and then the author of the submission expressed doubts as to whether the stringent provisions of US law were in fact fully enforced, and then made reference to a letter from the US Assistant Secretary

for Health to the Chief Medical Officer at annex B. I had meant to come back to that and didn't.

So if we could go to the document at annex B, which is DHSC0100001_036.

This isn't specifically concerned with the Armour application but it's a rare example of a communication directly from the US to the Chief Medical Officer, then Dr Henry Yellowlees, and so I thought it worth perhaps just bringing up onscreen.

We can see it arises in the context of the Granada Television programme enquiries, and Dr Cooper says to Dr Yellowlees:

"I am writing to apprise you of inquiries which have been directed by a Mr Michael Gillard of Granada Television, London, to members of the staff of our Bureau of Biologics in the Food and Drug Administration regarding US export of plasma derivatives to the United Kingdom, specifically export of Antihemophilic Factor ...

"The general gist of Mr Gillard's inquiries seems to rest on the premise that the American pharmaceutical industry is sending material to the United Kingdom which is so unsafe as to be unacceptable in the US. He was apprised of the following facts, which reflect many of his areas of

interest."

So these appear to be the facts that the Bureau of Biologics articulated to Granada TV.

"1. All injectable plasma derivatives manufactured in the US or manufactured outside the country and shipped to the US are subject to licensure as biologics and must be made in licensed facilities in compliance with organisational of our standards.

"2. Plasma derivatives made outside the US and not shipped into the US are not subject to the regulation by the Food and Drug Administration, regardless of whether or not the manufacturer is a subsidiary or overseas partner of a US pharmaceutical firm.

"3. Source plasma used in manufacturing licensed plasma derivatives, in the US or overseas, must be collected in facilities with US licences. (Mr Gillard requested a list of the names and addresses of these facilities). Source plasma collected in the US for export to unlicensed overseas fractionators must be collected and processed in facilities with US licences. Source plasma collected outside the US and shipped to overseas consignees manufacturing products not licensed by us are not subject to any US regulations.

"4. Our hepatitis test requirements, published in 1972 and 1975, apply only to source material. We have not required that final products such as plasma derivatives, which are made from pooled plasma, be tested or be non-reactive for hepatitis B surface antigen ..."

That's what is said to be the Bureau of Biologics' understanding of the position of licensing in the US.

There are then a series of queries set out by Dr Cooper addressed to the CMO, and if we go to the last page, last paragraph, the US Assistant Secretary for Health asks if someone can be identified who could correspond directly with the Bureau of Biologics within the FDA.

If we go back to the first page, we can see there's a handwritten entry. I don't know whose handwriting that is. It seems to be "HG" but it could be "HY", so it could be Dr Yellowlees himself.

"For your early comment please and for any factual answers to queries in the text which may be readily available? Which of you will act as 'contact man'?"

So it seems likely that there will be some further communications or correspondence arising from this, and we'll pick that up when we return to Government decision-making in the spring or at some stage in the

early part of next year. But I just thought I should flag that up rather than leave it as a loose end.

SIR BRIAN LANGSTAFF: The bit in question marks in handwriting, what does that say?

MS RICHARDS: I think it says:

"Which of you would act as 'contact man'?"

SIR BRIAN LANGSTAFF: Yes, that's what I thought it probably said. Thank you.

MS RICHARDS: Presumably that's a response to the request to identify someone on your side to communicate with the FDA.

SIR BRIAN LANGSTAFF: Yes.

MS RICHARDS: So we'll see whether there's a further thread of correspondence and, as I say, pick that up perhaps when we look at further material relating to the Chief Medical Officer, Dr Yellowlees, next year.

The second point rising from yesterday, is this -- sorry, sir.

SIR BRIAN LANGSTAFF: When it said, in the original minute, there were grounds for thinking US law had not been fully enforced, where is the supporting material for that? Because it says in appendix 2 or something.

MS RICHARDS: Well, there isn't. So the reference then is to annex B, which is to this letter.

SIR BRIAN LANGSTAFF: Yes -- that's this letter?

MS RICHARDS: This is annex B.

SIR BRIAN LANGSTAFF: So this is the letter which, in the opinion of the author of the minute, leads me to think that the US law was not being fully enforced?

MS RICHARDS: I'm not sure I would read it in that way. If we go back to the submission DHSC0003742_078.

SIR BRIAN LANGSTAFF: Page 3, paragraph 10?

MS RICHARDS: Yes, exactly. I don't read paragraph 10 as relying upon the annex B letter as that, I read that as being --

SIR BRIAN LANGSTAFF: I see, yes.

MS RICHARDS: That's the author's view:

"There are ... grounds for [doubt about] whether the stringent provisions of US law are in fact ..."

SIR BRIAN LANGSTAFF: That doesn't arise from the annex.

MS RICHARDS: Exactly.

SIR BRIAN LANGSTAFF: That arises independently of the annex. And the annex is, in effect, the official response from the United States Government.

MS RICHARDS: Yes. And there are other annexes to this submission but they don't relate to that issue.

SIR BRIAN LANGSTAFF: Yes, I follow.

MS RICHARDS: We can take those down, thank you.

So the second matter arising out of yesterday afternoon is this: you asked about whether there was

any further material which might cast light on why Armour occupied a particularly dominant position in the UK market. We will, when we look at the materials relating to Bayer, either later today or tomorrow, see that there are quite a lot of observations in internal Bayer/Cutter/Miles minutes and memoranda and other records which look at the position of competitors. And there's some quite useful information in that. I'll wait until we get to that with the Bayer presentation. But in the meantime there are a couple of letters from 1978 from Armour which might provide some further explanation.

If we look first of all at BPLL0002161, please. This is a letter dated 1 July 1978 from Armour addressed to the consultant haematologist. So it would appear to be, as it were, a letter that may have been sent to a number of haematologists. It's effectively a marketing exercise in relation to Armour. I don't mean that in an inherently pejorative sense.

So:

"In view of the increasing number of haemophiliacs receiving treatment in hospitals other than designated centres, we feel it important, in case you are not already attached to a Haemophilia Centre, that you

should be familiar with the latest information relating to our product, FACTORATE.

"As you probably know FACTORATE was introduced two years ago in June 1976 and has become firmly established as a leading conversion concentrate in the majority of UK centres."

Then this:

"The proven quality of the product, the flexibility of the presentation, and the economical price structure outlined below present a good case for the inclusion of FACTORATE in your routine or emergency treatment programmes."

Then we can see there's information there set out about the price, on a sliding scale, depending upon the quality of units. And it's asserted that:

"The above prices are the lowest on the existing contract for Factor VIII concentrate by 23-42%."

Then the letter continues to talk about the "New High Potency Factorate". We looked at the licensing documents in relation to that yesterday.

If we just look over the page, we can see there are then various other matters set out which are said to be relevant to a decision as to whether or not to buy Factorate, so the shelf life, facility of storage, and then the new home treatment pack. So a redesigned

kit. If we pick it up about three or four paragraphs from the bottom:

"We are confident that this new kit which benefits patient and hospital alike will be just as enthusiastically received as the original version."

So matters relating to pricing and then matters relating to, as it were, the usability or the attractiveness of the kit which accompanied the provision of the product are being identified as reasons why the consultant haematologist should buy Factorate from Armour.

Then there's a second letter, again from 1978, at OXUH0003868_011.

This is -- you'll see it's a letter -- in fact, sorry, it's from November 1977. This is addressed to Dr Biggs at Oxford. And we can see information there set out in relation to the price, and below the table it says:

"As in previous years, we have tendered our best prices right from the start of the contract in order to ensure the least disruption to the work of your Centre. It is not our intention to amend these in any way during the period of the contract."

If we go over the page, we can see again the issue of price emphasised:

"We are very conscious of the fact that all Centres are working to very tight budgets. We're also fully aware of the implications of the new contract prices in respect of maintaining or increasing current levels of treatment and home therapy programmes within the limits of these budgets.

"An analysis of the new terms will reveal the true economic advantage of placing some, if not all, of your commercial concentrate business with Armour.

"By purchasing FACTORATE against a given sterling budget, your centre will be able to obtain between 50% and 97.5% more Factor VIII concentrate than other commercial products proved for sale on the DHSS market. By purchasing Factorate there will be no need to reduce your programmes involving the use of commercial concentrate in order to keep expenditure within the confines of your budget for 1978. Coupled with this considerable price differential are the added benefits of our presentation."

SIR BRIAN LANGSTAFF: The figure of 97.5% there is quite remarkable, if it's effectively saying it's half the price.

MS RICHARDS: Yes. You'll see, sir, this is a letter from Mr Bishop to Dr Biggs and it may be that Mr Bishop will be able to cast some further light on the

approach that was taken by Armour when he gives his evidence in November.

SIR BRIAN LANGSTAFF: Could we just go back to the very start of that letter, the heading, the roundel.

MS RICHARDS: The stamp, yes.

SIR BRIAN LANGSTAFF: Is that 1540 or 7540?

MS RICHARDS: 1540 donors, is how I'd read it and that's consistent with the figure we saw in -- we'll come on to it when we look at donors again shortly, I think it's in the response to the Department's queries, but 1,540 is certainly a figure which appears elsewhere in the material.

SIR BRIAN LANGSTAFF: So can you help at all to what that relates?

MS RICHARDS: I'm going to come on to donors. The information that we have is largely drawn from material provided by Armour. There's no, as it were, independent verification of the material but there are two or three documents which deal with pool sizes and numbers of donors or donations around that time. So I'll come back to that.

Soumik, was that the end of the document? Thank you.

So those were the two matters I wanted to go back to from yesterday. If I now pick matters up where we

left them at the end of yesterday afternoon, we were looking at Armour's clinical trials certificate relating to the Factorate heat-treated product and just to remind those listening of where we had reached yesterday, we'd looked at the application that was made in August 1983 and we looked at the protocol for the study, which involved the recruitment of mild haemophiliacs and those previously untreated into a study. That application was granted in November 1983.

In December 1983 -- I'm not going to put the documents up for these purposes -- Armour replied to the Department for permission to extend the study of its heat-treated Factorate include an investigation of the pharmacokinetics. That was also to be carried out by Dr Rizza as the existing investigator. So that was a separate study relating to half life, et cetera, and that involved a small number of severe haemophiliacs, and that extension to the CTX was granted in January 1984.

If we just go back to, then, the subsequent product licence variation application, so the application for the licence to cover the heat-treated Factorate that was subsequently made in January 1985 at ARMO0000164. We looked at this yesterday. If we

just go back to page 32 of this, we'll see that the half life study was completed, so there's the American study which I referred to briefly yesterday and then the bottom of this page, last paragraph, Dr Rizza's half life study. Those studies were undertaken and completed.

However, the study to determine non-A, non-B hepatitis infectivity and whether infectivity was reduced through the heat-treated Factorate was effectively abandoned, and there are a handful of documents that cast a little more light on that.

If we start with HCDO0000270_031, these are the minutes of a meeting of the Hepatitis Working Party of UKHCDO, 14 September 1983. Just pausing there, before we look at what it says, you'll recall, sir, from other material that we've looked at that the Armour study of its heat-treated Factorate, to see whether it had made any difference to the transmission of non-A, non-B hepatitis, was not the only study being undertaken around this time in relation to so-called hepatitis reduced products.

If we look further down this page we can see there's a discussion. So this is, as I say, September 1983 and there's a discussion at (A) of prospective studies of Factor VIII and IX associated

hepatitis:

"Dr Craske said that after discussions at the Haemophilia Reference Centre Directors meeting in January, he had drawn up a protocol for use in trials of hepatitis reduced factor VIII concentrates as a model for any studies which might be undertaken by Haemophilia Centre Directors. This had been circulated to each Haemophilia Centre Director in March 1983 with a covering note from Dr Craske, Dr Rizza and Professor Bloom."

We've looked at that on a number of occasions, and then this:

"Products of commercial factor VIII were at present being considered for trials. These were the dry heat treated Travenol Laboratories product and the Armour product. The Travenol product had been granted an exemption from a clinical trial certificate and Armour Laboratories had applied for exemption for their product.

"In discussion, it became apparent that there was still considerable concern about the possible transmission of an infection related to [AIDS]. It was not known whether the inactivation procedures used in various products inactivated the putative AIDS related virus. Any director considering using the

commercial products in such a clinical trial would, therefore, have to take this into account when considering the best product to use. It was proposed to discuss this problem at the annual meeting of the Haemophilia Centre Directors."

So there, at around the time that Armour is seeking approval from the Department of Health for its clinical trial, under the CTX procedure, we can see consideration being given by the Hepatitis Working Party of the possible implications in terms of the chances of transmitting AIDS, and directors -- well, it effectively being said that directors would need to give consideration to that.

If we then go to CBLA0001861, this is a letter dated 5 July 1984. If we just go to the second page first of all, we'll see it's from Dr Craske -- if we go back to the first page -- and it's to Dr Smith at the Plasma Fractionation Laboratory in Oxford. It's in the context of a protocol for the study of the BPL/PFL hepatitis-reduced product, and we see from the first paragraph.

But then we can see, in the third paragraph what happened in relation to the Armour trial, according to Dr Craske:

"The two patients first treated with Armour heat

treated factor VIII contracted non-A, non-B hepatitis two to three weeks after their first transfusion with this material. One patient has become quite ill, sufficient to require admission to the Local Infectious Diseases Unit, but there is no evidence of hepatic pre-coma. So far as is known, there are no complicating factors which might contribute to the severity of this illness. When the full details of this clinical history are available, I think we should consider whether this trial in its present form should be allowed to continue. It will also be necessary to consider whether this will have any effect on any other trials we are proposing. I do not see that the information at present available suggests that we should not proceed with the study of NHS 'hepatitis reduced' factor VIII, but I thought that you should be aware of the results of the use of the Armour material. This case has been reported to the Medicines Division of the DHSS and the relevant batch of Armour factor VIII has been withdrawn from the trial."

So there's an update in relation to two patients treated pursuant to the Armour trial.

Then if we go to HCDO0000561, we can see this is the September 15, 1984 meeting of the Hepatitis

Working Party of UKHCDO.

If we go further down the page, we can see in the paragraph headed "Trials of heat treated factor VIII":

"The results of trials of heat treated commercial factor VIII were reviewed.

"i) Dry heat. The Hemofil HT trial showed a 63% incidence of elevated transience in patients who had previously not received factor VIII concentrate. One patient had also had CMV infection, though it was not known if this was related to factor VIII treatment."

Then it turns to Armour:

"The trial of the Armour heat treated product had been suspended by the Company after the occurrence of 2 cases of symptomatic short incubation, Non-A, non-B hepatitis in one Haemophilia Centre. The results so far suggested that 'dry' heat treatment of factor VIII has little effect (if any) on the incidence of Non-A, non-B hepatitis in first time treated patients."

So that is what happened to -- that element of the clinical studies being undertaken by Armour. I don't have the reference to hand but the application that was consequently filed for the product licence in January 1985 made clear that the trial had not proceeded to completion.

In fairness I think, perhaps, to Dr Rizza, there's

one other document which I think we should perhaps look at. We have looked at it before. I think probably at the time of the Oxford Haemophilia Centre presentation. But it's about the issue of these types of trial.

It's PRSE0000609. This is a letter from Dr Rizza to Dr Watt at the Scottish National Blood Transfusion Service dated 1 March 1983. If we pick it up the -- well, I'll pick it up in the second sentence:

"I was glad to hear of the progress you are making in the preparation of hepatitis reduced risk factor VIII concentrate specially since 3 drug companies have been in touch with me in the past 3 weeks pushing strongly to formalise studies of their different preparations in mildly affected haemophiliacs. I think it will be necessary to use infrequently or previously untransfused haemophiliacs, von Willebrand's patients and carriers of haemophilia to ascertain to what extent hepatitis risk has been reduced. I see no ethical problem with this. The difficulty with this kind of study has been and always will be I think the small number of previously untransfused patients who come for treatment. At this Centre we have managed to collect about 30 suitable patients over a 2 year period but the patients were

not recruited all at once but came in for treatment in the usual random manner and I think that this should be remembered. In other words although we may have a group of 500 mildly affect patients on our books, only a few of those per year require factor replacement for surgical procedures. I do not think it would be ethically justified to give the material without a good clinical indication."

So that was Dr Rizza writing in March of 1983 -- of course, the protocol we looked at post-dates that by several months -- but it perhaps fleshes out the picture a little more.

We do not, I think, have at the moment a clear understanding of how many centres actually entered patients in that trial, or which centres, but we may be able to find more information out about that.

Picking matters up, then, with the product licence variation application for the heat-treated product, that was approved by the Licensing Authority in February of 1985 in principle. Up until that point the product was being marketed effectively on a named-patient basis in the United Kingdom by Armour.

If we then go to ARMO0000167, we can see a letter from Dr Duncan at the Department of Health to Armour, dated 27 February 1985, saying in the second

paragraph:

"... we cannot accept the proposal that the name [High Potency Factorate] should remain unchanged. The Licensing Authority is acting on the advice of the Nomenclature Sub committee of the British Pharmacopeia which stipulates that the name of all heat-treated products should have the suffix 'Heat Treated' or 'HT'. In consequence this condition applies not only to High Potency Factorate ... but also to Factorate ..."

And you've got the two product licence numbers set out there.

"If you confirm in writing that you accept this condition the variation of these 2 licences can be approved without delay."

So that was a condition imposed by the Licensing Authority. I don't think we have the actual product licence, but no reason to doubt that the licence was issued.

If we then go to ARMO0000181, we can see that in January of 1986 Armour submitted an application to vary the product licences for both the Factor VIII heat treated and the High Potency Factorate heat treated. And if we turn to page 3, we can see what the proposed variation was on the right-hand

side. It was the addition of information to the effect that:

"All units of source plasma are tested for antibodies to ... (HTLV-III) and found to be negative."

And the reason given is that this test is now being carried out routinely on all plasma collected.

So that was the formal variation to the product licence to reflect HTLV-III screening.

If we go on two pages we can see under the heading "Presentation", third paragraph down, we can see there again reference to the particular heat treatment method that was utilised by Armour. That will become of greater significance when we look at the issue of seroconversions from the Armour product in November:

"... heated at 60°C for 30 hours."

Then we can see the next sentence:

"All units of source plasma are tested for antibodies to human T cell ... (HTLV-III) and are found to be negative."

And those changes were permitted. We don't have the precise date, but certainly those changes had been permitted by July of 1986.

If we then just, in terms of interactions with the Licensing Authority, go to ARMO0000504, this is an

internal memorandum dated 5 March 1986 from Dr Harris of Armour. And it says:

"As you know, we discussed the summary data on this work ..."

We can see from the heading it's "Viral inactivation data for Factorate and other blood products":

"The DHSS were superficially happy with the data. They have, however, requested that we furnish them as soon as possible with the fullest documentation on methodology and test results of all our blood products.

"May I please start to receive these data urgently, and starting with Factorate generation I."

