**Tuesday, 5 October 2021**

**(10.00 am)**

**Presentation from Counsel to the Inquiry on the Pharmaceutical Companies (continued)**

**MR HILL:** Sir, we're going to return today to the Speywood presentation, focusing in particular on porcine Factor VIII, and then turn to the last of our company presentations in the current stage, which is on Alpha, Abbott and Grifols. Before I go to porcine Factor VIII with Speywood, I would like to just return to one point about Speywood's licensing and importation of the product Humanate, and you will remember, sir, that Humanate was Koate in a rebranded bottle that Speywood imported, having ceased to have an agreement directly with Cutter.

In January 1981, as we saw, the Committee on Safety of Medicines had advised that the product licence be varied because of concerns about tracing the origin of the product back to the manufacturer and, indeed, back to the donors. You will also recall, sir, that the accountant's report we looked at said that Speywood continued to sell Humanate until June 1981, and there was that difference between January and June that we couldn't explain.

With thanks to Mr Evans, a document throws



a little further light on this. Can we have on screen, please, Soumik, MHRA0000049.

This is a document taken from the NIBSC archives showing what was done with batches of Humanate that were received. We can see the top entry is for batch number 4802. It is stated that a protocol and samples were received on 31 October 1980, and the fifth column along says that there were four times 270 units of product that were provided.

The next column says, "Date substance released", and it's either 13 or 23 December 1980. The next entry for batch number 2805 shows that the samples were received on 21 January 1981, which is around the time of the CSM meeting, two times 520 international units. The date the substance released says -- has brackets around it saying 20 March 1981 and the comments are "Release not recommended".

An interpretation of this document is that the first batch that's listed there was released in December 1980 and, obviously, was available for sale from Speywood after December 1980, and it may be that that batch was still being sold as of June 1981, and that the next batch received was not released, and the brackets may indicate, perhaps, that it was returned to the importer.



We don't know, but that may explain why there is this gap between January 1981, and the CSM meeting, and June 1981, the point at which the last part of Humanate was sold.

**SIR BRIAN LANGSTAFF:** On the face of it, one would expect the batch release system to operate in advance. Plainly, that appears to be the case. The samples and the protocol are received, and Factor 4802 in October, and it's released three months later, in effect, at the end of December, 23 December. I read that certainly as a "2" and not a "1".

There is a three-month interval, November, December, January, before 2805 goes for its protocol. That's the next batch. So presumably a batch covers a good three-months' supply, and the only question then is when the batch starts to be sold, because presumably by the time it's released, there is still sufficient in the stores which is being cleared to cover a few weeks' supply. You wouldn't expect just-in-time management in those days, the same way as you might today, so it's perfectly conceivable -- it's likely it would have gone beyond the end of March, supply, for a short while. That would fit with the information you gave me last week.

**MR HILL:** It would sir, yes.



**SIR BRIAN LANGSTAFF:** At the moment, those are the inferences which occur to me. I will obviously listen in due course to anyone who may want to take a different view.

**MR HILL:** Thank you, sir. I will move, with that, to porcine Factor VIII.

We heard a little about this on Friday. We asked some questions of Ms Middleton about porcine Factor VIII. Her involvement in the product was limited, as we know. But we do have quite a lot of documentary evidence about it.

We know that from its establishment in 1973, Speywood Laboratories had investigated the development of animal Factor VIII for the treatment of haemophilia patients with high inhibitor levels. There was initially work done on bovine and porcine Factor VIII, but increasingly, the porcine Factor VIII became the better route that was being explored. The initial product rights and basic know-how were purchased from a firm called Maws Limited and that seems to have worked in cooperation with the Protein Fractionation Laboratory in Oxford under Dr Biggs. The references there are IPSN0000167_004, IPSN0000089_001.

In 1975, Speywood registered the trade name "Hyate"; the reference for that is IPSN0000089_001.

There's evidence from various documents that show some financial support, albeit at a limited level, from both The Haemophilia Society and the Department of Industry during the 1970s for the development of that product.

Professor Bloom wrote an article in 1978 in the British Journal of Haematology, volume 40, pages 21 to 27, which referred, among other matters, to the use of porcine products in patients with Factor VIII inhibitors. He said, and I quote:

"This material, however, causes thrombocytopenia. It is also expensive and may increase the immunological logical response. It is rarely if ever needed."

The reference for that, sir, is SHPL0000108_034.

When writing this section of the article, Professor Bloom referred to Speywood as a provider of porcine Factor VIII but it's not clear whether or not his cements are specifically related to the Speywood product or are a more general comment on the view of porcine Factor VIII at that time, 1978.