I'm not going to go into the story of how that further unfolded. Again, we'll be looking at the question of what information Armour had about the success or otherwise of its viral inactivation methods in 1985 and 1986, what information it provided to the Department and how the Department responded, when we come back to that issue in November.

If we then just pick matters up in July 1986 at ARMO0000557. Again, this is an internal Armour, here headed "Rorer Health Care Limited", memorandum, this is to Mr Bishop. We can see under the heading "Heat

treatment" there's a discussion of switching to a different method, a 68 degrees for 72 hours cycle for future heat treatment of Factorate. Then if we go to the third paragraph, we can then see reference to ALT testing. What's said is:

"With regard to ALT testing, please note that all batches produced since March 1986 have been screened for ALT, the limit for acceptable donations is not more than 75/ml."

Then there's reference of chasing up details of the procedure used by Plasma Alliance, the organisation which ran the plasmapheresis centres, for the ALT test, and then a discussion about product labelling. We'll come back to some aspects of labelling in due course.

SIR BRIAN LANGSTAFF: Just before we leave that highlight, can we go back to it, please, Soumik. It's the third paragraph under "Heat treatment", the second sentence:

"Robin James is working out what this means in terms of our current inventory at Eastbourne."

So what's been said is the batches produced since March '86 have all been screened for ALT. This is written four months later. So to work out what it means in terms of the inventory at Eastbourne, what's the implication of that? Is it that there is stuff

stored in the warehouse which is made from the pre-March unscreened plasma?

MS RICHARDS: Certainly, I think the inference is they're looking to see the extent to which they have stored material that may not have been tested for ALT. I don't know the answer as to what was found. Again, hopefully we can come back to this in November and tell you if we have an answer or not.

SIR BRIAN LANGSTAFF: We may find out more, we may not?

MS RICHARDS: We may.

Then just to complete the picture in these very outlined terms, in relation to the heat-treated product and its licensing, if we go to ARMO0000602, we can see that on 7 October 1986, in relation to Factorate, Armour -- or Rorer -- wrote to Dr Duncan Thomas at the National Institute for Biological Standards and Control saying:

"I refer to our telephone conversation today, in which I informed you of the withdrawal of FACTORATE from the UK market.

"I enclose for your files, a copy of the recall letter and the press release."

Then if we go to the third page we can see a letter dated 7 October 1986, which refers -- sorry, if we just look at the heading, you'll see it refers

to both product licences, so the Factorate IP, that's the intermediate purity, and the Factorate High Potency:

"With immediate effect, Armour Pharmaceutical Company Limited is with drawing from the UK market the Factorate products detailed above. The Company has relinquished the relevant product licences. This action follows consultation with the DHSS after notification by a UK physician of two cases of HIV antibody sero-conversion associated with the use of Factorate.

"Armour is not yet in possession of the complete clinical profile concerning these two sero-conversions. However, the decision to withdraw Factorate was made even though the material used in these two cases is not that currently on the market. In view of the decision taken yesterday we advise that no further administration of Factorate should be given. You should return all Armour Factorate in inventory to Armour Pharmaceutical Company Limited, [Eastbourne]. "

As I say, the detailed steps which led up to that decision will be examined in November.

Then just deal very briefly with two other Armour products. Monoclate-P, if we go to ARMO0000212.

You'll see this is a later letter, July 1988, to Armour, and it's headed "Application through the Community Concertation Procedure. Monoclate Lyophilised Powder".

I'm not going into this in any great detail. Monoclate-P was a product derived from monoclonal antibodies, dry heated at 60 degrees for 36 hours.

There was an application by Armour which was unsuccessful, various concerns being raised by the Department, and then a product licence application for the product was made in February 1988, and there were objections raised to the application.

Then we can pick up the picture in 1988 with this letter, and it's really not so much because of the need to investigate what happened with Monoclate but just to show how it might be said that the degree of rigour with which product licence applications were scrutinised by the Licensing Authority may be thought to have changed over the years.

Here we have a number of concerns being expressed by the Department. We'll see in the first paragraph:

"Acting as the [UK] rapporteur for the Committee for Proprietary Medicine Products ..."

We can see under the heading "Safety":

"There was insufficient evidence of safety. In

view of the transmission of HIV by a previous Armour product with an identical heat treatment schedule [presumably Factorate Heat Treated], an efficacious virucidal procedure against HIV would be applied to the product. Dry heat at 60°C for 30 hours was inadequate."

Then there were a number of concerns expressed by other authorities, under the heading "Safety" and, indeed, a number of concerns raised in relation, I think, to quality, as well, in terms of the method of preparation.

Ultimately, I think there is evidence to suggest that, towards the end of 1989, these issues may have been resolved and a product licence for Monoclate-P was granted but I don't think we need to go into the detail of that. There was also a subsequent Factor IX product called Mononine licensed by the UK in, I think, February 1993.

That's the overview, sir, of matters relating to licensing applications for Armour products. I'm going to turn now, then, to the issue of donors. So if we start just by quickly returning to ARMO0000005. This is a letter we looked at yesterday afternoon when we were looking at the licensing application process in relation to the Factor VIII product. So it's a letter

from Armour, 2 February 1976.

If we go towards the bottom of the page, we can see there, sir, the figure of 1,540, which you asked about earlier this morning, when we looked at that letter to Dr Biggs. So:

"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 as at 1976 in terms of pool size.

SIR BRIAN LANGSTAFF: Just pausing there for a moment, the roundel that we looked at earlier spoke of donors, did it, rather than donations?

MS RICHARDS: Yes, I think it did, sir. Sorry, I don't have a --

SIR BRIAN LANGSTAFF: If we just go back to that for a moment.

MS RICHARDS: Soumik it was OXUH0003868_011. Yes.

SIR BRIAN LANGSTAFF: Yes.

MS RICHARDS: Yes, you're right.

SIR BRIAN LANGSTAFF: So this is now donations rather than donors in this?

MS RICHARDS: Yes. So the letter at ARMO0000005, which pre-dates the letter to Dr Biggs by about 18 months, talks about 1,540 donations per batch.

SIR BRIAN LANGSTAFF: Yes.

MS RICHARDS: But you're absolutely right, sir, the later letter then seems to have translated that into 1,540 donors. In any event, that's the pool size information given to the Licensing Authority at the time of the product application. Then if we go over the page, in terms of the source of plasma, and again we looked at this yesterday, this just a reminder, (f):

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

We discussed yesterday, sir, the slight ambiguity in that latter phrase.

We then pick up the picture in terms of information about the plasma supply from PJON0000055_001. Sir, you'll recall looking at this earlier with Mr Hill. This is Dr Jones's note referring to a Paris trip in September 1979 and a meeting with Robert Taub and Wolfgang Marguerre. I think, sir, you queried, if we look at the second paragraph, what the recently purchased company covering Germany might be, and I'm afraid we don't, at the moment, know the answer to that, or whether it's accurate.

Mr Taub was subsequently involved with Octapharma

but my understanding of Octapharma is that it was set up in 1983, so some four years later, and in Switzerland not Germany. So precisely what that refers to, we're currently unclear. It may not matter in any event. In any event, we can skip over the paragraph that deals with Travenol, because Mr Hill's already dealt with that, and go to the bottom of the page where we can pick up a discussion about Armour and Factorate:

"It was suggested by Marguerre that the true cost of plasma was presently around 12p/factor VIII unit and that this cost did not take into account any research and development. To his knowledge no research and development was intended in any company other than Armour. The cost of Factorate in the [UK] would be increased in December, and it was expected that Koate would follow. An increase in costs within the [UK] would then allow for some research and development. The price is likely to be 10.5p/unit."

If we go over the page -- sorry, and I should say that, although I'm looking at the question of donors as a theme, this document covers a number of different issues but I don't want to keep coming back to it so we'll look at the whole document.

So we then see Dr Jones's reflections or thoughts

on, or understanding of, the organisation of the Revlon Health Care Group:

"Headquarters of Armour are in Phoenix, Arizona. Plasma phoresis headquarters is in Phoenix with the biggest centre in Knoxville, Tennessee.

"Fractionation is carried out at Kankakee ... which is 100 miles south of Chicago. The plasma phoresis centres cover a block of mid States from Chicago to Tennessee. One million litres of plasma are drawn within a year from centres under the direct control of Armour ..."

That's the relevant point in terms of plasma supply. What is being described here are centres that are effectively part of the Armour group:

"... this being 20% of the US production. It is claimed by Marguerre, who says he has figures to support it, that no outside source plasma is necessary for the Armour products."

There's then a discussion about other companies that I don't think we need look at. Then if we go to the next paragraph, it says:

"On Monday, 17th September, 1979 in session with Marguerre and Taub the following points -- in addition to those already mentioned -- emerged."

The first point is about Hyland. Then the second

is this:

"Marguerre and his colleagues were highly critical of the management of plasma sales from Armour, particularly with regard to the [UK]. They had successfully taken over half the market by using unrealistic price structure [which again may reflect issues of cost being responsible for the success of the Armour product in the UK market] which allowed for no service commitment or research or development. It was the intention to change this image, but this could only be done by increasing price.

"Specifically, there emerge two objectives.

"The first is to try and validate the Bonn approach, this almost certainly being connected with a recent acquisition of the company for Taub in Germany.

"The second ..."

And again, this is the relevant point in terms of considering the issue of donors:

"The second was to throw open the whole of the plasma collection and marketing in the United States to independent scrutiny. The attitude to the other companies if this were done, would be that there was no intention of attacking them, but nor was there any intention of supporting the introduction of plasma from developing countries.

"In order to achieve these two objectives and later hazily sketched ideas to develop a major commitment to funding national and international meetings, symposia and research and development in the clinical sector, it was proposed that PJ [Dr Peter Jones] became a 'consultant' with direct access to Marguerre and Taub and with authority to approach any physician or scientist he wished in order to set up programmes."

There's then a discussion about what was said to be the first objective, and some work being undertaken in Germany. We don't, I think, need to look at that.

If we go to the last paragraph on this page:

"With regard to the second objective, it was suggested that within the coming weeks a gradual dialogue be established between PJ and Revlon Health Care and that this should culminate in a visit to the facilities in the United States. It was stated that PJ could invite anybody from the scientific field (Arthur Bloom in particular being mentioned) to accompany him on this trip, the purpose of which would be to validate the company claims of collection and fractionation independence. It was also mentioned that Revlon presently put 9% of their profit into research."

So we have here the genesis of the idea that Dr Jones wound undertake an inspection of some of the fractionation -- sorry, some of the plasma collection centres from which the plasma for fractionation by Armour was obtained.

If we just go over the page:

"PJ stated that he would go along with the project with the provisos that it was fully understood that there were no strings attached, that he remained in Newcastle, and that any commitment made by either the company or himself was known to his colleagues. This was agreed."

Then there's a reference to a need to look into possible long-term side effects of intensive transfusion therapy.

If we go to the conclusion:

"No finances discussed, apart from statement of full financial support for studies conducted through PJ with complete expenses and reimbursement for personal time".

And then in capitals and speech marks:

"WE INTEND TO UTILISE YOUR BRAIN."

Which is presumably the message which Dr Jones was given, or his understanding of why he was being approached by Armour.

So that's what I think appears to be a record made by Dr Jones for his own purposes. There's no evidence of this document being shared with or sent to others. We can then pick matters up by looking at the report of the trip that Dr Jones then subsequently undertook. And that is at PJON0000040_001. So it's headed "Confidential. Revlon Health Care Group. A Report on Plasmapheresis in the United States".

If we go to the next page we can see it's said that:

"This report is confidential to Mr W Marguerre, Vice President, Biological Products, Revlon Health Care Group ..."

Then we can see, if we go on to page 4, the "Introduction", which says this:

"In 1979 Mr W Marguerre, on behalf of the Revlon Health Care Group, invited Dr Jones to visit Group facilities for the collection of blood products in the United States.

"Revlon's interests in the medical field had been strengthened by the acquisition of Armour International, and by the creation, in late 1978, of an organisation for the plasmapheresis of donors within the Group. It was Group policy to achieve self-sufficiency in source plasma, and to this end

Armour Pharmaceuticals had acquired the company Plasma Alliance, operating in the United States of America."

Just pausing there, we've obviously seen a lot of material about the objective of self-sufficiency as a governmental objective for the United Kingdom. Here is self-sufficiency being articulated in 1979 and 1980 as a discrete policy of Armour, that it will be able to fractionate and create its products from plasma collected under its control.

And then -- sorry, it could be thought that saying, "It was Group policy to achieve self-sufficiency in source plasma", might suggest that that objective hadn't yet been achieved. But it's not clear.

"Dr Jones' brief was to visit a number of plasmapheresis centres managed by Plasma Alliance, to talk with management, staff and donors and to report his findings to Mr Marguerre. It was an essential understanding within this agreement that 'there was nothing to hide', and that the open nature of the visit was designed to demonstrate that Plasma Alliance were a sound, healthy and ethical organisation. On his part, Dr Jones agreed to report back, in confidence, directly to Mr Marguerre.

"It is the purpose of this report to set out the

results of the United States visit."

The report is signed by Dr Jones and dated June 1980.

If we go to the next page, we can see the centres that were visited by Dr Jones, and I think it's six centres in total. So there's a Knoxville Centre, there's then a visit to the Plasma Alliance Laboratories and Offices.

Then we can see the Chattanooga Centre and the Atlanta Centre, then the St Paul's Centre, the Minneapolis Downtown Centre and University Centre, and then the final visit is to the Kankakee Plant, which is not, obviously, a plasma collection centre but was where the fractionation was undertaken.

If we then turn to page 9, we can see Dr Jones's general description of Plasma Alliance's centres:

"Plasma Alliance employ 888 staff (full and part-time) for the collection, testing and shipping of plasma obtained from paid donors in 22 Centres. Of these, 75 are '40 hour' employees. Total donor beds is presently 1,037, with an average Centre size of 40-45 beds. Bed occupancy runs at about 60 per cent. Each Centre has a Manager and an Assistant Manager, a Donor Room Supervisor, a member of staff with specific responsibility for quality control and a Physician,

who is not necessarily in attendance throughout opening hours. When the Physician is not in attendance, arrangements exist with a local hospital for cover ..."

So you'll see from that, sir, there are 22 collection centres run by Plasma Alliance, and, as I say, it appears to be I think five or six centres that were visited by Dr Jones.

If we carry on down the page it is said that:

"Donors are looked after by Registered or Licensed Practical Nurses or their equivalent in terms of training.

"In each Centre an Immunisation Programme was used; details of this were not available, nor were they in the brief of the visits.

"All Centres were administered under FDA rules. An in-house Standard Operating Manual ... was available in each Centre visited."

If we go to page 11, we then see Dr Jones's description of the plasmapheresis procedures.

"The regulations for the acceptance, screening, medical examination and plasmapheresis of donors is laid down in the [standard operating manual] SOM, and was followed through in detail in Knoxville, and in a curtailed form in the other Centres visited."

What's meant by that is, I'm afraid, unclear.

"In all cases all operating procedures were strictly observed, and the standard of professional expertise and donor care was impressive.

"Of special merit were firstly, the safety checks used by Plasma Alliance to guarantee donor safety and plasma/red cell identification, and the institution of the NABSAF coded system in addition to donor details and signature and bed number is applauded. Secondly, the standards of the donor room staff were exceptionally high."

Then he talks about his impression at the bottom of the page:

"A first class organisation with a sound commitment to quality control. The recommendations made at the end of this report are made in the light of this overall judgment. Donors questioned ... had no complaints about the procedures and most seemed to enjoy the experience of taking a rest during plasmapheresis. This impression is not in accord with the reportedly low rate of reattendance."

Over the page, there's a heading, "A Note about Reactions", and Dr Jones says this:

"Reactions had been noted in each Centre, and from the Recommendations in this report, it will be seen

that these were of special concern to the author. This is because any organisation which relies on blood/plasma donation must ensure the safety of its donors."

Then there's a reference to emergency equipment and the like.

Then this:

"It is not unusual for donors to lie to questions, and the SOM and the staff are to be commended for the instructions about recognising fraud and how to deal with it. However, in one Centre it was admitted that two epileptics had not been spotted during the screening procedures. People like this, and those who experience reactions (on average twice a week in the Centres visited) should be covered in planning emergency procedures."

Then if we go over to page 14, Dr Jones is, we will see from there, in general terms complimentary about the centres, and general standards were, he said, "excellent".

There's then a visit on the next page to Kankakee, which is the fractionation plant. Although there's a particular criticism there about "the number of outdated Red Cross and Community Blood Bank whole blood packs lying around", which might suggest that

Kankakee was not only receiving blood from Plasma Alliance, but there's no further illumination of that issue in this document.

If we turn on to page 19, we can see Dr Jones saying:

"It would appear that the FDA ruling 640.62 is not always followed. This regulation states:

"Medical Supervision

"A qualified licensed physician shall be on the premises when donor suitability is being determined, immunisations are being made, whole blood is being collected, and red cells are being returned to the Donor."

So, for present purposes, considering issues of the donor suitability, the requirement is for the attendance of a qualified licensed physician at the premises.

Then Dr Jones says:

"To my knowledge the careful requirements for nearby hospital staff to be 'on call' in the event-off an emergency ... laid down in the Plasma Alliance SOM, are not in accord with this regulation.

"In general, the absence of a Physician from some Centres during plasmapheresis worried me. I realise that the practices in the USA are different from those

employed in the UK, with which I am more familiar, but I think serious consideration should be given to continuous medical supervision."

Then if we go over to the next page, we can see at the top of the next page:

"In addition the SOM lays down at least 16 occasions when a Physician's judgment is required. Continuous supervision by well-motivated medical staff should save waiting timetable for 'problem' donors, expose more of the community to the knowledge that it is company policy to ensure donor health, and may well have a 'spin-off' effect in increasing the average number of times a donor attends from the present 4-5."

So there are some concerns expressed by Dr Jones about the apparent absence, in non-compliance with the FDA regulation, of a physician.

We can then, I think, skip over the next few pages and go to page 25. "Company Image" is the heading:

"The 'bad' image associated with procedures involving paid donors has not been helped in any way by secrecy. The organisation managed by Revlon Health Care and Plasma Alliance Inc, is, in my opinion, of so high a standard that it lends itself to a more open attitude. I strongly recommend that consideration be given to more exposure (within the

bounds of necessary industrial security) and suggest that:

"- an article on plasmapheresis by Plasma Alliance be approved by Revlon and submitted to the medical press for publication."

And there is a subsequent publication which we will look at. Secondly:

"- the occasion of the World Fair in Knoxville in 1981 be used to teach the public and the medical professions about the ethical standards maintained by industry."

If we go over the page next to the heading "Source Plasma", Dr Jones says this:

"It is imperative that the Revlon Health Care Group become totally self-sufficient in terms of source plasma. Whilst the need for buying in plasma from other organisations exists -- even when these are FDA approved and of impeccable character -- there will be doubt within the medical profession."

Again, an inference that may be drawn from that is that at the time of Dr Jones's visit or report, his understanding may have been that Revlon/Armour had not achieved total self-sufficiency in terms of source plasma and were therefore still reliant upon other sources. That's an inference that can be drawn from

this document. But we'll see what's said elsewhere about that.

That, I think, is all we need to look at within Dr Jones's report of his visit.

We can then go to ARMO0000229 for a subsequent publication, which is dated July 1981. It's called Plasma Perspectives. And we can see -- well, it's perhaps worth, I think, reading the introduction under "A New Interface" because it will help you place this document in context.

It says this:

"It is clearly outside the scope of standard product literature to examine current and controversial issues relating to the supply and use of blood products. However, it is important that the views of both manufacturers and medical profession should have the opportunity of being voiced. Indeed, one of the recommendations contained in the International Federation Pharmaceutical Manufacturers Association's ... 1980 report on blood products was that although 'care should be taken to avoid over-promotion of the various products made from human blood, full information on such products should continue to be made fully available'. It is the intention of Plasma Perspectives to be the vehicle of

these views and to form an interface where the opinions of both producers and users can be seen. Clearly for such a publication to be of real value it has to be seen to take an objective and impartial view. Much of this objectivity will be dependent on the contributions, correspondence and reports which are received from those with a special interest in the administration of blood products. The newsletter will be published by the Plasma Division of the Armour Pharmaceutical Company and ..."

So it's an Armour publication, although the aspiration appears to be that it will be something that provides objectivity and impartiality.

And we can see at the bottom of that column:

"It will be distributed on request free of charge to members of the medical and allied professions.

"The first issue of Plasma Perspectives is, for the most part, based on a report by Dr Peter Jones, Director of the Haemophilia Centre at Newcastle, following an invitation to visit some of Armour's plasmapheresis centres and their Fractionation plant in the USA. We believe that this impartial report will go a long way to correct many of the misapprehensions and misunderstandings which have arisen in relation to the collection and distribution

of plasma from commercial sources within the USA."

Then we can, I think, for present purposes pick matters up on page 2, under the heading "Armour - Plasma Collection and Control". What is said, if we just go to the top of the page, left-hand column:

"Plasma collected for the production of Armour's Factorate both, Standard and High Purity, is SOURCE PLASMA which is a Federally defined and regulated product in the USA."

Then we can skip over the rest of that paragraph and go to the next one, where it says this:

"The practice of collecting plasma from Third World countries where blood products are already in short supply and where, in some cases, hepatitis B is endogenous has been severely criticised."

Then this is the claim made by Armour:

"All of Armour's SOURCE PLASMA is collected from Federally regulated plasmapheresis centres on the USA mainland."

So this is what is said by Armour in 1981.

"In 1975, in order to help achieve self-sufficiency and total control of its operations, Armour purchased Blood Plasma Services which maintained 12 centres in 11 cities. Since that date, other plasmapheresis centres have been acquired and

Armour has rationalised the network into one highly organised subsidiary, Plasma Alliance Incorporated, which now coordinates the activities in 22 centres, all of which are located in North America."

Go to the next paragraph:

"Plasma Alliance's 22 centres are responsible for collecting from approximately 22,000 donors registered at any one time, records for whom are centrally controlled by computer at the Company's principal plasmapheresis laboratories in Knoxville Tennessee which are among the largest of their kind with over 9,000 donors per month."

So that's the core information about Plasma Alliance. If we then turn to -- sorry, still on this page -- the right-hand column, you'll see a heading partway down, "Armour In-House Standard Operating Procedures Conform to FDA Regulations" is the heading:

"Embodied in the above is a rigid and sophisticated record control which, for example, covers the following critical areas ..."

Then the first heading is "Processing of Source Plasma Donors", and a number of points set out: records, general criteria, identity, age, weight, appearance, health criteria. And then this is, as we understand it, what's said to be the screening process

in relation to donors:

"Questionnaire on medical history especially transmissible diseases."

Then this:

"Frequency and volume criteria, addictions, previous donation history. Heart, lung, liver, kidney performance."

Now, quite what it was said was undertaken by reference to these criteria, what tests, examinations, questions, is not clear from this material.

Then at the top of the next page it continues by reference to haematological and medical examination.

Then I think if we go down towards the bottom of that column, that left-hand column, we see a heading then, "The Major Concern is testing for Hepatitis B Surface Antigen":

"There is still no, completely reliable laboratory test available to detect all potentially infectious plasma donations."

Then there is an explanation that Armour uses the radioimmunoassay, and if we look at the last sentence in that section, it says:

"The test is carried out on each donation and pool as well as the finished product."

We then have a heading "Absolute Traceability to

the Individual Donor is Achieved", and we can see it's said this:

"If a donation, when first tested, gives a positive result the test is repeated and if a further sample from the donation is positive and this is confirmed by a neutral isolation test, then the donor is classified as positive and excluded permanently from donating.

"No unit is shipped if a positive result is obtained even if the positive is shown to be false."

Then if we pick it up towards the bottom of the page, we then come back to the question of pool sizes. So it's said:

"Small Factorate Batch Sizes Facilitate Control.

"All batches offer pooled plasma from which Factorate ... is produced comprise donations from [and then the word 'only', whether that's an accurate description will be a matter for your judgment] only approximately 2,000 donors. Should the need ever arise, under the foregoing system and control, location of the finished product and traceability back to donor is quick, simple and efficient."

So how the 2,000 -- or said to be approximately 2,000 fits with the 1,540 is unclear. Of course this is a couple of years further on. This is July 1981,

so the pool sizes may have increased.

Then it's asserted, bottom of that column:

"Difficulties associated with tracing donors from large pools containing many thousands of donations obtained from plasma brokers and independent collection centres do not arise under the system operated by the wholly owned and controlled Armour Plasmapheresis Centres."

Then we can see there's then a heading "Non-A Non-B Hepatitis", and it's explained four lines down:

"Specific laboratory tests for the identification of this most recently recognised type of hepatitis are not yet available so that diagnosis can only be made by exclusion of hepatitis A and B."

Then if we go further down, it's said in the last paragraph:

"When reliable serological markers for non-A, non-B hepatitis are available, Armour will be ideally positioned to take the initiative. Meanwhile research and development is an ongoing activity aimed at providing increasingly safe therapeutic blood products."

Then we have the heading "Confidence is Important":

"All Armour Plasmapheresis Centres are fully

controlled by trained, qualified, Armour personnel as are the distribution, fractionating, processing, control and research facilities. This self sufficiency, control and long term commitment to the field of plasma fractionation has an important bearing upon the quality, reliability of and confidence in the products produced."

If we go over the page -- and I'll finish this document before we break, if I may -- we can see, if we go to the bottom of the page, there's a heading, "Dr Peter Jones, Director of the Haemophilia Centre at Newcastle comments as follows", and then there are various quotes from the report that we have looked at a few minutes ago.

If we go to the next page, the bottom of the page, the quotes continue, and then in the right-hand column it reverts to the text of the Plasma Perspectives publication, and says this:

"Armour's participation in human plasma fractionation has grown into one of the largest fractionation facilities in the world today."

Then there's a description of investment in a new plasma fractionation and sterile filling facility at the Kankakee location, et cetera.

Then if we turn to page 8, we can see the heading

"Armour follow 'nothing to hide' policy":

"To allay the emotive and unsubstantiated allegations which have been made in connection with the supply of blood derivatives from commercial sources, Armour opened its doors to Dr Peter Jones ... Dr Jones's brief was to visit a number of Armour Plasmapheresis Centres to talk with management, staff and donors to report his findings."

At the bottom of the page:

"In general, he found 'a first class organisation with a sound commitment to quality control' ..."

Then we can see recommendations from the report set out in -- of which one is the need for closer liaison between the Director of Medical Services and the physicians working in the centres.

Then if we go to the right-hand column:

"The recommendations made by Dr Jones have been implemented wherever possible in order to maintain the highest standards throughout the Plasma Alliance Group.

"The Publication of Dr Jones' comments on what he saw follows his own recommendation, couched in the following terms ..."

Then we see the reference that we saw from Dr Jones's report to the organisation being of such

a high standard that it lends itself to a more open attitude.

The last reference I just draw attention to is page 23. So there are a number of photos and other materials. Here there's a section headed "The Plasma Alliance donor", described as:

"A normal, healthy individual who is carefully screened, selected and monitored."

What's said is this:

"The quality of the Plasma Alliance product is largely due to the quality of the donor. In each of our centres nationwide, special care is given to the screening of each individual before he is allowed to join the plasmapheresis program. An initial physical examination is conducted by a Plasma Alliance physician ..."

Pausing there, you'll recall that one of Dr Jones's comments had been that not all centres had a physician on site:

"... followed by a check-up each time he comes in to donate. In fact, a regular Plasma Alliance donor is checked and tested more often than the regular population.

"To make certain the prospective donor has not been rejected for any reason in the past, current

files and extensive cross-referenced microfiche records are checked daily.

"Once a donor is approved, the entire plasma collection procedure is thoroughly explained. Since plasmapheresis is unique in that a donor must be reinfused with his own red cells, the donor must be completely familiar with the process. During donation, Plasma Alliance nurses and technicians check and double check each donor frequently to insure his safety, and thus, the safety of our product.

"For Plasma Alliance and for the many people needing the products derived from plasma, a donor is a valuable asset to his community and to the quality of our product."

So that, I think, is all I need to show you --

SIR BRIAN LANGSTAFF: I think if we get the same idea, if we look at what's underneath the photograph on the left.

MS RICHARDS: Yes:

"We're looking with the kinds of donors who are healthy young people who are local, repeatable donors. We are not looking for people who are in the hard roads of life", is what is said.

So that's what is set out about the approach to donor selection and donor screening and, indeed, pool

sizes, by Armour, in this publication in July 1981.

Sir, that's probably a convenient point at which to take the morning break.

SIR BRIAN LANGSTAFF: Yes, well, we will take a break until quarter to 12. Quarter to 12.

(11.18 am)

(A short break)

(11.45 am)

MS RICHARDS: Sir, we next pick up documents which provide information about pool sizes and donor procedures.

In 1983 -- if we go to ARMO0000243 -- this is a Revlon Health Care Group inter-office memorandum dated 27 April 1983. And we can see the subject is "Trip Report - Plasma Alliance Reviews".

And what -- it's from SH Mueller, and it records as follows in the first paragraph:

"On April 20-22, 1983, I visited five Plasma Alliance Centers in Indiana and Ohio ... Each center was toured physically, and basic operating and documentation systems were reviewed at each. Plasma Alliance's current program for screening donors who are at high risk re AIDS was discussed with the Center Managers."

Then we see the centres visited were West Lafayette, Indianapolis, Columbus, Akron and

Cleveland.

"Overview: Each of the centers we visited was clean, well-organised and quite professional in appearance. The personnel I met were knowledgeable and aware of current regulatory issues. The centers' operations conform to current regulatory requirements. Appropriate controls are in place to assure donor safety and product quality, screen out inappropriate potential donors, prevent overly-frequent donations, and to limit overbleeding."

So that's the overall assessment, what's said to be a satisfactory picture.

Then if we look at the next paragraph, it refers to the Plasma Alliance centres being -- and this is the fourth line, "regularly audited by Knoxville QA".

Then the last sentence of that paragraph:

"It is certainly worth noting that PA's [Plasma Alliance] FDA inspectional track record recently has been excellent."

"Facilities/Equipment: The centers we visited [you'll recall there were five of them] are located either adjacent to university campuses or in near-downtown areas. All of the locations appeared to be acceptable, ie, the neighborhoods seemed relatively stable and did not evidence adverse street

activities."

The top of the next page says:

"The donors we saw were both students and neighborhood residents ..."

Then if we go down to the bottom of the page, we can see under the heading "Operations/Documentation":

"All of the centers visited were using uniform procedures in compliance with PA policies and SOP's [standard operator procedures]. New donors are photographed after presenting adequate identification, and receive a pre-donation physical exam, at which time informed consent is obtained. Repeat donors are identified via their filed photos. In locations where other plasmapheresis operations exist nearby, centers exchange information concerning permanently-rejected donors, and also use a UV-florescent finger stain to detect and prevent overly-frequent multi-center donations. All donors are screened on each visit, for blood pressure, pulse, weight, temperature, hematocrit, evidence of drug abuse, and symptoms of hepatitis or other diseases which would affect ability to donate. Long term donors receive annual physical examinations."

Pausing there, of course this is describing procedures as at April 1983, when, as is clear from

this document, they are alive to the issue of AIDS, so it isn't necessarily a reflection of the procedures that might have adopted in previous years. I don't think we know one way or the other.

And in relation to the passage we just looked at, what we don't get from this, perhaps unsurprisingly as it is just a trip report, is a description of how this screening is undertaken. So we're told, for example, that donors are screened for evidence of drug abuse or symptoms of hepatitis, but it doesn't tell us how that screening is undertaken.

Third paragraph on that page then refers to the documentation system, and it's said that:

"The documentation system employed by PA is excellent, and the centers demonstrated uniform adherence."

And further details given in relation to that.

Two paragraphs further down records that:

"Each center was found to maintain a daily log of rejected donors ..."

Then we have a heading "AIDS":

"Plasma Alliance has implemented a program to screen out high risk donors, per current FDA requirements. A factsheet concerning AIDS has been posted in each of the screening booths. Donor product

cards now include a screening question to determine whether a donor is in a high risk group. Also, each donor is being asked to sign a questionnaire verifying that they have read the AIDS fact sheet and that they do not belong to a high risk group. The signed questionnaire is being kept in the donor record folder.

"Each of the Center Managers I spoke with thought that the program was working reasonably well. Each reported that some donors have voluntarily eliminated themselves from the program. The screening questionnaire has not caused any adverse donor response, and in fact, apparently has engendered some serious conversations about AIDS among donors and potential donors. Center Managers advise that in some cases they personally spoke to donors who they suspected of being in a high risk group (after the donor signed the questionnaire to the contrary), and these donors also voluntarily withdrew. I was quite impressed by the sensitive fashion in which Center Managers are approaching this task ..."

Again, we'll look in more detail at some of the ways in which the risk of AIDS was responded to by pharmaceutical companies, but you'll note that this is what is being described by April 1983, and you may

wish to consider in comparison what was happening in the United Kingdom at that stage in transfusion centres. We know that the leaflet, for example, was not -- the first leaflet was not in operation at this point in time, not for some months, until 1 September 1983, so it may provide a degree of contrast in that respect.

So that's that 1983 report. If we then pick matters up with BART0000863. This is a letter dated 19 May 1983 from Armour "To All Haemophilia Centre Directors", and we can see it's said in the first paragraph:

"The Armour Pharmaceutical Company is acutely aware of the current concern of the Medical world regarding ... (AIDS) and its possible implication to Haemophilia care and treatment.

"Despite the fact that there is a little evidence to associate plasma component therapy with the transmission of AIDS [you may wish to consider in due course, sir, whether you think that's an accurate characterisation of the state of knowledge as at May of 1983], Armour, through its affiliate organisation, Plasma Alliance, has had programmes in operation for several months, which have been designed to help prevent the utilisation of plasma obtained from

members of high risk groups associated with AIDS in the production of clotting factor concentrates."

SIR BRIAN LANGSTAFF: Just pausing there, if in truth there is little evidence, there was nonetheless, it would appear, enough to persuade Armour that it should take that action.

MS RICHARDS: Yes, indeed.

And if we go over the page, we can pick matters up in the second paragraph, which refers to.

"Data reported by CDC in May, 1983, indicate that since the initial cases were reported, approximately 1,500 cases of AIDS have occurred. Of even more alarming nature is the increased rate of incidence of reporting; an accession rate of 100 patients per month appears to be current. Approximately 40% of the reported AIDS patients have died ..."

So acknowledgement there of the high mortality rate.

We can then pick issues up relating to Armour's plasma collection processes in the bottom paragraph of the page, where it says this:

"Of additional concern to Armour Pharmaceutical Company and to others in the health care field is the indication, from data generated by the CDC, that AIDS is being seen in recipients of blood, blood

components, and blood derivatives. In a summary presentation made in May, 1983, the CDC stated that 14 haemophiliacs have apparently contracted AIDS, and that an as yet unidentified number of non-haemophilic recipients of blood and blood components also have developed the syndrome. The CDC is investigating the possible relationship between AIDS and the use of blood and blood derivatives, and is attempting to determine whether transmission of AIDS via transfusion is indeed occurring."

Then if we go to the next page, we can see what's said about identification of high risk groups: homosexual or bisexual males, drug abusers, immigrants from Haiti.

Then there's a discussion of those groups having a high incidence of hepatitis B infection. And you'll see in the second paragraph -- again, these are issues we will be returning to -- there's reference to the possibility of testing for laboratory markers of hepatitis B, which wasn't at this point in time being implemented.

If we pick matters up then at the bottom of the page, under the heading "Plasma Collection and Utilisation by Armour Pharmaceutical Company USA":

"Armour Pharmaceutical Company USA, through its

subsidiary, Plasma Alliance, operates 16 centres located in the Midwest and Southeast portions of the United States."

I'm not entirely sure why we've gone from 22 to 16 centres over the preceding couple of years.

"None of these centres are located in the AIDS high incidence areas of the country (New York City, Miami, San Francisco Los Angeles) mentioned earlier, nor is plasma used in the manufacture of clotting factor products obtained from facilities located in these areas. Furthermore, no plasma is obtained from collection facilities located outside of the United States. Nevertheless, the AIDS issue cannot be treated solely on the basis of geography, since incidence of the syndrome is scattered over a wide area."

Then we see set out the steps that Armour is telling the Haemophilia Centre Directors it's been taking.

"Taking the first of several steps designed to avoid collecting plasma from members of groups shown to be at high risk for contracting AIDS, informational posters were displayed at our centres in December, 1982. These posters advised potential donors about AIDS and its possible impact on the

treatment of haemophilia, and requested donors in any of these groups to defer themselves from plasma donation."

That's said to be the first step.

We then see the next step in the following paragraph:

"In February 1983, a more aggressive programme was initiated, following discussions with organisations such as the US [FDA], Office of Biologics, the National Haemophilia Foundation, the Centres for Disease Control, and other commercial manufacturers of clotting factor concentrates. This programme included direct communication with each donor in the form of written and oral information and questions, designed to defer from the donor population individuals at risk for contracting AIDS. Each donor is presented a fact sheet describing the high risk groups thus far identified with AIDS, the seriousness of the syndrome, and the possible link to the treatment of haemophilia. Furthermore, all donors are questioned by trained processors as to their being members of high risk groups and as to the presence of any signs (night sweats, diarrhoea, chills, etc) that might be indicative of AIDS. Donors are required to affirm in writing that they are not members of the several high

risk groups involved, without having to reveal any facet of their personal and private lives. Periodic physical examinations performed by plasma centre attending physicians also include evaluations for possible signs and symptoms of AIDS.