You may recall, sir, that on Friday Ms Middleton referred to the traditional view of porcine Factor VIII as having a very bad reputation because of all of these complications with it, and she mentioned



thrombocytopenia, which is the below platelet count, that was particularly connected with it and the risk of a response creating inhibitors, rendering a patient who was already difficult to treat even more difficult to treat.

That article was written before Speywood concluded a licence agreement with Monsanto. That happened, we think, in 1979, and it was the licence agreement for the use of polyelectrolyte technology. The reference is IPSN0000134_001. We heard from Ms Middleton what polyelectrolyte technology involved, and it was used both for the porcine product and for the human product and, indeed, it seems to have been more successful in terms of the porcine product, and more successful in separating the Factor VIII molecule from other molecules within the pig plasma.

By the 7 December 1979, Hyate:C was, according to a letter to Professor Bloom, "ready for clinical use" following extensive animal trials.

It doesn't appear that a clinical trial certificate was obtained at this time, and its use was restricted to response to medical emergencies. So it would have been on a named-patient basis and only in extremis. References are of the -- the reference is IPSN0000334_001 and a further reference at



IPSN0000324_011.

That's 7 December 1979 saying that it's ready for use. The first usage appears to have come in June 1980, and if we could have on screen, please, Soumik, IPSN0000331_001.

This is a letter to Dr Aronstam at Treloar dated 30 July 1980. We looked at it I think on Friday in another context, but I'm just going to concentrate now on the porcine element. The letter is from Mr Williams, the marketing director. He wrote, in respect of porcine Factor VIII:

"The first successful result of our research programme [this is the second paragraph sorry], is the availability of a preparation of porcine Factor VIII:C, Hyate:C, for the treatment of inhibitor patients. This product has now been used for the first time in man. We are delighted to report that the treatment, in a life-threatening situation, was entirely problem-free. Thrombocytopenia was completely absent and there were no antigenic reactions. It would therefore appear that the criteria for use of porcine material can be relaxed."

The points that I take from this letter, sir, are this: firstly, that this is a reference to a new generation of porcine material using the



polyelectrolyte fractionation; second, that it has led to a product of increased purity; and third, that the first use had shown that the thrombocytopenia that had previously been such a concern about the use of porcine Factor VIII wasn't present in that patient and, indeed, that there were no antigenic reactions.

So an optimistic report of a first use. The reference to the criteria for the use of porcine material being relaxed, as I understand it, is a reference to the fact that the previous stipulation that this should only be used in life-threatening emergencies could perhaps now be relaxed and it could be used with other patients.

There is no clinical trial certificate. There is no product licence. So it would have had to have been used on a named-patient basis.

There does appear to have been some additional use of the product because, by October, we can see that there have been more than 60 uses. Could we have IPSN0000338_001, please, Soumik.

This is a letter to Dr Evans at the Royal Manchester Children's Hospital, dated 31 October 1980, again from Mr Williams. We looked at this letter before about the section dealing with Humanate and the fact that Dr Williams is telling Dr Evans that it is

actually Koate but he asked him to keep that information confidential.

If we go to the fourth substantive paragraph, starting "Incidentally", Mr Williams wrote this:

"Incidentally, we have now had considerable successes with our new porcine factor VIII:C preparation, Hyate:C. It appears that we have completely removed the thrombocytopenia activity and that other clinical side-effects are minimal. In over sixty transfusions, we have seen around five minor shivering episodes, which can be adequately covered with hydrocortisone and Piriton.

"The thing that we did not expect, is that Hyate:C, [I'm afraid I can't quite decipher that] in [something] cases so far, has not resulted in a rise" --

**SIR BRIAN LANGSTAFF:** I think it's probably something typed over, but it looks like "all the", with the something underlying it.

**MR HILL:** I think that's right, sir. Yes, it's typed over, so it's:

"... the thing we did not expect, is that Hyate:C, in all the cases so far, has not resulted in a rise in the pig antibody levels, even several weeks post treatment. Two of the cases treated have



received multiple injections at varying intervals for different bleeding episodes. In no case has there been a problem, even in the most desperate life-threatening circumstances.

"If you have an inhibitor problem, I would be very grateful if you can consider using this material."

So we can see there the report from Mr William's perspective on over 60 uses by October. I note, sir, the prohibition that was in place at the time on advertising products which did not have a product licence.

The use of Hyate:C attracted comment in the medical literature from 24 January 1981. Could we have on screen, please, IPSN0000005_023.

This, sir, is the first reference to Hyate:C that I have found, at least, in the medical literature.

We can see -- if we could expand the page, please, Soumik. This is from the British Medical Journal, volume 282, 24 January 1981. The report comes from Dr Mayne and Drs Madden, Crothers and Ingles from Belfast. It is a letter, and it refers to the highly purified porcine Factor VIII in haemophilia A with inhibitors to Factor VIII. So it's



specifically referring to the use of this product in inhibitor patients.

The start of the letter refers to the difficulties in treating such patients. In the last sentence of the first paragraph, the authors say:

"Therefore, we would like to report our experience with a new compound, highly purified porcine Factor VIII, (Hyate, Speywood).

"A 16-year-old boy was admitted with haemarthrosis in his right elbow and right knee. He had been diagnosed as having haemophilia A six months after birth with a Factor VIII:C level of less than 1 ..."

I'm afraid I can't decipher that.

**SIR BRIAN LANGSTAFF:** That's 1 per cent.

**MR HILL:** Is it 1 per cent?

"Ten years later, an inhibitor to Factor VIII was detected. After that, bleeding episodes were treated with FEIBA (Immuno Ltd) or Factor IX concentrates from Oxford. His new inhibitor varied from 2.0 to 78 RB units (New Oxford). On this occasion, his haemarthroses was treated with Factor IX concentrate and subsided. However, he then had a melaena and subsequently passed frank blood per rectum. A total of 2,720 units of Factor VIII



concentrate was given, but despite this, he continued to bleed. We then decided to change to Hyate. This was given as an infusion of 2,200 units over 6 hours. This was continued for 36 hours, and a total of 13,200 units were given. There was a very satisfactory rise in Factor VIII levels [there's reference to a table that is contained in the article], and his bleeding came under rapid control. There was a modest rise in human Factor VIII antibody noted, but porcine Factor VIII antibodies failed to develop."

Final paragraph:

"Previous attempts at treating haemophilia A with porcine Factor VIII were abandoned because of allergic reactions and because the presence of platelet aggregating factor caused thrombocytopenia. Neither was a problem in this patient. Therefore, we conclude that highly purified porcine Factor VIII (Hyate) is of value in treating haemophiliacs who have developed antibodies to Factor VIII."

So an optimistic -- sorry, not optimistic, but a positive report on Hyate:C from Dr Mayne in January 1981, specifically referring to the importance of the fact that the purified product didn't seem to do what the old product did, in terms of low platelet counts and in terms of creating inhibitors in the

patient.

There is some evidence from within Speywood that, by January 1981, considerable optimism was being shown and considerable ambition about the prospects of this product. If we could have, please, IPSN0000260_010.

This is a handwritten document. We don't know who the author is. It's headed "Monsanto". It's recovered from the Speywood files. What the author wrote is this:

"I am now reasonably confident that porcine Factor VIII can completely replace the need for human Factor VIII preparations. The timetable for such an operation is complex and difficult to predict. However, a product licence in the UK should be feasible within 3 years; USA within 5 years. Third-world countries could supply an almost immediate market, and sales without a licence to inhibitor patients could be very substantial.

"To protect our interests, we must ensure that the polyelectrolyte patents are strengthened and policed properly. The polymers must not get into the hands of our competitors. Monsanto can and must provide this protection, including registration of new patents.



"In the anticipated agreement with Monsanto, we must try and establish the right to sell animal Factor VIII:C worldwide in perpetuity at a 5-year lead time before Monsanto can manufacture animal Factor VIII:C itself."

So we can tell from that that this is an internal Speywood document. The reference to porcine Factor VIII completely replacing human Factor VIII is made as of January 1981, but with the, you may feel, significant caveat that the timetable is complex and difficult to predict.

In the medical literature, there was a little more circumspection. Could we have, please, IPSN00000005_024, please, Soumik.

This is a case report from the British Medical Journal, dated 20 June 1981.

It is from the Department of Haematology in the Glasgow Royal Infirmary. It's Drs Erskine and Davidson. The case report deals with a severe anaphylactic reaction after the use of Hyate:C in a patient. The case details are given, I won't go through them. I will just turn to the comment, which is:

"Use of porcine factor VIII concentrates has previously been severely restricted because of



allergic reactions and thrombocytopenia. Hyate:C is a highly purified preparation of porcine factor VIII that contains only trace amounts of non-factor VIII protein, thus reducing side effects. Unfortunately, the severe reaction after its use in our patient suggests that, as with other porcine products, allergic reactions that might limit its usefulness may occur. A small test dose should therefore be administered before infusion of therapeutic doses to identify more clearly patients who might be at risk of developing such problems."

Then if we could go to page 2, please. This is a letter in response to that from Drs Kernoff and Tuddenham, from the Royal Free. They say, in the second paragraph:

"There is no doubt that polyelectrolyte-fractionated porcine factor VIII [Hyate] should be used with caution, but transfusion reactions severe enough to necessitate stopping therapy are unusual. Over the last year we have given 34 courses of PE porcine VIII therapy to eight patients with circulating antibodies to factor VIII ... Of a total 216 infusions, only one was followed by a reaction judged sufficiently severe to justify stopping treatment. Although reactions of lesser



degrees of severity are relatively common -- 27 infusions were followed by some significant reaction and 21 courses of therapy were complicated by at least one -- reactions were generally short lived, well tolerated by patients, and did not give rise to serious clinical concern."