"We will continue to move forward, in cooperation with other responsible segments of the health care team, both governmental and non-governmental, to implement additional plasma collection activities and programmes deemed to be effective and appropriate."

Then if we look at the bottom of the page, it says this:

"The plasma collection actions described earlier in this statement are designed to prevent the use of plasma obtained from individuals in one or more of several high risk groups in the production of clotting factor concentrates. They are predicated on the possibility that AIDS may be transmitted through blood and certain blood derivatives, although it must be re-emphasised that no agent responsible for transmission has yet been identified. However, one must consider that an infectious organism may be involved, and that the appearance of AIDS is prevalent in groups with high incidence of Hepatitis."

There is then reference to heat treatment in the

following paragraph.

Then the last paragraph says:

"The Revlon Health Care Group, of which Armour Pharmaceutical Company is a member, is firmly committed to providing safe and effective products to the medical community, and will continue to devote considerable time and attention to the problems associated with AIDS and haemophilia treatment, and to efforts undertaken to resolve them. We believe that, given the level of today's knowledge regarding AIDS and its transmission, the programmes in place at our plasma collection centres provide an effective way to reduce the potential for use of plasma obtained from high risk groups."

And as we saw from the first page of this letter, it was sent to all Haemophilia Centre Directors, and was, you may infer, designed to provide a degree of reassurance in the hope that Haemophilia Centre Directors would continue to use Armour products.

It's around this time that there are a series of requests for information from the Department of Health to Armour, and indeed to other pharmaceutical companies, about issues relating to donors and donor selection procedures, and indeed plasma supply.

We don't have a complete set of documents at

present but we can start, I think, at ARMO0000260. This a telex dated 16 June 1983, the date is at the very bottom of the document, from the Department of Health, Health Services Division, to Armour Pharmaceuticals, and we can see it starts by saying:

"Re telecon of 15 June 1983 ..."

So there had been some form of telephone discussion:

"Please supply following information urgently by return telex if possible."

Then there are a series of questions:

"1. Does your company manufacture coagulation factor concentrates for use in the UK? If yes, name the products and state how much of each is supplied annually.

"2. From which country or countries is the source plasma obtained?

"3. If from the USA, is all plasma collected at FDA-licensed plasma collection centres? Please give the names of the centres and their locations.

"4. If non-USA plasma is used, name the countries involved and state whether the plasma collection centres in these countries are licensed by the national regulatory authorities.

"5. Are you able to identify the origin of the

plasma included in each batch of final product and the date on which it was collected?

"6. Is the plasma from each selection centre fractionated separately or is the plasma from several collection centres pooled prior to processing?

"7. If the plasma is of USA origin are you able to supply final products which do not contain plasma from the major 'epidemic' areas for AIDS eg New York, San Francisco, Los Angeles, Miami?

"8. Can you confirm that all plasma of USA origin in your products is being collected in conformity with the FDA Directive of 23 March 1983?

"9. Did your company institute, in advance of the FDA requirements, any special precautions to be taken by plasma collection centres in respect of AIDS? If so, what were these precautions and when were they introduced?

"10. If USA plasma is used, are you able to confirm that all future supplies of coagulation factor concentrates to be sold in the UK will be manufactured from plasma collected in accordance with the FDA Directive of 23 March 1983 (or in accordance with the special precautions, if any, instituted by your company at an earlier date)?

"11. If the answer to (10) is no, from what date

can you meet this requirement?"

So those were the questions posed by the Department of Health. I'm just going to go through the correspondence in chronological order. If we go next to ARMO0000264, this is from Mr Tarbit of Armour to Dr Rodell, so from Armour UK to Armour in the US. It's dated 20 June 1983, and it says:

"Thank you for your comprehensive telex responding to the questions raised by our DHSS."

We don't, unfortunately at the moment, have or haven't been able to locate that telex. But, in any event, this a request for some further bits and pieces of information. So Mr Tarbit continues:

"We would appreciate your comment on the following points arising from these responses, together with certain other additional queries which we have now received from the Supplies Division of the DHSS ...

"1. Should we assume that all haemophiliacs developing AIDS have received Factorate as well as other products.

"2. Your telex indicates that new procedures were implemented in February which conflicts with earlier information we had received stating that these started in October/November 1982, could you please clarify.

3. With respect to the donor identified in your

telex, it is not clear whether this donor is now no longer giving plasma. (We would like to know whether any of the batches identified have been supplied to our market.)

4. We understand that plasma may be sourced from centres other than those of our Plasma Alliance Group and would like further information on these particularly with reference to their frequency of use, name and location in respect of recognised high risk areas. We assume that any such centres would be FDA approved and subject to corporate audit periodically.

5. We would be interested in information on the effect the more stringent screening procedures have had on the donor panel in terms of the deferment and if known the comparable effect on donors of other manufacturers.

"In view of the situation we would be grateful to receive urgent responses to these queries."

Then the next letter, or the next telex, is 21 June. It's ARMO0000266. We can see the date, 21 June, this is from HL Shaw, and -- at least I think that who it's from -- yeah. It says this:

"Thank you for" --

SIR BRIAN LANGSTAFF: Well, if it's from HL Shaw, why is it copied to HL Shaw?

MS RICHARDS: I don't know. Go to the second page. It's quite difficult to --

SIR BRIAN LANGSTAFF: It looks as though it is, yes. Curious.

MS RICHARDS: It is curious.

SIR BRIAN LANGSTAFF: Anyway. Somebody else has written that on. So that may be why, I think.

MS RICHARDS: Yes, HL Shaw was based in Armour in Eastbourne, so with Armour Pharmaceutical Company in the UK, as I understand it. As you say, someone else has written that on. So this is 21 June 1983, and then we can see -- well, it says:

"Thank you for your telex of 16 June on the above subject."

So it's a response to the DHSS queries.

"Certain of the specific questions you ask require responses in more detail than the information we have available and these have been referred to our associate company in the USA for more comprehensive responses. These latter will be transmitted to you as soon as they are available to us.

"In the interim our responses to the points you raised are as follows:

"1. Our company manufacturers Factor VIII concentrate (trade names Factorate and High Potency

Factorate) in the USA and these products are imported and sold in the UK. Approximate annual sales of these products are follows ..."

We can see the figures set out, 15 to 20 million international units of Factorate; 1 to 1.5 million international units of High Potency Factorate.

"2. Source plasma is of USA origin and processing of this to the finished product also takes place in the USA.

"3. All plasma is collected at FDA licensed centres. Routinely all plasma used is collected at plasmapheresis centres owned by Plasma Alliance, which as with Armour Pharmaceuticals is a subsidiary of the Revlon Health Care Group. These centres are focused as follows ..."

Then we have a list of them: Akron, Atlanta, Chattanooga, Cleveland, Colombo --

SIR BRIAN LANGSTAFF: Colombos.

MS RICHARDS: -- Colombos, sorry -- Dayton, Knoxville, Lexington, Louisville, Nashville, Oklahoma, Omaha, West Lafayette, University of Minnesota and St Paul.

"On occasions plasma has also been obtained from other FDA-licensed centres."

So it does appear that Armour was not entirely self-sufficient in the sense of receiving plasma only

from its Plasma Alliance centres, at least according to this document.

"We are seeking further information on the names and locations of these centres from the USA."

Then if we go over the page:

"4. Only USA plasma is used.

"5. We believe that the comprehensive labelling and record requirements of the FDA Code of Federal Regulations and the additional corporate in-house requirements per MIT identification of the origin of plasma included in this batch to specific donor level as well as centre. Confirmation of this is awaited from the USA.

"6. Plasmapherised plasma is collected from the Plasma Alliance centres and processed at Armour Pharmaceutical Company, Kankakee, Illinois. We believe that plasma from several centres is used in the production of a batch of material.

"7. None of the Plasma Alliance centres are located in any of the areas associated with high risk of AIDS transmission. We believe this to be also the case with other centres used by the company. Thus our Factorate products will not contain material derived from plasma collected in these areas.

"8. We confirm that all plasma used in the

production of our blood products is now collected in conformity with the FDA Directive of March 23, 1983.

"9. We believe that a full programme of special precautions regarding screening procedures and dissemination of information to donors was initiated in our Plasma Alliance centres in February of this year. Before that time information on the risk of AIDS had been relayed to donors by means of posters displayed in the collection centres since October/November 1982 although the revised screener procedures had not been finalised and implemented. Confirmation of this is being sought from the USA.

"10. We believe that all future supplies of our products, Factorate and High Potency Factorate, sold in the UK will have been processed from plasma collected under the new procedures."

So that's the response to the DHSS questions and then, if we go to ARMO0000263, this is a further telex. I think the date of this is 23 June 1983. There's certainly a stamp to that effect in the top right-hand corner. It's not entirely clear but, in any event, it's a response to the further questions in the telex of 20 June, and I think it would appear to be from Dr Rodell:

"The following is in response to [your telex] of

6/20/83

"1. Information furnished by the Centers for Disease Control indicates that those haemophiliacs diagnosed as having contracted AIDS have received multiple products, including cryo, from multiple sources. There does not appear to be any instance in which a haemophiliac patient received one product exclusively. We are not certain as to whether each of them indeed received one product inclusively. We are not certain as to whether each of them indeed received Factorate concentrate as part of haemophilia treatment, but assumed such a likelihood.

"2. I cannot comment on information given to you earlier as to when procedures were implemented in Plasma Alliance centers. The centers in December ..."

I think there might be a word missing sorry I think after "Plasma Alliance centers".

SIR BRIAN LANGSTAFF: There's something there and it doesn't read on easily.

MS RICHARDS: Yes:

"... the centers in December, 1982 and that more formal steps were taken in February, 1983, are correct to the best of my knowledge."

That would be consistent with what was set out in that letter to Haemophilia Centre Directors in

May 1983, which said posters in December 1982, and then screening procedures in February.

"[Please] bear in mind that industry discussions as to action steps did not begin until December, 1982.

"3. The donor discussed in my earlier telex has not participated in our plasmapheresis programs since late February, 1983. Factorate concentrate derived from pools containing units of plasma from this individual have been distributed domestically and have been exported, some of this material did go to the UK.

"4. Armour Pharmaceutical Company uses only plasma collected by the Plasma Alliance centers in the manufacture of Factorate concentrate. To that extent, we are unique among all other manufacturers, who rely upon outside source material quite heavily."

So it appears to be being asserted here by Dr Rodell or by Armour in the US that, in fact, Plasma Alliance does supply the entirety of the plasma.

"5. Within our own organization over 150 individuals have deferred themselves since the AIDS program was initiated in February, 1983. I must point out that Plasma Alliance centers are not located in any of the 'hot spots' associated with AIDS, ie New York, Florida, California. Alpha Therapeutic Corporation has stated that over 400 individuals have

deferred themselves. I have no data from other manufacturers."

So that's the further information supplied to Armour UK by Armour in the US.

There is then, if we move to later in 1983, a telex at ARMO0000302. The date of this is 4 November 1983. It's to Mr Bishop, so it's addressed to Armour in the UK. It's from, it looks like, I Regier. I'm afraid I don't know off the top of my head who that is.

It refers, in the first part of it, to a recall of products by Cutter:

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

I'm not quite sure what that next word is.

SIR BRIAN LANGSTAFF: Berlin, is it?

MS RICHARDS: It probably is. That would make sense.

SIR BRIAN LANGSTAFF: That would stand with BGA.

MS RICHARDS: It would, indeed, which is effectively the German regulatory or licensing body.

"I am also concerned about suggestions that paid donors are less likely to be truthful when asked questions which would disqualify them as donors.

"Under the circumstances I suggest that we have a meeting ..."

Then a suggested date is given, prior to what's described as the BPI meeting:

"At the hotel Kempinski. The Cutter incident is under investigation now and Dr Rodell will have detailed information available for our meeting.

"We regret the unfortunate circumstances of the Cutter incident. However, the possibility of something like that happening to any plasma manufacturer cannot be included. It should be to our advantage to remind our customers in an appropriate form, that Armour processes plasma from our wholly owned and fully controller plasma pheresis centers."

SIR BRIAN LANGSTAFF: It must be 'fully controlled', I think.

MS RICHARDS: Yes, I think there are a handful of typographical errors in the telex. I think that must be what was intended.

"Plasma Alliances has a worldwide reputation for

excellent quality and highest standards. Although it is obvious that it is actually not know how to avoid [it should be 'not known'] transmission of AIDS, it should also be emphasized that we have recently introduced Factorate HT [heat treated] to improve the safety of our product.

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

So that's November '83. Then if we go to CGRA0000319. This a Cutter internal memorandum, dated 13 March 1984, and it refers to a meeting held on 6 March. You'll see that there were attendees from a number of different pharmaceutical companies including in relation to Armour, Dr Mike Rodell. You'll see under the heading "In Summary" that, for discussion at the meeting, was the question of beginning hepatitis B core antibody testing of source plasma donors.

It says:

"... following 5 [hours] of discussion, a vote was taken [three are identified as voting in favour]. All others [with the exception of one who abstained] were not in favour."

If we go to the bottom of the page and I'm really going to pick up what was said by Dr Rodell,

reflecting his role with Armour. It says:

"Immediately prior to the conclusion of our meeting it was recommended that the Industry should refrain from starting anti-HBc testing. Carr was adamant that Alpha would not begin, Rodell said Armour would not use the test unless a competitor was using it to competitive advantage."

Then it continues in relation to representatives of other companies.

If we go to the third page -- sorry, actually, if we pick it up at the top of the second page, first of all, my apologies. Under the heading "General comments", it says:

"After an introductory/background statement, Rodell asked that each of us give comments and thoughts on anti-HBc testing. Both the original statement and subsequent comments by each attendee, in the order presented, are summarized."

Then we have contributions again from various different individuals. If we go to the bottom of the third page, we will see what was recorded in this Cutter memorandum as being said by Dr Rodell:

"... questions if anti-HBc test is sufficiently specific to be effective. It would exclude only 50% of donors with AIDS prodrom. Provided figures showing

anti-HBc testing and rejection of positive donors should cost several million [dollars] per year. 14 to 15 Plasma Alliance centers collecting about 850,000 liters per year. Armour currently derives all plasma from Plasma Alliance, no contract centers."

So obviously the last two sentences pick up upon the question of what the sources of plasma were used by Armour, and it appears to be said it's entirely Plasma Alliance centres.

Dr Rodell's opposition to or hesitancy in relation to introducing hepatitis B core antibody testing appears to be twofold. One, it's said it would exclude only 50% of donors with AIDS prodrom and, secondly, it talks about the costs.

There's a further document on the issue of the introduction of hepatitis B core antibody testing, and that is at ARMO0000138. So this is a letter of 15 March 1984 from Dr Rodell to Dr Duncan Thomas at the National Institute for Biological Standards and Control in London, and he says this:

"Dear Dr Thomas:

"As a result of the December, 1983 meeting of the FDA's Blood Products Advisory Committee, a study Group was formed to consider the appropriateness of testing potential blood and/or plasma donors for core antibody

to hepatitis B ... as an additional means of identifying members of high risk groups associated with AIDS.

"The Study Group met on March 6, 1984, at which time each member presented views, information, and data relative to the issue."

So that's presumably a reference to the meeting that was discussed in the Cutter memorandum.

"We felt it appropriate to issue a summary statement regarding our findings and conclusions in advance of a full report to be prepared in the near future.

"I am enclosing a copy of the Study Group's Interim Summary Statement, and hope it will be helpful to you."

If we go over the page we can see the summary statement is authored by Dr Rodell. The first paragraph refers to the meeting at which the issue of testing blood or donors for core antibody to hepatitis B was discussed.

Paragraph 2 says:

"The purpose of the meeting was to review all aspects and ramifications of the use of testing for Anti-HBc as an additional means of determining whether potential donors were members of high risk groups

associated with [AIDS]. Although a full report of the Study Group's deliberations and conclusions will be furnished to the [FDA] in the near future, it was felt that an interim statement should be made available at this time.

"The Study Group was divided in its position on testing for Anti-HBc as a means of identifying AIDS high risk group members, with the majority believing that such testing was not appropriate for that purpose. However, members of the majority group indicated that they would likely be compelled to follow suit if any of the organizations represented initiated Anti-HBc testing programs."

Then there are various further matters set out, including in the last paragraph a suggestion for some pilot studies.

I think we can pick up consideration of matters relating to donor screening at ARMO0000425. This is a letter dated 14 August 1985 from Dr Rodell, to Dr Peter Jones, and it's part of the bigger saga of seroconversions in relation to treatment with heat-treated Factorate and we can see Dr Rodell saying:

"I have been requested ... to respond to your letter ..."

We'll look at all the underlying correspondence in November.

Dr Rodell says:

"In my capacity as designated Responsible Head of Armour Pharmaceutical Company to the USA FDA, I am directly involved in issues associated with the plasma collection and processing ..."

If we go over the page, we can see in the top paragraph, Dr Rodell saying this, picking it up in the fifth line:

"Although testing for Anti-HTLV-III is not mandatory in the US, our Plasma Alliance subsidiary implemented system-wide testing of each donation of plasma very shortly after the availability of the test. Units of plasma found to be positive for Anti-HTLV-III are not used in the manufacture of clotting factor concentrates, and donors of these units are permanently deferred from further participation in our plasma programs. In addition, the donor education programs that we implemented in 1982 [presumably a reference to the posters in December 1982 and then the subsequent February 1983 procedures], designed to discourage members of high risk groups from participating in plasma donation programs, have been augmented and are still in place."

It's not clear what's meant by reference to them being augmented, either in terms of how they were augmented or the date of augmentation.

And then we can see if we pick it up in the third paragraph, Dr Rodell says:

"In your letter to Mr Miller, you requested specific information on the movement of plasma and plasma products internationally. Armour Pharmaceutical Company has never utilised plasma collected outside the continental United States in the production of clotting factor concentrates, nor do we intend to in the future.

"Additionally, for the manufacture of clotting factor concentrates, Armour has not used plasma collected from cities in the [US] designated by the CDC as 'high risk AIDS areas'. A listing of the center location of our subsidiary Plasma Alliance is attached."

Then there's a reference to the conference that we know Dr Jones was organising in relation to AIDS in February 1986, and an offer is made by Dr Rodell that information could be provided, and then it's said at bottom of the page:

"Equally, Mr C Bishop from our [UK] operation would be pleased to help you with the organisation of

the Congress."

The Plasma Alliance centres locations are then listed on the following page. I'm not going to read them out. Sorry, the page after that. We can see them there set out.

Well, sir, there's obviously a lot more to the involvement of Dr Jones in the context of bringing to the fore the issue of seroconversions from heat-treated Factor VIII, but we'll explore that in more detail in November.

Can I just then pick up some references to pool sizes. So we saw the figures from 1976, we saw the figure in July 1981 in that publication of approximately 2,000 donors described, I think, effectively as a small pool.

If we then go to BAYP0004375. This now January of 1983. It's a letter dated 21 January 1983 from a senior vice president at Alpha, to Cutter. And it refers to a meeting which was held on 14 January 1983, and there's a list of those in attendance at the meeting. It includes Bob Johnson, Armour, but you'll see representatives of the major pharmaceutical companies all involved.

We can see it's said:

"The purpose of the meeting was to develop

an industry position in relation to AIDS.

"The following was agreed to ..."

Various matters set out that I don't need to trouble you with. But if we go to the second page there is a reference to issues of batch sizes, as it's described in the second paragraph:

"Any attempt to reduce batch sizes of AHF was considered ineffective because Haemophiliacs received product representing hundreds of thousands of donors during the year regardless of batch size. Also so little is known regarding the effect of dilution that a batch size reduction could conceivably have a detrimental effect. Finally, batch size reduction could have serious negative repercussion on productive availability an, most especially, on cost.

"Cryoprecipitate which is the ultimate in batch size reduction is felt to be at best a delaying action since it can so substantially alter the lifestyle of Haemophiliacs."

Again, that's a discussion that we'll need to come back to. There's a reference there in the context of developing an industry position.

Then if we go to ARMO0000242, this a short telex from Mr Bishop, so Armour UK, dated 27 April 1983, to a number of -- well, it's addressed to Anita Bessler

but then there are a number of people copied into it, and its subject is "AIDS - Armour Policy", and it says this:

"Further to our telecon 26th April I would confirm that the circulars sent by Travenol and Cutter to the UK Haemophilia Centre Directors are on their way to you, and that sent by Alpha will be following shortly, under separate cover.

"I would like to emphasise the urgency of a similar definitive statement from our own operation, along similar lines, together with a more simplified statement, which can be passed on to the increasing number of UK haemophiliacs who are beginning to ask questions of their individual centres."

Then this:

"I understand that Ingo Regier will be discussing this with you in detail. I should like to receive your recommended circular, painting as positive a picture as possible and emphasising our small batch/donor pool sizes."

That appears to be -- and again, it's a document we can ask Mr Bishop about in due course -- a characterisation of the Armour pool size as being small. Whether that's by way of comparison with others or not is unclear from the document.

We then, in terms of discussion of pool sizes, move to 1986, and ARMO0000501. This a document dated 5 March 1986. It's an inter office memorandum from Mr Christie to Dr Harris, and it refers to a "Meeting with [the Department of Health] on Factorate Heat Treated, 3 March 1986".

This is, again, part of the series of communications between the Department and Armour concerning possible seroconversions from heat-treated Factorate.

For present purposes, the salient paragraph is the second paragraph under the heading "Manufacturing Process", where it says this:

"We were asked the size of our donor pool which was defined as between 5,000 and 20,000 donors."

Then there is a suggested calculation in relation to what's described as the "maximum virus challenge".

Now, why those figures appear in circumstances where very much smaller figures have earlier been used is currently unclear.

SIR BRIAN LANGSTAFF: There may be a question about the use of the word "pool". I can see -- it's a possibility, I'm not passing any comment on it -- that "donor pool" may refer to the number of repeat donors who are, if you like, on the books. The pool

of donors, as opposed to the way in which we have been interpreting this, as the pool of plasma from which the product is then made. It's a possibility.

MS RICHARDS: Yes, it is. Unfortunately, I don't think any of the individuals who were present at the meeting are individuals that we're going to be able to ask about this issue, so I don't think we can cast any further light on it, other than bringing it to your attention.

SIR BRIAN LANGSTAFF: Well, although I can see that possibility, it may perhaps be the less likely of the two in the context, because the context goes on to talk about "pool" in the last sentence. And there the pool really only makes sense if it is the pool of plasma from which product is made.

MS RICHARDS: Yes.

SIR BRIAN LANGSTAFF: So it's difficult to think that the author would switch from one meaning of "pool", pool of donors, to another meaning, of pool of donation, donated plasma, in the same paragraph.

MS RICHARDS: Yes. I'm just looking to see whether there's anything further in this document which casts light on it, but I don't think there is.

There is then, towards the bottom of the page, a repetition of all plasmapheresis centres being in

areas of low risk for AIDS and all the centres being Armour's own centres.

SIR BRIAN LANGSTAFF: On the question of pool again, there's a paragraph above that.

MS RICHARDS: Yes.

SIR BRIAN LANGSTAFF: "... the risk of potential positive donations to a pool ..."

And that must be a pool of plasma from which manufacture is made.

MS RICHARDS: That would appear logically and linguistically to be correct, sir.

SIR BRIAN LANGSTAFF: So unless there's actual positive evidence that "donor pool" means the number of donors, I'm inclined, but I'm open to submission on it in due course, to think that it is referring to the manufacturing plasma pool.

MS RICHARDS: Yes. The only other reference to "pool" that I can see is the top of page 3, but that's looking at a specific pool of plasma which contained a donation from an individual who subsequently developed AIDS.

SIR BRIAN LANGSTAFF: Yes.

MS RICHARDS: And the issue of that particular infected batch and what was done in relation to it is an issue we're going to be looking at in more detail in

November.

SIR BRIAN LANGSTAFF: But if it's 5-20,000 donors feeding into a pool, it's a large pool.

MS RICHARDS: Yes.

SIR BRIAN LANGSTAFF: Much larger than the earlier references.

MS RICHARDS: Yes. Certainly we've not, I think, uncovered any other documentation which suggests that the pool sizes were of that magnitude for Armour. Having said that, all the documentation upon which we're relying is, I think -- it's all Armour-generated documentation, so I don't think we have anything which, outside of Armour's own publications, addresses the issue of pool sizes, at least not contemporaneously.

If I can then just deal very briefly with the question of the collection of plasma from prisons, I think the document here is CGRA0000545.

Again, this is a Cutter document. It's described in terms of its subject as referring to a "Fractionator Meeting, April 12, 1985".

If we go to the second page, we can see the heading "Prison Plasma". It says this:

"This subject [elicits] even more diverse viewpoints. Cutter and Alpha believe that science has

progressed to the point that we can screen this plasma through testing (HTLV-III etc) and we now heat treat the products. Hyland says they have no current prison plasma sources (!) and Armour states they will never have any."

And then it goes -- well, I'll read the whole paragraph out, although that's the only reference to Armour.

"Reilly is perpetually gloomy on the subject, and feels we are destined to fail. Nevertheless, we agreed to hang together for a try with the FDA. We will propose to begin using prison plasma cryo and abandon our 'Gentlemen's agreement' unless the FDA takes issue and threatens regulatory action. We will further agree to do whatever testing the FDA deems necessary to answer any academic concerns."

Picking it up in the penultimate sentence:

"The argument for using prison plasma is the additional testing (HTLV-III) and heat treatment which provides product safety."

In any event, what's said there to be Armour's position is they will never have any. It's not terribly illuminating, but --

SIR BRIAN LANGSTAFF: I think the "will" sounds more like an expression of determination --

SIR BRIAN LANGSTAFF: But words which I thought, when I saw them, would suggest that any prison donations would be excluded on that basis, if it is accurate.

MS RICHARDS: Yes. I think the only -- and "question mark" is probably putting it too high -- the only slight gap in information is the question of whether, at all times -- at least from the late 1970s onwards, once Armour had acquired Plasma Alliance -- they were able to obtain all the plasma they required for fractionation from the Plasma Alliance centres, which don't appear to have included any prison locations, or whether there were ever occasions in which they drew or obtained plasma from non-Plasma Alliance centres, which, although US-based and FDA licensed, might not have precluded collection of prison plasma.

But there is no -- I should put it this way, I think: there is no positive evidence that we have seen which suggests prison plasma being used by Armour in the period of time with which the documents are concerned.

SIR BRIAN LANGSTAFF: Thank you.

MS RICHARDS: The last issue just in relation to donors and the screening of donations is -- if I can just touch on, and again, then, defer for more detailed consideration in November -- the issue of screening

MS RICHARDS: Yes.

SIR BRIAN LANGSTAFF: -- than a prediction.

MS RICHARDS: Yes. Whether it is intended as a comprehensive account of the past is impossible to say from the document. This is a meeting that was looking at whether prison plasma should now be used as at 1985, given the availability of testing. So it probably doesn't help in any understanding as to the past position.

I should say we've not seen any contemporaneous documents or any primary source documents to demonstrate Armour collecting or using plasma collected in prisons.

So I have drawn this to your attention, sir, because it's a passing reference to prison plasma.

SIR BRIAN LANGSTAFF: And in the Plasma News or whatever the title of the document was you showed us earlier, the objective presentation -- or presentation which aimed to be objective, written by or on behalf of Armour, which exhibited Peter Jones's comments on his visit, the photograph on the top left-hand side which I drew your attention to, that, I think, says that: we don't take plasma from people who -- circumstances show a hard life. Or words to that effect.

MS RICHARDS: Yes.

donors for HTLV-III. So there are just, I think, three or four documents from 1986 that I'll briefly refer to.

If we start at ARMO0000496, this is described as a "Report of a meeting held in Fort Washington to discuss Factorate on 27.2.86". A number of people present, including, we'll see, Dr Rodell.

And then the document at the bottom is dated 28 February 1986. It's I think probably from Dr Harris, and it's copied to Dr Christie and Mr Bishop, so it's sent to Armour UK, although it's a meeting that takes place in the States.

Then we can see in the first main paragraph:

"The meeting then reviewed on a case by case basis every instance of sero-conversion that has been reported anywhere in the world ..."

Again, that's the issue we'll come back to. And if we pick it up about five lines down, six lines down:

"The net result of these discussions was that, in the opinion of everyone at the meeting, there is no problem with Factorate drawn from unscreened donors."

So that's donors not screened for HTLV-III.

"However, it was felt that, just as with any ongoing improvements which have been made with

Factorate, adding the screening to the donor pool is an improvement to the product, and we should, first of all, withhold from distribution all non-screened product, under one stipulation. This is that, withholding that non-screened product does not result in patients being unable to obtain a product or the potency they want when they order, or hospitals or physicians not being able to have access to the particular product that they have designated for the use of the specific patients."

"In other words, the meeting felt that there [were] no reason to believe there was a problem with non-screened product but, at least in theory, by screening, we will improve the product even more and we should do as much as we can to implement those improvements as quickly as possible."

Then the last paragraph -- actually I should read the whole document.

"In the meantime, it was considered there was no reason to cause any problems in terms of the normal day to day delivery of Factorate to our customers, etc, based on all the information available to date. In terms of the US and UK and everybody else who has non-screened product in inventory, we will continue to withhold the distribution of that product as long as,

or unless, we only have that type of product to distribute within the market. In other words, it is a voluntary withholding and not a withdrawal from the market."

Then the next paragraph:

"The meeting agreed that it was very important to gear up production in Kankakee and to, as rapidly as possible, be in the position where not only will we not be distributing product from non-screened donors but that we will reach a point that where, without interrupting the supply to the patient, we can exchange un-screened product with material that has already been screened."

So it's a slightly torturous account of the discussion. I don't mean that in a critical sense.

SIR BRIAN LANGSTAFF: Who is this addressed to?

MS RICHARDS: Um ... I am not sure, I'm afraid, sir. It's an internal document. The very top of the page refers to a "Telephone conversation PAG/CB/Anita Bessler", dated 28 February, and then it's "Report of a meeting held in Fort Washington to discuss Factorate on 27.2.86", and we see those who attended.

At the bottom of the page it is CC'd to Mr Christie and Mr Bishop, who are Armour UK. I'm not sure whether -- "PAH" I had assumed was probably

Dr Harris, who is Armour UK, but I might be wrong, but I can't remember -- I'm not sure I know who the initials "LEW" stand for.

So it appears to be an internal document and it is being provided, amongst others, perhaps only, to Mr Christie and Mr Bishop, to inform them of what has been discussed in the States.

SIR BRIAN LANGSTAFF: The curiosity of it is that it's proposing to introduce a screening, which is bound to be expensive, it's proposing to not -- effectively to recall or withhold batches which have not been screened, which is going to be expensive and lead to the loss of product already manufactured, all on the basis that there is no evidence that it has any effect at all, which is -- just makes me curious about the document.

MS RICHARDS: Yes. Well, it may be that Mr Bishop will be able to assist us with it, although of course he is not the author of the document itself and was not a participant in the meeting.

Then there is, of course, a proviso or stipulation, which is that withholding that non-screened product does not result in patients being unable to obtain the product, or hospital or physicians not being able to have access to the

particular product, so it contemplates, I think, the possibility that there might be circumstances in which the unscreened product might --

SIR BRIAN LANGSTAFF: Well, it does, but the overriding message is: we're going to carry out something which is going to be expensive in more than one way, which we have no reason to believe will make any improvement.

MS RICHARDS: Yes.

SIR BRIAN LANGSTAFF: Apart from the show of it.

MS RICHARDS: There are then a handful of other documents on the same topic, so if we go in chronological order to 13 March 1986, so the following month, PJON0000034_022.

This is a letter dated 13 March 1986. It is from Dr P Harris, medical and technical director at Armour Pharmaceutical Company Limited. This is a version addressed to Dr Jones but we have also a version which suggests that it was sent more widely to Haemophilia Centre Directors.

I think we can pick it up -- it deals in large measure with issues about viral inactivation, but we can pick it up in the last paragraph on that page where it is said:

"As you may already know, all our plasma

collection centres are situated in the American mid-west away from the known areas of high risk for AIDS. Our typical donor is a multiple visitor and undergoes thorough medical examination and follow-up at each attendance. Each donation is now specifically screened for HTLV-III antibody and all product being supplied is donor tested."

The top of the next page:

"Before donor testing it was estimated that the risk of including an HTLV-III contaminated donation in a plasma pool was from 0.25-0.3%. By introduction of our donor testing, it may be assumed that this risk has been minimised.

"However, it should not be overlooked that there may be material in centres, or in the home that is not derived from donors tested for anti-HTLV-III. We do appreciate that this information would aggravate the potential for distress to the haemophiliac, because of the patient's inference that non-donor tested material may be less safe with regard to the AIDS risk. Further, we recognise that any decision to give a patient this information rests with you as the unit director."

Then the last paragraph explains:

"I am sending this letter to UK Haemophilia Centre

this:

"I wrote on 13th March to all UK Haemophilia Centre Directors who were considered likely to have used Factorate Heat Treated during the preceding 12 months ..."

That's the letter we have already looked at.

Then the next paragraph:

"On the 23rd June 1986 however, our American parent company wrote to all US based Blood Bank Directors and/or Haemophilia Treatment Co-ordinators recommending to them the return for exchange of any non-donor tested material. In line with our corporate policy, and having obtained the agreement of the DHSS, I am now recommending the return of all non-donor tested Factorate so we can exchange this for material manufactured from screened donations.

"Would you please review your stocks of Heat Treated Factorate, including that issued for home treatment, and if you have any from the batched listed overleaf, please return these to Armour Pharmaceutical Company Limited ... These will be exchanged for donor-screened product. All Armour material supplied in the UK since January 1986 has been donor-screened."

So that's what is said in July 1986. Again, it's an issue we'll need to come back to but you'll see

Directors who are likely to have used 'Factorate' in the preceding 12 months."

There's then a letter from Dr Jones, not to Armour but to a fellow haematologist in Manchester Children's Hospital. That's at ARMO0000517 -- I'm sorry, Soumik, can I give you a different reference? HCDO0000271_075.

As I say, it's from Dr Jones to Dr Evans at the Royal Manchester Children's Hospital. Again, it's part of the bigger issue of seroconversions from heat-treated Factor VIII, but on the issue of individual donor testing, in the second paragraph, Dr Jones says this, picking it up in the second line:

"The really worrying thing to me is that there is evidence that there are still concentrates being used which have been derived from plasma which has not been individually donor tested. This I know to be true of the Armour product but I suspect that it might also be true of other commercial concentrates as well."

Then it goes on to discuss a range of other matters.

Then, if we go to ARMO0000554, we can see a letter dated 11 July 1986, again this is from Dr Harris of Armour Pharmaceutical Limited in the UK, to a Dr Mustafa at a hospital in Darlington, and it says

there the statement that's made of "All Armour material supplied to the UK since January 1986 being donor-screened", but the meeting which was the first meeting we looked at in relation to this issue was a meeting 27 February 1986.

SIR BRIAN LANGSTAFF: The Fort Washington meeting?

MS RICHARDS: The Fort Washington meeting. That doesn't mean that the statement that "All Armour materials supplied in the UK since January 1986 has been donor-screened" is incorrect or inaccurate, but we will need to come back to this to see whether we can bottom out in more detail the correct factual position.

The final document that I just wanted to draw to your attention on the issue of donors is CGRA0000570. So the date of this is 25 July 1986, and it's a memo from Dr Harris, and we've got the heading now "Rorer Health Care Limited" to Mr Thomas, copied to various people, including Mr Bishop and Mr Christie and Dr Rodell.

Again, what's set out in this first page is something we'll be coming back to, but if we go to the second page, we can see a paper headed "Review of Factor VIII products with respect to possible freedom from viral contamination. Factorate Heat Treated --

Armour". Then we've got the heat treatment method, 60 degrees centigrade for 30 hours.

Then some additional observations:

"(a) our own collection centres away from known high risk areas.

"(b) Donor education.

"(c) Pre-donation screen by questioning and physical examination."

Then this:

"Unfortunately, experience has shown that prospective donors do not always tell the truth."

So that's an observation worth flagging up.

There is then a more detailed discussion in this document about seroconversions from heat-treated concentrates. If we go to -- no, in fact there is nothing which casts any particular further light on the position in relation to donors. I think we'll pick up the rest of this document in November.

So, sir, that completes the theme in relation to donors. The next issue in relation to Armour that I want to pick up is issues about communication of risk, and looking at some of the product labels and data sheets, and we can perhaps do that at two o'clock.

SIR BRIAN LANGSTAFF: Yes. Well, let's take a break now

until 2 o'clock. 2 o'clock.

(12.57 pm)

(The Short Adjournment)

(2.00 pm)

MS RICHARDS: Sir, I'm going to turn to consider questions of the communication of risk by Armour, largely in terms of product labelling, data sheets and the like. But before we look at any specific documents, I'll just set out an observation which has been made to me by a representative of Core Participants -- not specific, I should say, to Armour but on the question of warning labels and data sheets and so on more generally -- and that's to just point out there may be a question mark as to the extent to which those are written materials that would have been seen by patients, or at least seen by certain cohorts of patients.

Leaving aside the question of whether what's in a product label or product insert can ever be a substitution for the clinician's discussion of risk, there will be some cohorts of patients who will never have seen that in any event: children, those treated in hospital, not at home, and the like.

So that was just an observation made to me on behalf of a number of Core Participants that I said

I would draw to your attention.

SIR BRIAN LANGSTAFF: If I may just comment for one moment, one of the documents you showed me this morning described telling others and users, it said, of certain features about the product. By "users", it was quite clear from the context it meant doctors.

MS RICHARDS: Yes, absolutely.