If we could go down, please, to the penultimate paragraph beginning "Bleeding in patients", thank you:

"Bleeding in patients with anti-VIII [that's anti-Factor VIII] is often severe and difficult to control, and risks of therapy must be weighed against likely benefits. We have found PE porcine VIII to be highly effective in stopping major bleeding which has failed to respond to human factor VIII. It has also been used successfully to cover elective surgery. The material lacks several of the disadvantages of earlier or alternative preparations and we believe its introduction to be a real therapeutic advance. Porcine heparin and insulin given intravenously are rarely complicated by transfusion reactions and one is optimistic that the problems with [polyelectrolyte] porcine VIII can be similarly resolved. Meanwhile, we suggest that the material should be used only in major haemophilia centres, where adequate facilities and expertise are available for stringent monitoring. In

particular, we would urge that no surgical procedure should be undertaken without a full preoperative assessment of the characteristics of the patient's anti-VIII."

Dr Kernoff and Dr Tuddenham there responding to the letter which had cast some doubt on Hyate:C by giving their more positive experiences.

We looked on Friday at Dr Tuddenham's Toronto lecture from 1981. If we could have that on screen, please, IPSN0000156_101.

If we go to the fourth page of this, please. On Friday, we were concentrating on what Dr Tuddenham had said about human Factor VIII. In respect of porcine Factor VIII, he said this:

"Porcine [Factor] VIII is of course used for treatment of inhibitor patients, thrombocytopenia has been virtually eliminated as a side-effect and other adverse reactions are much less severe than with previous animal preparations. Haemophilia centres which have used Hyate:C report dramatic improvements in the life-style and morale of their inhibitor patients. The possibility of porcine [Factor] VIII:C being used for non-inhibitor patients in countries with a shortfall of human [Factor] VIII should now be seriously considered. Of course, viral hepatitis is



not present in porcine plasma and the product thus presents no risk of infection."

Professor Tuddenham gave evidence to this Inquiry on 22 October last year. I won't take you to that, sir, but he does comment on this at pages 54 to 55 of that evidence. He said that he was thinking primarily of countries in the developing world when he was saying that but we can see that, again, the prospect of Hyate:C porcine Factor VIII being used in non-inhibitor patients is being considered.

Can we have on screen, please, IPSN00000005_024, please, Soumik. Can we have page 3 of this document. A further piece of the letter from the medical journals. This from The Lancet dated 27 March 1982, so a little later in time, from doctors Hewitt, Mackie and Machin at the Middlesex Hospital. In the first paragraph, they say:

"The management of patients with haemophilia A who have an inhibitor to factor VIII:C, especially those who have previously had a classical anamnestic antibody response after infusion of human factor VIII, remains problematic. Excellent clinical responses have been reported with polyelectrolyte-fractionated highly purified porcine factor VIII concentrate [Hyate:C]. Most important has been the low incidence



of any appreciable rise in anti-human or anti-porcine inhibitor levels, despite prolonged therapy. We wish to report the use of this material in an inhibitor patient who responded at first but subsequently had a marked increase in an anti-human inhibitor and acquired a significant anti-porcine inhibitor with severe clinical bleeding unresponsive to highly purified porcine factor VIII."

The details are given; I won't go through those. If we could go to the penultimate paragraph, please, beginning "Although":

"Although haemostasis was at first well controlled the infusions of porcine factor VIII stimulated a brisk rise in an anti-human inhibitor followed by the rapid appearance of a discrete anti-porcine inhibitor. A subsequent infusion of porcine factor VIII failed to control bleeding and there was no rise in factor VIII:C level. Individual haemophiliac patients with inhibitors vary considerably in their clinical and immunological responses to the various therapeutic materials available. In particular, any new material should be carefully assessed in each inhibitor patient. In contrast to the previous reports we observed a marked [anamneasic] response ..."



**SIR BRIAN LANGSTAFF:** I think it's "anamnestic".

**MR HILL:** Anamnestic, sorry.

"... when purified porcine factor VIII was infused alone. This prohibited further effective therapy of this material when secondary haemorrhage occurred."

So a concern raised there about the development of an immune response to the porcine Factor VIII and, indeed, to human Factor VIII which renders the patient still harder to treat.

If we could have page 4 of that document, please, Soumik. A further report, this, from Thromb Haemostas of Stuttgart, volume 48 edition 2, page 238 from 1982, the letter is entitled "Immune Response Induced by Porcine Factor VIII in Severe Hemophiliacs with Antibody to [Factor] VIII", and it is from F Verroust and JP Allain of the CNTS in France.