With that general observation in mind, we'll then turn to some of the specific materials relating to the Armour Factorate product.

If we start with ARMO0000002.

This is from the 1975 application for the product licence for Factorate, much of which we looked at yesterday. If we go to page 60, please, we can see some of the materials -- the warning in other materials that accompanied the application, or at least formed part of the file containing the application, and we can see there "Caution", so those are the last three lines:

"This product is prepared from pooled human plasma. Despite careful selection of donors, it may contain causative agents of viral hepatitis."

Then within the same document if we go to page 66, this is described as a "Revised package insert leaflet", and again, it appears in -- as part of

a file, which suggests it was being put forward as part of the application. And we can see there the heading "Warning" on the right-hand side:

"Antihaemophilic Factor (Human) - FACTORATE is prepared from human plasma, each donation of which has been found negative for Hepatitis B Surface Antigen ... by the ... (RIA) method. In addition, this lot, after reconstitution as directed in this insert, 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."

So that was material at the time of the licence application for Factorate.

If we go on to ARMO0000006, this is a letter, 17 May 1976, from Armour to the DHSS Medicines Division, and we can see it refers to the data sheet -- this is in the last paragraph of the letter:

"The data sheet for Factorate are now in draft form. I enclose a copy for your attention."

Then if we go to page 3, top of the right-hand side, we'll see year after year the terminology and language used is almost always the same, so we see here the warning:

"Factor VIII is prepared from human plasma ..."
There's reference to the testing of donations for hepatitis B surface antigen, there's reference to testing the batch, and by the RIA method as well, and then the same general statement: the risk of transmitting viral hepatitis is still present.
If we move to 1977, ARMO0000017, the date is in the bottom left-hand corner, October 1977, and the product licence holder is identified as Armour Pharmaceutical Company Limited, Eastbourne.
We can see it's a data sheet for Factorate, and if we turn to the second page, top right-hand corner, we've got the warning again. The language used has not changed from the draft submitted in 1976.
If we then go to 1978 and the High Potency Factorate, it's at ARMO0000023.
If we turn to page 10, we can see here -- and this is part of the draft package insert -- "Warning". Again, essentially the same points being made: testing of the donations for hepatitis B surface antigen, testing of the batch, but "no completely reliable laboratory test", so the "risk of transmitting viral hepatitis is still present".
If we go on to page 12, in terms of packaging, bottom of the page there's the heading "Caution:

"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 hepatitis cannot be assumed."
So put in a slightly different way there and the reference to "selection of donors", but the same essential method it might be thought.
If we go next to ARMO0000035, I'm not going to go to the details of it, sir, I'll just ask you to note we're now in June 1979, and we have a draft package insert, a further version, being sent, but it has the same terminology, and you'll see that -- I don't think we need to go to it -- from pages 5 and 7, exactly the same language used as that which was enclosed with the original product licence application for High Potency Factorate.
That brings us then, therefore, to 1979. If I then just pick matters up by reference to the ABPI Compendium of data sheets, for 1980 to '81, if we go to ABPI0000040. And I hope I've got the right page reference here because I've only got the individual sheets. Page 5 I'm hoping will be the right one. Yes.
So the point here, if we look at the bottom

right-hand column, Factorate, as in the Armour product Factorate, the trademark product, is not listed in the index.
If we go to page 14 -- no, if we go to ABPI0000039, sorry, Soumik, and go to page 14. Other Armour products are included in the 1980-81 ABPI Compendium but not Factorate.
If we then move on to 1981, ARMO0000091, and if we go to the bottom of page 2, we'll see the date. This is described -- sorry, Soumik, top of the page first of all, my apologies -- this is described as an application for a product authorisation for Factorate double fill presentation. Some form of variation, essentially.
September 1981 is the date at the bottom of the page.
If we go to page 5, we will see, under the heading "Warnings", paragraph 12 -- again, this is the draft package insert submitted with the application -- as at September of 1981 it's essentially the same terminology as was used consistently, really, from the late seventies onwards:
"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 in this leaflet, 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."
So the language is, as we will see from that, unchanged.
And if we go to page 8, and if we can zoom in to the top part of the page, we've got the warning there, top left-hand corner. It's essentially the same language on that label.
I don't think I need show you the 1981-1982 ABPI Compendium of data sheets. I'll give you the reference. It's ABPI0000042. Again, although Armour participated in the sense that there are other Armour products listed in the Compendium, Factorate still doesn't feature in the ABPI Compendium of data sheets.
If we go, however, to the 1983-84 Compendium, which is ABPI0000045, and go first of all to page 2, we can see the heading "New Products", and the italicised sentence at the top:
"The following names appear in the index to this issue of the Compendium but not appear in the 1981-82

edition. It does not necessarily follow that they're recently introduced products".

And of course Factorate wasn't.

Then if we go down towards the bottom of the page left side, the index for F, we can see that Factorate is there listed.

Then if we go to ABPI0000046, page ... try page 14, would you, Soumik? Yes.

If we just zoom in there, we've got there "Factorate" set out.

If we go to the next page, halfway down the page, we've got "Contra-indications, warnings, etc":

"Warning: Factor VIII is prepared from human plasma, each donation of which has been found negative for hepatitis B surface antigen ... In addition, each batch, after reconstitution as recommended, has been tested and found negative by the RIA method."

Then the same terminology:

"... the risk of transmitting viral hepatitis is still present."

This Compendium was, I think, published in January of 1983. I can double check that. I mention that because you'll see, of course, that there is no reference there to HIV, HTLV-III or AIDS.

If we go to the right-hand column we see there

"High Potency Factorate" is also listed in the Compendium, and if we turn over the page, we'll see at the very bottom of the left-hand column, under the heading "Contra-indications, warnings, etc", the same terminology is used. So it's the same language for High Potency Factorate and Factor VIII. I don't think I need read it out.

Sticking with the ABPI, if we go to ABPI0000050, this is the ABPI Data Sheet Compendium for 1984-85. If we try page 3, Soumik. Yes.

So if we look at the heading "Date of preparation", halfway down on the right-hand side, it says:

"The data sheets included in this Compendium were prepared or reviewed during the final quarter of 1983 and the compendium itself was published in April 1984."

Then if we go to page 14, we see the entry at the bottom right-hand column for Factorate, and then the warnings are on the following page, top half of the page, right-hand column.

So the contraindication/warning there, again, is in relation to the testing for hepatitis B surface antigen, and the fact that the risk of transmitting viral hepatitis is still present. There isn't, as far

as I'm aware, in this any reference to AIDS.

And the same is true, I think, in relation to the High Potency Factorate, which starts at the bottom of the page. If we go over to what should I think be page 16, the contra-indications/warnings, halfway down the right-hand column, are in identical form to that for Factorate itself.

If we then leave the ABPI and go back to the licence application documentation, ARMO0000145, sir, we'll see this is the application submitted in May 1984. It's essentially for renewal of the product licence for High Potency Factorate. And if we turn to page 11 we can see "Warnings and Adverse Effects", again in largely the same language. There's a slight modification, so it reads:

"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 [et cetera, et cetera] has been tested and found negative. However, since no completely reliable laboratory test is yet available to detect all potentially infectious plasma donations, the risk of transmitting viral hepatitis to patients is still present and personnel administering and handling this material should also exercise

appropriate caution."

So there's that slight refinement, and I think that's the only reference in this document. So that's as at May 1984. If we then turn to 1985, ARMO0000165. This is a letter dated 13 February 1985 from Armour to the Medicines Division at the Department of Health, and it refers to enclosing label texts for the above products, which are Factorate and High Potency Factorate.

If we go over the page, to page 2, we can see the -- so it's "Important: see leaflet for complete information". Then the "Caution":

"This solution is of human origin, despite careful selection of donors and processing, it cannot be assumed to be free of hepatitis virus."

Then bottom of the page, the "Caution" in the left-hand -- thank you:

"The product is prepared from Pooled Human Plasma. Despite careful selection of donors and non-reactivity of the reconstituted solution for hepatitis B antigen, and the radio-immunoassay procedure, freedom from causal agents from viral hepatitis cannot be assumed."

Then if we go to the next page, just turn it round. I think we've got the same language there, and then the bottom of the page, left-hand corner, yes.

So the same terminology used.

So no reference -- sorry, if we just go over the page. I'm not quite sure, sir, whether these are just multiple copies of the same labels or there's a difference between the labels. It may be there's a difference in terms of sizes, I'm not sure. Again, we've got similar caution, the solution is of human origin, despite careful selection of donors and processing it cannot be assumed to be free of hepatitis virus.

So the terminology there is all relating to the hepatitis virus, so you'll see no reference there to HIV or to HTLV-III or AIDS.

If we go to page 5, we can see the proposed data sheet test for High Potency Factorate here set out, and if we turn on to page 7, under the heading "Contra-indications, warnings", the warning is in the same terminology as we've seen really from the late 1970s onwards, with the risk of transmitting viral hepatitis being identified as still being present.

That's as at February 1985, when this material is being sent to the Department of Health and Social Security, Medicines Division. No reference there, you'll see, to HIV or AIDS.

There is actually a document at ARMO0000366, which

shows that the Department did pick up upon an issue relating to the content of the data sheet and package insert, but it's not -- in terms of the language of the warning, what's said is:

"... the DHSS have insisted that we, as for all other manufacturers/suppliers of such products, include the temperature and time of the heat-treatment in the data sheet (and package insert) ..."

And:

"Additionally, we have had some minor 'autocation' [I think that should be altercation] with them over the names of the products in that they require the words 'heat treated' in the product name whereas we wanted these words prominently on the label but with the product name intact."

So the Medicines Division pick up on aspects of the contents of the sheets and the labels but not in terms of the warning.

If we then turn to the next ABPI Compendium for 1985 to 1986, should be at ABPI0000022. If we turn to page 15, bottom right-hand corner, we have the entry for Factorate. If we turn over the page, halfway down the page on the right-hand side, again under the heading "Contraindications, warnings", it says "Factor VIII is prepared from human plasma", and it's

the same terminology, the same language used in relation to testing for hepatitis B surface antigen and the risk of transmitting viral hepatitis still being present.

So no reference there to, again, HTLV-III or AIDS. The same is true for the High Potency Factorate. Yes, I should say that compendium was published in July 1985, the introduction to it explains that it's prepared, or the data sheets have been prepared for reviewed during the last quarter of 1984.

SIR BRIAN LANGSTAFF: Just go back to it for a moment. The side effects, bottom right-hand side.

MS RICHARDS: "Products of this type are known to cause mild chills, nausea or stinging at the infusion site."

SIR BRIAN LANGSTAFF: Yes.

MS RICHARDS: Yes, I should have said a lot of the labels over the years contain a similar description of side effects, but yes, it's mild side effects there being described, and nothing associated with HTLV-III or AIDS.

If we then pick it up with a further application to vary the product licence at ARMO0000181, this is 9 January 1986, an application by Armour to the DHSS enclosing applications to vary the above product licence.

We looked at this earlier, if we go to page 3 we see what the proposed variation was on the right-hand side, under the heading "Proposed". It was the inclusion of the fact that units of source plasma were tested for HTLV-III, and it says, "Proposed data sheet text attached".

If we go on to page 5, we can see what I think is the proposed data sheet as at January 1986. So under the heading "Presentation", and we looked at this previously, there is reference there to HTLV-III, it's the fourth paragraph under "Presentation", in the context of their having been tested, and the units of source plasma having been found to be negative.

If we turn to page 7, the "Contra-indications, warnings, etc", at the bottom of the page, the language is unaltered. So it still refers to hepatitis B surface antigen testing, in terms of both the plasma and the batches of reconstituted product. It refers to the risk of transmitting viral hepatitis, and then has the same terminology in relation to side effects that you pointed out, sir:

"Products of this type known to cause mild chills, nausea or stinging at the infusion site."

So no inclusion as a warning or side effect of the possible transmission of HTLV-III.

Then we can see, if we go to ARMO0000531, this is May 1986. So we can see active consideration being given to the content of the data sheet and leaflet. It says:

"The Factorate data sheet has recently been amended to include details of heat treatment and testing for antibodies to HTLV III virus."

Which is essentially what we saw under the heading "Presentation" in the earlier document:

"Therefore, please arrange to update the leaflet to include the following statements at the end of the section of composition and standardisation:

"This product has been heated at 60°C for 30 hours. This step has been introduced in order to reduce the risk of transmission of infectious agents.

"All units of source plasma are test for antibodies to [HTLV-III] and found to be negative."

Again, in terms of where it appears in the data sheet and in the leaflet, it's not in any headings on warnings or any side effects that that reference is there set out.

Then I think we can see that, if we go to ARMO0000192, this is 9 June Armour submitting copies of applications for variations to the product licences for the heat-treated Factorate and heat-treated High

Potency Factorate. If we go to the second page, if we look at the bottom half of the page, typed in, there's a cross in the box "Other ... Additional information on data sheet".

So the variation to the product licence is because they're going to include additional information on the data sheet, and then, if we go to the right-hand side -- sorry, if we go to the next page. We can see the proposed change, which is:

"As at present but additionally the following information to be included ..."

We're now in relation to ALT testing:

"In addition all units are tested for ALT ... and found to be less than twice the established upper normal value for the test kit."

Then, if we go over the page, we see -- no, in fact those are the present changes not the proposed changes. If we go to page 8, we'll see what's said to be a proposed change. But I think that's the same terminology we've already seen, so again it's explaining that the units of source plasma have been tested for HTLV-III, rather than anything additional by way of text.

Yes, if we go to page 14, under the heading "Contra-indications, warnings", the language in

relation to both the warning and the side effects is as set out in the previous documents that we have looked at.

SIR BRIAN LANGSTAFF: Do we know why the language is "all units", as opposed to "All donations"? It depends what units is what units covers.

MS RICHARDS: I'm sorry, sir, where?

SIR BRIAN LANGSTAFF: This is "All units are tested for", whatever it is, ALT, in one case.

MS RICHARDS: Oh, sorry.

SIR BRIAN LANGSTAFF: Yes, it's referring to units, which I've taken to be individual donations but I may be wrong. Because it could be a larger unit.

MS RICHARDS: I'm afraid I don't know the answer to that, sir. We can look at it further and see whether we can work out whether there's a significance to be attached to that wording or not.

SIR BRIAN LANGSTAFF: It's yet another different word --

MS RICHARDS: It is.

SIR BRIAN LANGSTAFF: -- donations, donors, units. They may all mean the same thing, pretty much, but they might not.

MS RICHARDS: No.

If we then just have a look at ARMO0000534, this is a letter or memo, 10 June 1986, from Mr Bishop to

somebody else within the company. It says:

"Further to our previous correspondence, I enclose a copy of Cutter's packaging (one of our competitors), from which you can see they are now adopting the suggested labelling.

"Please advise whether there is any progress with regard to our own labelling."

Then if we go -- sorry, let me read the whole of that. Go back to the letter, my apologies, Soumik.

"If necessary, and to save time, I suggest a label be produced just for the outers containing the 10 vials, although ideally each individual vial should be so labelled."

And the Cutter leaflet to which reference is made is on the next page -- sorry, not the leaflet, it's the packaging. We can see the bottom -- if we look at the left-hand side:

"Warning: Koate HT is a purified dried fraction of pooled plasma obtained from many donors. The presence of hepatitis viruses should be assumed and the hazard of administering Koate HT should be weighed against the medical consequence of withholding it particularly in persons with few previous transfusions of blood or blood products."

We'll look tomorrow in more detail at the various

Koate labels and data sheets used from time to time and we'll see if there's any difference there in the way that's described and the Armour labels. But I think it's the -- however, the strip of white and the language there that Mr Bishop was probably referring to, although again I doubt he'll be able to clarify that for us, where it says, "Each individual unit of plasma has been tested for antibody to HTLV-III by an FDA approved method and found nonreactive".

Now, of course, that's still not a warning, but it's a piece of information that it would seem Cutter was placing on Koate HT.

SIR BRIAN LANGSTAFF: It's almost an opposite to warning, isn't it?

MS RICHARDS: Reassurance.

SIR BRIAN LANGSTAFF: Yes, it's basically saying: We're aware of this risk, we've excluded it by testing. Or at least it might be read that way.

MS RICHARDS: Yes.

Then if we go to ARMO0000556, we've got a memo from 14 July 1986 to Mr Bishop from AS Clark about "Factorate labelling":

"We now have approval from the Department of Health and Social Security for the use of a label

relating to HTLV-III antibody testing on Factorate outers."

So this would appear to be the response to Mr Bishop's communication.

"The wording is as per that on the data sheet.

"We still await approval from the National Drugs Advisory Board."

And then go over the page.

SIR BRIAN LANGSTAFF: Just -- you may not be able to answer this, I suspect you might not, but the Factorate outers, there's only reference to vials, individual vials, being labelled.

MS RICHARDS: Yes.

SIR BRIAN LANGSTAFF: So the issue might be whether the outer is the label on the vial, which sounds less likely, than it is on the packet, where -- rather if one goes to an off-licence and buys a 12 pack, it may come in -- if you do -- it may come in cardboard, with labelling on it.

MS RICHARDS: Yes. I'd certainly read it that way. If we go back to the way in which Mr Bishop expressed his communication at ARMO0000534, he draws a distinction between the outers containing the 10 vials as compared to each individual vial. So, yes, I'd read that as the pharmaceutical equivalent of the 12 pack.

SIR BRIAN LANGSTAFF: Yes.

MS RICHARDS: If we go back to ARMO0000556, it would appear that what's been done, whether for reasons of speed or for some other reason I don't know, is the label is going to be on the outers as opposed, one assumes, to the individual vial. Then it says the wording is as per that on the data sheet.

The next page of the document is actually a licensing authority response to a request. So it's presumably the Department of Health's approval of what Ms Clark is describing to Mr Bishop, and we can see -- sorry, if we just go back and look on the left side, "Present" it says:

"On the outer, containing 10 vials, labelling as per attached sheet."

Then:

"As at present but additionally a sticker with the following wording:

"'All units of source plasma are tested for antibodies to human T cell lymphotropic virus type III (HTLV-III) and found to be negative.'

"This wording has previously been approved for use on the data sheet."

I should just perhaps make that point, it's probably obvious from everything we've looked at, but

the various forms of wording that we've looked at on the data sheets and the like are all material that is submitted to the licensing authority. So it's not the pharmaceutical companies such as Armour simply going it alone. They've submitted their wording to the licensing authority and we've seen from time to time the licensing authority raises issues, but there's no evidence of any issue being raised about the absence of any warning about HTLV-III or AIDS.

So that's where we get to as at the middle of 1986. If we go to ARMO0000566, there's a further communication in 1986 in relation to labels, and it just says:

"... in order to get more definitive information on the rationale for the statement it has been proposed to make on Factorate labels, we have obtained a copy of the test procedure used by Plasma Alliance."

Then we can see reference there to the ALT testing:

"Plasma donations having an ALT titre above 70 units per ml at 30 degrees C are excluded from plasma pools for Factorate production. This is consistent with the label text proposed ..."

So this appears to be a label text amendment in relation to adding some form of information about ALT

testing.

Lastly, the 1986-1987 ABPI Data Sheet Compendium, which is, I hope, at ABPI0000024. So if we go to page 13, bottom right-hand corner, we have here the entry for "Factorate Heat Treated". If we go over to the next page, we see in the top left-hand corner, second paragraph down, the reference there to the heat treatment method. "This product has been heated at 60ºC for 30 hours. This step has been introduced in order to reduce the risk of transmission of infectious agents."

So there is explanation as to why there is heat treatment.

There is then reference in the next paragraph to the units of source plasma being tested for antibodies to HTLV-III and found to be negative.

If we then, on the same page, to bottom right-hand corner, we've got there "Contra-indications, warnings, etc", and we have the same terminology in relation to warnings so -- sorry, the same terminology as we've seen over the years: the reference to testing for hepatitis B surface antigen, the possible present risk of transmitting viral hepatitis, and then the side effects of mild chills, nausea or stinging. But nothing further. And the same is -- in this

compendium, it's the same information, I think, for the high potency heat treated Factorate.

So those are the documents that we presently have in relation to product labelling, package inserts, data sheets, in the period up until 1986. I should just, if I may, read a very short paragraph from the Krever report. I don't have it available to display on screen.

It's chapter 14 of the Krever report, which obviously was the Canadian inquiry into blood contamination. It's page 399 of that report.

It says this:

"When fractionators prepared their vials of factor concentrate in packages for shipping, they included printed information about the concentrates, their proper use, and possible risks in using them. In the autumn of 1983 and in early 1984, US fractionators added warnings about the risk of AIDS to the information in the product inserts. Armour for its Factor VIII concentrate in October 1983, Cutter for its commercial Factor VIII concentrate in January 1984, and Hyland for its Factor VIII concentrate in March 1984."

We haven't found sir, those -- there are no specific documents cited in support of that passage in

the Krever report. We haven't found any specific documents which show the addition of warnings about the risk of AIDS in the United Kingdom. So it's possible that the Krever report leaves open the possibility that there may be material that we haven't found. But what I've shown you, sir, is what was submitted to the licensing authority and what was included in the ABPI Compendium.

SIR BRIAN LANGSTAFF: If he's accurate in what he says, then the warnings that were given in the USA were not given in the UK.

MS RICHARDS: That's an inference -- the obvious inference to draw from what's said, combined with the absence of any material that we've --

SIR BRIAN LANGSTAFF: But the parent company involved is exactly the same.

MS RICHARDS: Yes.

SIR BRIAN LANGSTAFF: And the products are made in the same place in --

MS RICHARDS: In Kankakee, Illinois.

SIR BRIAN LANGSTAFF: -- Kankakee, yes.

MS RICHARDS: Yes. So it may be that there is material that we have not found, and it's for that reason that I wanted to draw your attention to what was said in the Krever report.

SIR BRIAN LANGSTAFF: Yes, thank you.

MS RICHARDS: In the interests of trying to be as fair and comprehensive as possible.

Sir, that's it in terms of data sheets, package inserts, product labels. I just want to turn to a few other aspects of what might be called communication of risk. The first is to draw your attention to a document which we may come back to at a later stage.

It's at BAYP0005366. This is a letter dated August 14, 1984. It's addressed to Cutter, and it describes in the first paragraph a meeting in Los Angeles between Cutter, Hyland representatives, and the organisational body which is sending this letter, the name of which, at the top left-hand corner, is not entirely clear. It looks like "Hill+Knowlton", not 100 per cent sure.

In any event we can see if we look in the first paragraph it says:

"We regret that we were able to meet also with people from Alpha and Armour, as we believe the four companies -- along with perhaps the Red Cross -- have a common need for a good, honest, straightforward education programme."

Then it goes on to talk about communication of information to patients, and to the public.

Now I'm not going to go through the detail of this letter, not least because it's directed to Cutter rather than to Armour. But if we go to page 5, what we see here is the text of what's said to be a public relations proposal by a public relations firm, Burson-Marsteller, I think, August 13, 1984. It's described as a:

"Public relations proposal for Hyland Therapeutics, Armour Pharmaceuticals, Cutter Biological, Alpha Therapeutics."

It may be that this is a document that never got to Armour, and so it may be, absent any further information that we find, that there are no particular conclusions that can be drawn, in relation at least to Armour or Alpha, who were not apparently at the meeting in Los Angeles.

But if we go to the next page, we see what's said under the heading "Situation":

"Four companies -- Hyland Therapeutics, Armour Pharmaceuticals, Cutter Biological and Alpha Therapeutics -- comprise an industry that provides an antihaemophilic factor to approximately 20,000 haemophiliacs nationwide."

That's obviously talking about the US.

"Last year it is estimated that 40 haemophiliacs

contracted and died of ... (AIDS) after receiving an infusion of an antihaemophiliac factor that was contaminated with the virus. Subsequently, haemophiliacs nationwide have reduced the frequency of their infusions because of the fear of contracting AIDS, even though their physicians in the haemophiliac associations have urged them to maintain normal infusion rates.

"Consequently, sales for the anti-haemophiliac factor have declined 15 to 20 percent in the last year.

"Alpha, Cutter, Armour and Hyland have asked Burson-Marsteller to develop a public relations proposal to address the problem of decreasing infusion rates of the anti-haemophiliac factor among haemophiliacs."

Now, that refers to this firm being asked by the four companies. Whether that was a statement of fact or whether this was a proposal reflecting the anticipation that all four companies would approach the firm is unclear, and that's why I want to be careful to say that it's not a thing possible to deduce from the information that is in this material, that this is something which Armour, or indeed Alpha, had signed up to.

But it is perhaps more telling in a broader sense, in terms of the pharmaceutical industry, and if we go to the next page, the objectives of this public relations proposal are set out:

"To increase the awareness among haemophiliacs of the dangers of reducing infusion rates, ie there is more risks involved of long-term complications from not conducting the infusions than in getting AIDS."

Then:

"To improve communications between haemophiliacs, their physicians, the haemophilia associations and the supplying companies."

Then it goes on to outline various suggested strategies, which I'm not going to necessarily go through.

Well, perhaps if we just go to page 12, there are various what's described as communication tactics that are identified on this page and then we go to the following page, which include the production of results in newsletters, producing booklets, having an advisory panel and various other things.

So, as I say, it may be of more general interest in terms of understanding at least what a public relations firm thought the pharmaceutical industry might want rather than assessing any action on the

part of any individual pharmaceutical firm.

The other aspect of communication of risk I just wanted to briefly explore is the response within Armour to various media reports of risks associated with the use of their products.

Sir, if we look, for example, at ARMO0000483, we can see here a report in the New Scientist, February 1986, "Blood treatment may not kill AIDS virus". This raised the concern that there was still seroconversions taking place with heat-treated products, and it's an article -- we've looked at it before and we'll certainly, I think, be looking at it again -- it refers to the allegations being made by Dr Jones of seroconversion and a case in the Netherlands.

It expressly refers to the Armour product, as well as a number of other products in the course of the article.

There's a second article at ARMO0000472 at around the same time. This is a publication in The Guardian so it's the left-hand side. Doesn't refer to Armour by name, but it talks about four men in the Netherlands and the US developing AIDS after taking heat-treated Factor VIII. You will note in here there is ascribed to Dr Donald Acheson, as we know the Chief

Medical Officer at the time, what's said to be criticism of Dr Jones for making this information public.

In any event, there are two media publications in February 1986, and we know that there came to be, in the course of 1986, this critical issue about the possibility of people receiving heat-treated Factorate being infected with HIV.

I just want to look at a few internal Armour documents which record discussions about how they might respond to such reports. We can pick it up at ARMO0000526. This is from Mr Bishop to Dr Harris, 25 April 1986, so it's an internal communication. Again, we can perhaps ask Mr Bishop about it in due course.

So it would appear Mr Bishop is requesting action to be taken in response to the New Scientist article and we can perhaps just look at the last sentence of Mr Bishop's memo:

"On the basis of the foregoing, I would again recommend that we write to the New Scientist and also to Dr Richard Lane to get an official statement from them [presumably BPL] that they do not consider their product any safer than ours in terms of inactivation of the HTLV-III virus."

We can see then, if we go to ARMO0000548, this is a memo now again, I think an internal memorandum from Mr Bishop, dated 4th July 1986, and on the topic of seroconversion to HTLV-III. This is now referring to an article in The Lancet -- the Lancet, 31 May, picking it up in the second paragraph -- sorry, it's two articles in The Lancet, 14 June, 31 May:

"Both these articles, besides attempting to clarify their own heat-treating procedure [I think that is a reference to Cutter] identify ours as being implicated in the cases quoted.

"The decision has been taken to respond to The Lancet within the next 2-3 weeks with a carefully prepared 'defence' statement setting the facts straight. As soon as this document is prepared, copies will be forwarded to you together with a Technical Bulletin from Robert Christie."

Then reference is made to enclosing certain documents and publications.

If we go over the page, there's what I understand to be the suggested information for inclusion within the defence statement. So the heading "Introduction":

"The suggested implication of Armour heat-treated FACTORATE ... is based on two cases, both of which received prior treatment with non-heat treated

products."

I'm not going to go through the detail of those cases, sir.

If we go to the bottom of the next page, having set out various matters in relation to ostensibly those two cases, the suggested summary is in the penultimate paragraph:

"... no sero-conversion on any other 'clean virgin' not otherwise at risk for AIDS has been reported and live virus has never [underlined] been isolated from Armour's heat treated FACTORATE.

"The above is subject to final ratification and updated communications."

So it would appear to be being deliberated within Armour whether there should be a robust response by way of what was described as a "defence statement" to the articles that were being published in The Lancet.

If we go over to the next page, page 4, we can see what I think is Mr Bishop's PS:

"There was a meeting held in Newcastle by the Reference Centre AIDS Committee at which the main topic of conversation was the double standards being applied by the industry with fully screened product, and the NHS who were still supplying unscreened product. Unfortunately, there are rumours going about

that Armour are supplying unscreened material and this is probably originating from competitor sources and you must please leave everybody in no doubt that all Armour material being sold is sourced from donor material which has been screened and tested for antibodies to HTLV-III."

So Mr Bishop appearing to hold clear views as to the way in which the company should respond. As I say, we can no doubt ask him about that.

If we then move on to CGRA0000527, this is again from Mr Bishop, 16 July 1986. The heading is "Proposed UK defence document", and we can see in brackets:

"(To: Lancet + Technical Bulletin to Sales Force and Review to Swedish Health Authorities)."

Not entirely clear what that meant, other than it seems to be a suggestion that there should be a response to The Lancet and then to some other publications.

"In light of the US refusal to originate a Defence Document as discussed, I propose the following to form a basis for a UK originated document ..."

Pausing there, the inference that seems likely from this is the American company, parent company, has decided it's not going to produce a defence statement

but Mr Bishop seems to be of the view that this should be a UK-based one:

"Objective:

"1. To nullify negative impact of the published 'sero-conversion' stories.

"2. To restore/confirm confidence in our heat treating process regarding HIV inactivation.

"3. To demonstrate our faith in our own product.

"Thus,

"4. To stop any further deterioration in sales -- UK + Scandinavia."

Then the "Suggested Format" for this UK-originated document is:

"a. Refer to the ... Cutter letters in The Lancet ... and correct the misleading nature of the article ...

"b. Defend the 60°C for 30 hours referred to by the Editor in the June 14th Lancet article by citing the Armour experience, both in vitro and in vivo.

"c. Summarise as per penultimate paragraph [that's referring to his earlier document that we looked at] and emphasise importance of comprehensive analysis of all data published and unpublished in the interest of the patient.

"I would emphasise that this document is essential

for the maintenance of FACTORATE business in our markets."

Then ARMO0000562. There's a further document from Mr Bishop dated a couple of days later, 18 July 1986. It's described as a house message from Armour Pharmaceutical Company Limited. The subject is "Factorate recall -- media response".

We can see in the first paragraph he refers to:

"... copies of the New Scientist and Guardian articles of the 17th July on the above mentioned subject", which presumably is the recall.

"I have it from an extremely reliable source that both articles were initiated by the actions of Peter Jones and, certainly in the case of the New Scientist, this took the form of him providing them with a copy of our recall/exchange letter together with his comments. This is obvious from the last paragraph of both articles which forms the 'pay-off' and is, in my opinion, an attempt to justify his previous outburst out the Newcastle AIDS conference in February which, you will remember, caused so much consternation to Doctors and patients alike.

"It may well be, and it is to be hoped, that the majority of Doctors will view the articles in the light of this objective and the contents immediately

discredited. This would appear to be the case from discussions both Mike Cross and myself have had to date with leading Directors.

"Nevertheless, I will just elaborate on various points made in the article starting with the New Scientist ..."

I'm not going through the details of Mr Bishop's comments. We can then perhaps explore that with Mr Bishop in due course. If we go to the third page, third paragraph, Mr Bishop says this:

"It is our feeling, and that of our advisers, (who include members of the UK Haemophilia Centre fraternity) that these are close be treated with the contempt they deserve and, therefore, we propose to take no further action other than discussion by you with individual Doctors who may express some concern which you are in a position to discuss on a sensible level.

"Unfortunately, the mention of Dr Michael Rodell's statement that we are reviewing our heat treatment process now prevents us from preparing an official 'defence document/article' to The Lancet, which would not be totally misconstrued by those wishing to cast dispersions on the Armour operation. We can not on the one hand defend our existing treatment and then

immediately introduce a new one, although the reasons for introducing the new process are primarily to attack the [non-A non-B] problem.

"However, you are in possession of all the facts which we, obviously, will continue to update you on and we will rely on you to relay the correct factual information to all of your contacts."

Now, as I've said repeatedly, we will be looking at the heat-treated seroconversion issue in November. I have drawn attention to these documents now, partly because they may help place in context some of the issues that we will want to explore with Mr Bishop in November but also because it is perhaps useful to see what was being said internally within Armour to public discussions about risks from their products.

Sir, that, I think, is probably -- actually, sorry, no, one further document on the same theme. ARMO0000568.

SIR BRIAN LANGSTAFF: 568?

MS RICHARDS: 568, yes. This Mr Bishop, I think, to the same recipients of the communication we looked at a moment ago, 7 August 1986, and again, it's in part on the issue of public discussions in relation to risk. He says in the first paragraph:

"I know enquiries to you regarding a review of our

heat treating procedure have been increasing lately, especially with the announcement in the press recently (Guardian/New Scientist) wherein Dr Michael Rodell declared this intent from the States.

"In order to help you tackle these questions with some degree of credibility, the following should be the lines upon which your official response is made."

Then there is set out a suggested line to take, in terms of constant review of product range, in order to upgrade and refine the products. If we look further down the page, so the last two paragraphs, this is, again, still part, I think, of the suggested line to take:

"We would emphasise again that this move does not imply any lack in confidence in our current procedure ... in terms of HIV elimination/inactivation, but is designed to improve still further the safety factor in the product in terms of total viral inactivation without the need for the addition of stabilisers ..."

Then he says this:

"Naturally, we have a considerable quantity of existing material in inventory and the last thing we need is for people to hold off ordering until the new product comes through".

Over the page:

"We would emphasise, therefore, that it will be a phasing-in process and not an overnight change and customers should understand this.

"If there are any queries resulting from this information, please let me know upon my return from holiday but, hopefully, this statement will enable you to 'scotch' any rumours as to our motives branded about by negative Directors or competition."

We know, of course, that exactly two months later Armour withdrew Factorate and High Potency Factorate from the market, the communication of 7 October 1986, and you may wish in due course to consider those discussions in light of that subsequent event.

So that's the material on communication of risk. There are then just a handful of documents I wanted to show you, sir, in terms of some of Armour's interactions with other Haemophilia Centres and Haemophilia Centre Directors.

This is in terms of some of the studies that were undertaken as between Armour and Haemophilia Centres, in addition to the ones that we've already looked at, and some of the financial assistance or support that was, from time to time, made available by Armour to Haemophilia Centres, so there's just a few documents in that regard to show you, starting with

HHFT0001201_003.

So here we have a communication between Armour and Dr Jones, December 1980, and it refers to:

"... a Protocol, revised according to our discussion in Alton on 1st December ...

"In addition to the modification to the protocol, we also discussed and agreed the following points:

"The two centres taking part will be Newcastle and Alton.

"Although each centre will recruit a minimum number of 6 cases, we would allow 10 sets of treatment of each product at each centre."

The study was said to start in January 1981. There is then a cost estimate put forward, which gives a total, I'm not sure whether it's per centre or for the two centres, of £6,840.

Over the page:

"You agreed that these costs will be met from Research Funds initially, and we will then reimburse you on receipt of your invoice.

"We agreed that the Hemofil 2 would be obtained and provided by us. We therefore need to know as a matter of urgency the quantities which you and Dr Aronstam calculate to be necessary."

So there is some funding proposed by Armour for

the study at Newcastle and Alton. We've looked, I think, at the details of that study -- there are so many it's difficult to remember sometimes -- when we looked at Treloar's.

Indeed, I think we've seen it discussed in various minutes of the UKHCDO and the Hepatitis Working Party.

So that's some degree of sponsorship by Armour of the study at Newcastle and Alton in 1980. Then if we move to 1981 and Oxford, OXUH0001624_004, we can see a letter dated 6 August 1981 from Mr Bishop to Dr Rizza at Oxford. It appears from the first sentence that someone from Armour has made a recent visit to the unit. There's a discussion about a paper, in the second paragraph, and Mr Bishop says:

"As I have indicated in the past, please let us help in any way we can regarding the preparation of this paper."

That was a paper on inhibitor treatment.

Then there's a discussion about possible future sponsorships. Mr Bishop says:

"[We will await] the outcome of your application to the [Medical Research Council] and the Haemophilia Society ..."

Then a cordial thanks in the last paragraph and looking forward to seeing Dr Rizza again soon. So

that's an example of an interaction with Oxford in 1981, I think we saw a little more of that when we looked at the Oxford Haemophilia Centre last year.

If we then, by way of an example of interactions with the Royal Free Hospital, look at ARMO0000236, this is a letter dated 15 March 1983 to Mr Bishop at Armour. It's from Dr Kernoff, as we know, director of the Haemophilia Reference Centre at the Royal Free. I ask you to note the date and then the heading. So the date is 15 March 1983. The heading is "Proposal for research support into AIDS at the Royal Free Hospital":

"Further to our previous discussions, I now enclose a brief formal proposal requesting support for our AIDS-related project in haemophiliacs.

"As you will see, the request is mainly for a 1 year period of salary support for a Senior technician (MLSO) in Professor Janossy's department here, starting 1st April 1983. The gross sum needed, which would of course be spread over the year, is a little over £12,000.

"I should of course be very pleased to supply you with any further information you need. Any help Armour is able to give us would be greatly appreciated."