I won't go through the entire document, sir, but it is another example of a patient who, having used Hyate:C, had an immune response to it. If we look at just the final paragraph, it states:

"In our experience, as already mentioned by Kernoff and Tuddenham, porcine factor VIII has been clinically effective and minimal adverse reactions were observed. However we have consistently observed

a significant rise of the antibody titre which does not allow to use Hyate C for haemorrhages but confines its use to life threatening bleeding episodes."

So a concern that there is a rise in inhibitor levels, which means that the product should only be used in extremis.

If we could also go, please, to BPLL0016008_034, this is a document that we looked at on Friday in the context of human Factor VIII. It is Dr Jim Smith's internal memo for BPL about a Speywood meeting at Uberlingen on 24 April 1982. As we know, Dr Smith was no fan of Speywood. He said that the meeting was intended to present the merits of porcine Factor VIII to influential German clinicians, and this is what he records of the meeting, in respect of porcine Factor VIII and, indeed, Factor IX, and he says:

"Only a few hundred treatments have been given, more than half by the Royal Free and many of those in one patient. Most clinicians would still give human VIII to low responders and possibly to high responders with a modest current titre. Some would use porcine VIII or FEIBA almost as a first resort in high responders, especially if an important organ can were threatened. One clinician had a patient on home-therapy with porcine VIII, which must be as



courageous (or foolhardy) as home-therapy on FEIBA. It was evidence that, especially on the Continent, there was a lot of 'me-too" among the less conservative clinicians, and also a great deal of patient pressure for whatever is new and preferably expensive.

"Most patients were said to get unwanted reactions at one time or another. The incidence of severe side-effects seemed to be about 5%. Only one frank case of a very severe thrombocytopenia had been seen, as one would expect from the low PAF (VIIIRAg) content; however, they hope to reduce the PAF content a further 10-fold by Sepharose chromatography. At least one serious reaction and clinical failure was attributed to early exposure to the old porcine concentrate. Most of the other reactions (pyrexia, bronchospasm, etc) seemed to be classified as alarming when first seen, but 'manageable' eg with adrenalin and steroids; some clinicians gave such cover through routinely along with the concentrate. This left an impression of a determination to try porcine VIII in a range of patients rather than to think clearly about optimal treatment for each individual.

"The other problem is that antibodies to either porcine or human VIII or both tend to develop,



although not always to the same titre or at the same time as would be expected after human VIII.

"Kasper [I take that to be a reference to Dr Kasper and we will come back to her] thought that there might be merit in treating mild haemophiliacs with porcine VIII to avoid the risk of transmitting hepatitis, but there seemed to be a consensus that this might risk production of cross-reacting antibodies."

We can see from both Dr Smith's report and from some of the medical literature that there is concern in 1982 about some of the side effects of using Hyate:C, despite the early optimism.

As of September 1982, the only formal trial of Hyate:C was taking place in the United States. The product was being used in the UK on a named-patient basis and had been since June 1980, as we have seen. The reference for that is IPSN0000398.

On 21 October 1982, Mr Williams wrote to Mr Sloggem of the DHSS about the regulatory position, and he expressed his intention to go for a full product licence for Hyate:C, as opposed to a clinical trial certificate. You will remember, sir, that the opposite approach was being taken for human Factor VIII and that an application for a clinical



trial certificate for that product was put in. The reference for that, IPSN0000277.

We saw on Friday a letter from Mr Heath to Mr Seymour of 26 November 1982, in which Mr Heath said that he had been advised by Mr Fowler of the DHSS that they were doing, and I quote "entirely the right thing" in going for a full product licence for Hyate:C. The reference to that is IPSN0000230.

Can we have on screen, please, but -- actually I won't put it up -- the Hyate marketing plan for 1983, a document that we looked at on Friday, IPSN0000025, set out an objective of a sales target of £1.32 million and capitalisation on probable regulatory approval in the UK in respect of Hyate:C.

It was said that the market segment most accessible to Hyate:C was "for high responder haemophilia A inhibitor market", which comprised about 1,688 patients in Western Europe, the USA and Japan. The value of that market -- sorry, I'm not -- that figure is incorrect, sir, forgive me. It's -- the inhibitor market in Western Europe, USA and Japan was valued at a total of £16.88 million based on various calculations that were contained in the business plan.

The same document records that in the UK the product was not licensed but was being used as a first

line of treatment at The Royal Free and at Belfast, and it was also being used as an alternate treatment in a further six centres.

If we could have on screen, please, Soumik, IPSN0000264. This is a letter from Mr Williams dated 16 February 1983. While the business plan had stressed the inhibitor market, Mr Williams, as we will see here, has some wider thoughts about the expansion of the product to non-inhibitor patients, as well. But what he wrote is this:

"During all the conversations which I have had with various clinicians in the past few weeks, the possibility of using porcine factor VIII:C for the treatment of non-inhibitor patients has been a major topic. In particular, Peter Kernoff and Margaret Hilgartner (Cornell University, New York), are most interested and I expect that one or other of them, hopefully both, will use the product for such a patient within the next two weeks.

"There are two prime indications:

"1. Mild haemophiliacs whose only normal exposure to human factor VIII is as cover for surgical procedures. They can thus be given serious liver problems from a single exposure."

I take that to be a reference to the risk of the



transmission of hepatitis.

"2. The growing body of patients who are refusing treatment with commercial factor VIII concentrates, because of the AIDS risk. Subject to availability, they can obviously be treated with single donor cryo for simple bleeds. However, when they have a major bleed or require surgery, there will inevitably be ..."

This is overwritten again, I think it's something --

**SIR BRIAN LANGSTAFF:** It looks like "dose volume".

**MR HILL:** "... a dose volume problem."

But the context suggests that the concern is that there is a risk of viral transmission of the product -- viral transmission when using human Factor VIII, which wouldn't be there if using porcine Factor VIII.

Back to the letter:

"All this places even greater importance on our programme for further purification of Hyate:C. I feel strongly that this should receive our major research effort during the next few months and would like to see a very tightly controlled programme, with material available for trial by the end of the summer. There is no doubt that other companies in our field will



also be looking at animal factor VIII. I know that some of them have expertise already available and we could very soon have a major competitor."

That is Mr Williams's letter to Mr Mottram, copied to Mr Heath, so an internal Speywood document, 16 February 1983 and, as we saw on Friday, sir, this is just before Speywood entered into a period of some corporate changes at the top of the company, with Mr Heath and Mr Williams, in effect, losing out to the investors' choice of executives and directors.

Correspondence from that same month, February 1983, showed some interest in Japan and the United States about the possible use of Hyate:C on non-inhibitor patients. The references are IPSN0000386 and IPSN0000224.

Despite that interest, as we will see shortly, when an application for a product licence was made, it was made specifically for the treatment of inhibitor patients.

That application was made on 29 November 1983. I note, sir, that the product will have been used for nearly three and a half years on a named-patient basis at that stage.

**SIR BRIAN LANGSTAFF:** Am I right in thinking it had never actually had a clinical trial as such?



**MR HILL:** It had never had a clinical trial certificate. It had been used in patients and reports had been given, but it hadn't -- as far as I'm aware, it was not subject to a formal clinical --

**SIR BRIAN LANGSTAFF:** So there had been no controlled trial? No drugs trial?

**MR HILL:** No, and there is some correspondence about this where Speywood point out that it's very difficult to establish such a trial because there are (a) very limited number of patients who might use the product, and (b) it was very difficult to establish what a controlled product should be because there was no equivalent product of porcine Factor VIII. There was ethical issues, I think, about trying to establish such a trial.

There had, however, been no application for a product licence, despite the product being used for nearly three and a half years.

The licence was eventually granted on 3 December 1984. The references for that are IPSN0000477 and MHRA0033477_011.

But it's helpful, I think, to look at some of the documentation about the product licence application. If we could have on screen, please, IPSN0000007_001.

We can see from the front page that this is the Speywood application for a product licence. If we could go to page 3, please, Soumik. This is the part four of that, which is the studies in humans.

On page 3, we can see that the name of the product is Hyate:C, but the application is being sought by Speywood Laboratories Ltd. The Wrexham address is given. And if we could go to the bottom of the page, please, the date is 29 November 1983, and it's signed by Mr Wain who was a director at that time.

If we could then turn to page 5, please. Section 4, "Uses", it's said:

"Hyate:C is intended for the treatment or prevention of bleeding in patients with haemophilia A who have inhibitors to Factor VIII:C."

So very expressly stated to be for the use of inhibitor patients. That was also stated in the covering letter, which I need not take you to, but the reference is MHRA0033477_003.

If you could go to the bottom of that page, please, there is perhaps some explanation as to why.

"Contraindications, precautions and warnings:

"There are no known contraindications to Hyate:C.



"Infusion reactions.

"Despite its very low protein content, Hyate:C may on occasion give rise to reactions such as fever, chills, headache, nausea, vomiting, and skin rashes. Such reactions are more common after the first infusion of a course of treatment and tend to lessen in frequency and severity as further infusions are given. Hydrocortisone and/or antihistamine may alleviate these effects and may be prescribed as a precautionary measure."

Over the page, please.

"Immune response to Hyate:C.