"We regard the acquisition of further information about the immunological defects in haemophiliacs and their relationships with clinical disease and blood product exposure, to be a matter of the highest priority."

Then we can see, under the heading "Facilities and expertise available at the Royal Free Hospital", set out why Dr Kernoff said that The Royal Free was particularly well placed to research this. If we go to the next page, "Work proposed":

"Preliminary studies using the limited laboratory manpower available have shown that immunological abnormalities in haemophiliacs are not confined to those patients who have received commercial concentrates and have close association with chronic liver disease. The objective of the proposed work, which will extend over a one year period, is to reach more definitive conclusions about the relative morbidity associated with exposure to different blood products, and the relationships between immunological abnormalities in the blood and those in tissue biopsy samples. Comparisons will be made with other groups of patients at increased risk of AIDS."

Then there is set out the various analyses that was proposed.

We can see the research proposal over the page. The title of the project is "Effects of blood products on the immune system of patients with haemophilia". The principal investigators are Dr Kernoff and Professor Janossy, who was head of the Immunology Department at the Royal Free.

"Background", refers to recent reports of abnormalities suggestive of impaired immunological function in haemophiliacs. You'll see reference in that first paragraph on the screen to patients having clinical evidence of altered immunity and a small number in the USA having developed AIDS.

If we go to the -- well, no, I'll read the next paragraph:

"The causes of these abnormalities are unknown, but may include transmission of a previously unrecognised virus or other agent. The predictive value of simple tests of immunological function is also unknown. However, the possibility that infusion of essential therapeutic products may be complicated by very serious hazards is causing extreme concern amongst patients and those responsible for their care. It has been suggested that profound changes may have to be made in management practices, particularly as regards the use of imported commercial concentrates.

The reason for requesting support from Armour is set out towards the bottom of the page. We can see what's being asked for is a year's bridging support, and it's said:

"Our immediate problem is the lack of skilled technical manpower ..."

Hence, the request is for funding for a trained technician. We see again, the overall figure given on the next page: £12,396.

If we go to ARMO0000238, we can see a response from Armour Pharmaceuticals from Mr Bishop to Dr Kernoff, 7 April 1983. He says he encloses a copy of the draft protocol compiled by Dr Helen Townsend, based on the recent proposal. It's been discovered by the Revlon plasma Executive Committee.

Then there is an invitation to Dr Kernoff and Professor Janossy to come to Eastbourne and discuss the matter with Armour's medical director and other members of the Medical and Marketing Departments. He's asked to prepare a presentation, and so on. If we go towards the bottom of the page, there's then a suggestion of a spot of lunch, and there's an indication of the number of people that will be present.

If we go over the page, we'll see it says, fourth

line:

"I confirm that we will do everything possible to provide a definitive answer to the proposal as quickly as possible."

I don't think I've got to hand any further correspondence, but this study was undertaken at the Royal Free. It's subsequently written up, I can't remember in which journal, but it's exhibited to the witness statement of Professor Christine Lee and I'm pretty sure we've looked at it in earlier hearings. And it thanks, amongst others, Armour, for their support. So the inference is I think that Armour provided the financial contribution. If we find anything to suggest that that's incorrect, we'll obviously bring that to your attention.

Sir, I've only a handful of further documents in relation to Armour. Probably about ten minutes' worth. So the question whether to do it now and then finish, or take a break and then start Bayer, or how you want to --

SIR BRIAN LANGSTAFF: Which would you prefer to do?

MS RICHARDS: Well, I think it might be sensible -- if those present don't mind -- if I just finish the documents in relation to Armour. There's just a few more documents on this theme of communications with

and funding for research by Haemophilia Centres.

SIR BRIAN LANGSTAFF: Well, we'll finish by 3.30 on that, I take it?

MS RICHARDS: Yes.

SIR BRIAN LANGSTAFF: Yes, let's go ahead.

MS RICHARDS: So those were the communications between Mr Bishop from Armour and Dr Kernoff in March and April 1983 specifically in relation to AIDS-related research.

We see around the same time communications between Armour and Dr Preston at Sheffield, also for research into AIDS, and we can see that from ARMO0000239. This is again from Mr Bishop:

"Dear Eric,

"Further ..."

Sorry, the heading is important:

"Proposal for research support into AIDS at the Royal Hallamshire Hospital."

There's an invitation then to Dr Preston and Dr Triger to come to Eastbourne to discuss the proposal, and an invitation that he do a presentation. Again, similar to the letter Dr Kernoff, then can have a spot of lunch before the return journey.

In terms of the details of the proposal for which funding was being sought, we can see that at

ARMO0000246. The summary of the protocol to be -- and the investigator's name is identified as Dr Preston. The summary of the protocol is:

"To compare various biochemical, immunological and cytological parameters associated with [AIDS] and Impaired Immunity states in Haemophiliacs, Age Matched Controls, and patients with Histologically proven chronic liver disease (Non-Haemophiliacs)."

Then if we go down we can see the funding that's sought is funding in the sum of £22,000.

Then if we turn to ARMO0000268, we can see a letter from Dr Preston to Mr Bishop, 22 June 1983:

"Research Project into [AIDS] in Haemophilia

"You will be pleased to hear that we are now in a position to embark upon the project and we have also found a suitable MLSO to undertake the laboratory investigations for the project. I am, therefore, writing to ask if you would formally accept my proposals for financing of the project ...

"If you are in agreement, I would be grateful if a cheque could be made payable to the Haemostasis Research Fund."

Then we can see in the last paragraph reference made to the project being:

"... already under way, in that one or two of

interest Dr Triger's own liver disease patients are currently being investigated."

We then go to ARMO0000272. We can see from this, although it's a letter about asking else, that funding was provided. So 19 July 1983, Mr Bishop wrote to Dr Preston. He's clearly met up with him at the conference that we know took place in Stockholm in the middle of 1983, and then he refers to the funding. And if we go to the bottom of the page, very bottom, it says:

"CC ..."

And Mr Bishop said:

"I will leave it to you to sort out the payments, which I understand is against a budgeted £7,000 for 83, £10,000 for 84, and £5,000 for 85."

I think it's reasonable to infer from that that the funding was being made available, and there are subsequent communications which enclose copies of cheques to Dr Preston for the purposes of the research.

The last set of documents within this category relate to communications with Dr Hill at Birmingham, ARMO0000370. This is a letter of 27 March 1985 to Dr Hill from Mr Christie at Armour.

"You will note from the enclosed copy letter that

I have paid our first 1985 donation to your research fund to the Finance Department of the Central Birmingham Health Authority.

"We continue to be very interested in the progress of this project, and of course, its extension into HTLV-III screening of children who have been treated with non-treated and latterly Heat Treated Factorate."

You'll recall, of course, sir, that Birmingham Children's Hospital was a hospital where the Armour Factorate product was in very substantial use indeed.

Then there's reference to an anticipated -- or:

"I hope to ... visit ... to discuss the current status of your research and the recent Hepatitis B problem."

And there's reference to a need to notify the DHSS of the findings.

There's one other communication with Dr Preston at Sheffield I meant to refer to. It's ARMO0000369. It's again from Dr Christie, director of clinical sciences at Armour to Dr Preston.

It's March of 1985, so it's two years further on from the material we looked at before. We can see reference to a cheque for £2,500 to "cover our first quarter 1985 support for research in your unit".

It's may well be that's an ongoing payment in

relation to the same research.

But the point I wanted to draw attention to is the rest of the letter:

"With respect to this research work and the publication of your experience with the heat treated Factorate in two patients, I hope to come and see you when next in Sheffield. Incidentally, do you have any information on the pre and post-dosing status of these two patients in respect of HTLV-III antibody. A negative picture before and after treatment in both cases would be valuable information for us if it could be demonstrated."

So a request there for specific information from Dr Preston about the HTLV-III status of two patients.

That's a flavour of some of the interactions with the Haemophilia Centre Directors and some of the funding that was made available by Armour to Haemophilia Centre Directors.

The other body, of course, with whom Armour's relationship in the UK is particularly important is the Department of Health and Social Security. We've looked at a number of the interactions in relation to the licensing application process. We'll look again in November at interactions in two specific points in time, anything more we find out about the 1983 --

middle of 1983 interactions between Armour and the Department, when consideration was being given within the Department to the way to respond to the fear of the dumping of pre-March plasma from the US, and then, secondly, the important interactions with the Department that took place in the course of 1986, and particularly with Dr Rotblatt of the Department in relation to the issue of seroconversion from HTLV-III. But I'm not going to attempt to deal with any of those issues in any more detail now. We will deal with that when we come back in November.

So that finishes the picture in terms of Armour for the purposes of this week.

SIR BRIAN LANGSTAFF: In which case we'll start up looking at Bayer at five to four.

MS RICHARDS: Certainly, sir.

SIR BRIAN LANGSTAFF: Five to four.

(3.26 pm)

(A short break)

(3.55 pm)

MS RICHARDS: Sir, before I start with Bayer there's just one further matter in relation to Armour I wanted to mention briefly.

Going back to the trial of heat-treated Factorate in 1983, 1984, so that issue of the protocol that we

saw with Dr Rizza identified as lead investigator, which we know was then stopped because of participants in the study developing non-A, non-B hepatitis.

It might have been thought from what I'd said that the patients who developed non-A, non-B hepatitis were Oxford patients under Dr Rizza's care. In fact, such information as there is available suggests as follows -- and I'm not going to put the document up onscreen but I'll give the reference: it's CGRA0000570, and it's the top of page 3. It's a document we looked at earlier for a different purpose.

That says:

"A multi-centre UK trial of Factorate heat treated was conducted in 1984. Two virgin patients were admitted in Sheffield and one in Glasgow. All three developed non-A, non-B hepatitis. Two had severe symptoms and the third exhibited markedly elevated ALT from five and a half weeks to four months following dosage but remained clinically well. The trial was stopped."

Then the document, which is an Armour document, says:

"Isolated reports have reached us since this date indicating that virgin or minimally treated patients

who have received Factorate heat treated have developed raised ALTs or jaundice and have been diagnosed as having non-A, non-B hepatitis."

So the specific patients whose -- the description of whose reaction seems to have led to the trial being stopped were either two Sheffield patients or a Sheffield and a Glasgow patient, and then broader reports since the trial was stopped of further patients developing non-A, non-B hepatitis.

I just wanted to clarify that before we turn to Bayer.

Sir, I'm going to start with the corporate structure, and it's not easy to describe. There will be four principal names that come up in the documents: Bayer, Cutter, Miles and Speywood.

Speywood had, as we'll see in due course, an arrangement whereby it distributed the product produced by Cutter and Koate for a period of time. That will become clearer both tomorrow and in the course to of the Speywood presentation on Friday.

Bayer, Cutter and Miles are all related entities. There will also be reference from time to time in the documents to a company called Tuta, which manufactured blood bags. To try to unravel them, I'll give the following by way of an introductory explanation.

If we start with an understanding of an organisation called Bayer AG, that is a German multinational pharmaceutical and life sciences company originally founded in Germany in 1863. It has a wide range of areas of business.

Bayer AG is the ultimate owner of Bayer plc, which is a UK-based company, and Bayer AG was, as we understand it, also at all material times the parent company of Cutter Laboratories Inc, and, from 1978, the parent company of Miles Laboratories Inc. Cutter Laboratories and Miles Laboratories were US-based companies involved in the manufacture of blood products supplied to the UK market.

So that is Bayer AG.

Turning then to the UK-based Bayer company, a company was registered in the UK in July 1968 called Bayer (UK) Limited, and it was so known from 1968 to 1974.

In 1974 it was renamed Bayer UK Limited, without the UK in brackets, and then in March 1992 it changed its name to Bayer plc. As indicated, the ultimate owner of Bayer plc is Bayer AG.

We'll see, therefore, materials from time to time which refer to Bayer UK, with or without the brackets, depending upon the date of the document. By way of

example, if we go to MHRA0009276, we will see here the grant of a licence in July 1976 by the Committee on Safety of Medicines to an application made by Bayer UK Limited, and we can see the name there written in handwriting.

Just to complicate the picture, the Koate product to which the licence related was distributed, as I say, for the first few years by Speywood.

And if we go to CBLA0000006_011 -- that's CBLA0000006_011. Okay, I can explain the document and we can correct its absence tomorrow when we look at the licensing documents in more details.

The document is referenced and I've given -- which for some reason we don't have to display -- is a product licence granted only a month after the one onscreen, which is now granted to Speywood Laboratories to distribute the same product, Koate, manufactured by Cutter Laboratories Inc in California.

If we try this document, Soumik, BAYP0000020_051. No? No. For some reason I don't think we've got the right documents available.

Soumik, let me just try one other because I can -- do you have that one? No -- I can do most of this without looking at the documents for the rest of the day.

WITN2988001. No? No, there isn't a different reference to that.

I'm sorry, sir, we don't appear to have the available documents for display.

Let me just spend a few minutes outlining the corporate structures, because I can do that, I think, without showing you particular documents, and then we can ensure that we've got the right materials tomorrow, and if I need to go back to any of the actual documents for the purposes of demonstrating what I'm talking about, we can do so then, but it'll make the best use of time now.

So the close relationship between these various entities is illustrated by the fact that in 1976, Cutter Laboratories International write to Bayer UK Limited thanking them for pursuing an application for a licence on behalf of Cutter Laboratories, which is a licence granted to Speywood. So really the important thing about all of these companies at this point in time is, whatever name appears, they are an associated group of companies with the -- Speywood is separate in terms of the company relationship, but there are -- Miles, Bayer and Cutter are all associated groups of companies which are dealing with the manufacture and distribution of Koate. That's the

principal product with which we're concerned.

There will be some other products which I come on to.

The contract with Speywood to distribute Koate was terminated in around 1980 and we'll hear more about this potentially on Friday. But for a period of time, Speywood continued to distribute Koate, but they distributed it under a different name, Humanate. So they imported it from the US and sold it as Humanate.

We also see the name of Bayer UK appearing on various documents later in the 1980s. Bayer UK become, for example, the distributor for heat-treated Koate in 1988, although the product licence is in the name of Miles Laboratories Limited. Then from 1990 onwards Cutter products are imported by Bayer UK in place of Miles Limited.

So we have this relationship with Bayer UK, with its various different name changes, and then, in the UK, Miles Laboratories Limited and Cutter Laboratories Limited, they are effectively sister companies. Cutter Laboratories Limited as a UK company was established in I think 1979. The US manifestation of Cutter was Cutter Laboratories Inc, which was acquired by Bayer AG in 1974. Cutter Laboratories Inc in turn had been originally founded in the States in 1897. So

that was one company involved in the manufacture of blood products in the States. And a lot of the licence documents that we'll look at tomorrow identify the manufacturer as Cutter Laboratories.

After Bayer acquired Cutter Laboratories in the States, it also acquired a company called Tuta (UK) Limited which supplied blood bags in the UK, and the name of TUTA was changed to Cutter Laboratories Limited. So that's the UK Cutter company. And that explains why there will be some documents that refer to Tuta.

Again, we'll see as we go through, when we get to 1980 we see product licence applications in relation to Koate being made by Cutter Laboratories Limited, and it's Cutter Laboratories Limited which is granted the licence, the product licence in relation to Koate, in the early 1980s.

We then have Miles Laboratories. The American company Miles Laboratories Inc was purchased in 1978 by Bayer, and Bayer therefore became the ultimate parent company of Miles Laboratories Inc, and then the UK branch, which was Miles Laboratories Limited, which was established in 1946.

Then in the early 1980s, there's a degree of rationalisation and merger between the companies.

Miles and Cutter in the US merge, and Cutter Laboratories Limited in the UK is acquired by Miles Laboratories Limited in the UK. There's a document, we wouldn't need to go to it even if we could, but I'll give the reference for the transcript, BAYP0004280, and page 4 of that document, which are the minutes of a board of directors of Cutter Laboratories Inc in the States in November '82, talks about Cutter and Miles having combined to form a single business with the critical mass necessary to compete successfully in the healthcare market.

We see then, if we look at what was happening in the UK, a meeting taking place around the same time, autumn of 1982, between the Department of Health and representatives of Cutter Laboratories Inc and Miles Laboratories Inc, to talk about the practicalities of transferring the responsibilities for Koate from Cutter Laboratories to Miles Laboratories.

What we will then see, quite often on the documents thereafter, is Cutter Laboratories described as a division of Miles Laboratories Inc in the US, and a lot of the documents will say "Cutter, Division of Miles", as a result.

We then, I think, get to a point in time, I think it's 1983, but we can check when we look at the

licence applications tomorrow, when the product licence begins to be held by Miles Laboratories Limited, rather than Cutter Laboratories Limited, but it's still the same product we're talking about, Koate, and certainly there's a product licence granted to Miles Laboratories August 1983.

Then, again, I'll pick it up as we look at the licensing applications tomorrow, the close relationship between these various entities is apparent when we look, for example, at a product licence application for the heat-treated version of the Factor VIII concentrate, Koate-HT. Miles Laboratories Limited in the UK is responsible for packaging and labelling, it's the product licence holder. The product is described as manufactured by the Cutter division of Miles Laboratories Inc in the US.

Then there comes a point in time, I think it's in the late 1980s, where the trading name effectively, or the way in which the organisation is described, is then Cutter Biological, described in one of the product licences as a trading style of Bayer UK Limited.

None of it, I think, particularly matters for the purposes of the issues with which you are concerned

but I hope that helps explain why we will look at documents at different times and they will all be about Koate, or sometimes they will be about Konyne, the Factor IX product, and they might say Bayer, they might say Cutter, they might say Miles, they might say two or three of those names at any one particular point in time. But we're talking essentially about companies which had relationships with one another and ultimately were owned by Bayer AG.

Sir, that's all I wanted to say about the corporate structure. In a statement that we have from the head of legal and compliance at Bayer plc, Mr Wilkinson, and again, I'll just read the reference into the transcript, it's WITN2988001, as well as giving a detailed account of these various companies and their relationships, he has set out in the statement his understanding of Bayer plc's archiving system and document retention policy, and he explains why there were certain documents that had been retained, not least because of litigation. He describes how there were documents that had been held by law firms acting for various incarnations of the corporate entities at different points, and explains how all material identified as relevant was then drawn together and identified to the Inquiry in the form of

a schedule.

So that's why we have documents that we'll often see with the URN "BAYP" for Bayer. They've been provided to us through that route. More often than not, they're more Cutter or Miles documents. So in view of the fact that we don't have any further documents to display and the fact that I'm going to go on to look at the licence application, for which we do need the documents, I am going to suggest that we take a -- have a slightly early finish and sort out the documents overnight so we can start again with Bayer's licensing at ten o'clock tomorrow.

SIR BRIAN LANGSTAFF: Right. Well, let's do that, thank you very much. So it's ten o'clock tomorrow for more about Bayer, Cutter, Miles and Speywood.

(4.14 pm)

(The hearing adjourned until 10.00 am the following day)

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