"In some patients, treatment with Hyate:C is followed by a rise in levels of inhibitor to both human and porcine Factor VIII:C. Inhibitor levels to both porcine and human Factor VIII:C should therefore be determined at regular intervals after treatment.

"Effect on the platelet count:

"A significant fall in the patient's platelet count has only very rarely been reported after infusion of Hyate:C. However, regular monitoring of a platelet count during the treatment period is recommended."

Then "Caution", in capital letters:

"Adrenaline, hydrocortisone and facilities for



resuscitation should be immediately available for the treatment of acute infusion reactions."

Page 17, please, Soumik. If we go to the third paragraph down there, "Hyate:C has been used". Thank you:

"Hyate:C has been used clinically in the United Kingdom, Italy, France, Sweden and the USA for the emergency treatment or prevention of bleeding episodes in inhibitor patients in whom no other form of treatment had proved effective. The product was used on a named-patient basis in all countries except the USA where an IND is held for Hyate:C."

That's the equivalent, as I understand it, of a clinical trial certificate in the UK, so there was a trial being done in the United States:

"The effectiveness of Hyate:C and its side effects were monitored as part of the normal course of treatment, and these results are presented in this section. Although the advantages of comparative clinical trials are well appreciated, it was not considered feasible to carry out such a study on Hyate:C for the following reasons."

This is the one that I was raising earlier, sir:

"Possible comparative forms of treatment."

And what it says in this paragraph is:



"The concentrates of clotting factors commonly used in the treatment of inhibitor patients are human VIII:C, non-activated prothrombin complex concentrates and activated prothrombin complex concentrates. The rationale for the latter two forms of treatment is not clearly understood, and their effectiveness cannot be assessed by objective laboratory methods and has thus not yet been fully evaluated. In addition, the activated prothrombin complex concentrates are not licensed in the UK. Human Factor VIII:C would therefore seem to be the most suitable choice of comparative treatment."

And we go on:

"It seems indisputable that human VIII:C should be the treatment of choice for those patients who respond favourably and do not show significant increases in inhibitor titre as a result of treatment. However, the patients for whom Hyate:C is most beneficial are frequently those for whom human VIII:C either is ineffective at practical dose levels or produces an undesirably high amnestic response in antibody titre. Thus, if patients are selected for treatment with Hyate:C on the basis of their unsuitability for treatment with human VIII:C, this negates the rationale for a comparative study of the

two concentrates."

You can see there, sir, why it is they felt it was difficult, or indeed impossible, to establish an effective trial with a controlled product.

I draw your attention, sir, to the first line of that sentence, in light of the discussion that there had been about the possibility of using Hyate:C for non-inhibitor patients. I read it again:

"It seems indisputable that human VIII:C should be the treatment of choice for those patients who respond favourably and do not show significant increases in inhibitor titre as a result of treatment."

So in the product licence application for Hyate:C, there is an acceptance that human Factor VIII is the product of choice for non-inhibitor patients. And as we have seen in the list of potential side effects, you can understand why that view was taken at that time.

At page 19 of this document, there is a list of the 144 treatment episodes that had been reported. I won't go through that, sir, but we can see there the number of reactions; a small number, but listed and set out in the application.

And if we go to page 20, please, the



conclusions, it says this:

"In the management of haemorrhagic disorders, prompt and effective treatment is vital. Any delay may lead to irreversible damage to the patient.

"Most haemophiliacs with inhibitors live with the constant fear that a major haemorrhage may prove unresponsive to conventional therapy and may lead to death or permanent disablement. Even minor haemorrhages may lead to hospitalisation, and surgery of any kind is hazardous, if not impossible.

"Hyate:C has indisputably proved life-saving in a number of cases and offers certain patients the opportunity of resuming a comparatively normal lifestyle. Under these circumstances, the small degree of risk related to the possible side effects of the product is thought to be amply justified."

That is the case made for Hyate:C, but it is made in respect of inhibitor patients only.

Submitted as part of that application is an article by Drs Kernoff, Thomas, Lilley, Matthews, Goldman and Tuddenham from the Royal Free. It's IPSN0000005_007.

The paper is entitled "Clinical experience with polyelectrolyte fractionated porcine Factor VIII concentrate in the treatment of haemophiliacs with



antibodies to Factor VIII."

And you will remember, sir, that the Royal Free, and particularly Drs Kernoff and Tuddenham, were two of the supporters, if I may put it that way, of Hyate:C. Two of the more enthusiastic clinicians.

If we could go to page 2 of the document, please, Soumik. Just to pick up in the second sentence that:

"Over an 18-month period, eight patients with Factor VIII inhibitors were treated with 45 courses, 297 infusions, of polyelectrolyte fractionated porcine Factor VIII."

So that's Hyate:C.

Then the document goes on to record the observations on those patients. I won't go through all of it.

If we could turn to page 18, please, the "Discussion" section. Again, I will summarise this, rather than reading from it. The authors found porcine Factor VIII to be an effective treatment. They developed a strategy whereby patients with low inhibitor levels were usually treated with human Factor VIII. Those with intermediate levels were generally treated with porcine Factor VIII, by which they meant Hyate:C, and generally had an excellent



clinical response to the product. And then over on to the next page, please.

**SIR BRIAN LANGSTAFF:** Well, if we go down just five lines there:

"The relatively high risk ..."

**MR HILL:** "The relatively high risk of adverse effects is acceptable only because of the inherently serious nature of the disorder and the lack of reliably effective alternatives."

**SIR BRIAN LANGSTAFF:** Yes.

**MR HILL:** The final stage of the strategy is that they found that porcine Factor VIII was of limited -- or their impression was that it was of limited effect in patients with high levels of inhibitors, although they had very few such patients.

If we could go over, please, to page 20. I think this captures the essence of the report. From the paragraph starting "Although", it says:

"Although porcine VIII is an obviously much improved version of the conventionally fractionated product, we have encountered all the problems of the older material, albeit infrequently and/or in a mild form. Of most concern has been the occurrence of infusion reactions which, because of their typical clinical characteristics, seem most likely to be

caused by contaminating pyrogens or endotoxin, rather than by porcine protein per se. We have only once encountered a reaction which was sufficiently severe to necessitate stopping treatment, and our general impression is that the problem has lessened markedly over the last year perhaps because improvements have now been made in blood collection and fractionation procedures.

"While it seems likely that this problem may be resolved in the near future, the fact that major reactions have also been seen elsewhere leads us to recommend that PE porcine VIII should not at present be used outside major Haemophilia Centres where adequate facilities and expertise are available for stringent monitoring. In our view, the product is not yet suitable for use in home treatment programmes."

Over to the next page, please.

"A principal disadvantage of conventionally fractionated porcine VIII -- the restriction in number and duration of courses of treatment which could be given to individual patients -- seems to have been largely overcome. In some patients, it seems likely that repeated infusions of porcine VIII over a long period may provoke changes in anti-VIII specificity which might diminish the advantage of the porcine



product. Whether this will prove to be a clinical problem will only be known by longer follow-up."

So a concern there that not all of the consequences are known at that time.

If we could go over to the final page, please. Final two sentences of this report:

"It will also be important to obtain evidence on the potential advantages of the material -- possible reduced or absent risk of transmission of human hepatitis viruses. It seems beyond doubt that use of porcine VIII to treat patients with inhibitors should result in conservation of human blood product resources."

So some advantages to the product, sir, but it's fair to say that Drs Kernoff and Tuddenham were clear that, at that stage in its development, its use should be restricted to major Haemophilia Centres because of the adverse risks associated with it.

The Committee on Safety of Medicines considered the application on 22 and 23 March 1984. I won't take you to it, but the reference is MHRA0033475_018. There were also reports from the sub committee on the safety, efficacy and adverse reactions, and on the biologicals sub committee. References are MHRA0033476_009.



The CSM supported the -- or advised the granting of the licence, subject to further information being provided. It seems to have taken some time before that information was provided, and the licence was eventually granted in December 1984.

An internal document from Speywood. IPSN0000378_001. This is a memorandum from Mr Mottram to the chairman and managing director of Porton International. It's dated July 1984, so in the period between the application and the granting of the licence. This is at a time when the new management of Speywood is taken over. And if we could have a look at the second page, please, we'll see what Mr Mottram says about price -- the price of the product.

He says:

"Eighteen months ago, Hyate:C was priced at 16p per unit to UK and European hospitals. The previous management considered that a low price in comparison with the two competitive products FEIBA and Autoplex was appropriate. This policy was a disaster. When distributors are employed, then any price to hospitals has to be discounted by 30%-50% to arrive at the net return to Speywood. The company's operating expenses, with the utmost economy, are unlikely to be less than £150,000 per month. It follows, therefore, that a 16p



list price involves less than 10p net return, and a monthly sales performance in excess of 1.5 million units is necessary to achieve break even."

So a criticism there of the previous pricing policy. If we could go down a couple of paragraphs, it says:

"For Speywood to be profitable, Hyate:C must have a USA list price of over 60 cents per unit and a European list price of 40p or more."

I won't go through the rest of this document sir, but we can see there the concerns that the new management had about the approach of the old management.

IPSN0000036_012, please, Soumik. This is another Speywood document, which goes through the current approaches to the treatment of inhibitor patients in the UK on a centre-by-centre basis. It notes that, out of the total -- this is based on 1983, the document is dated 2 November 1984, we can see that on the bottom left-hand corner of that page, please, Soumik.

It says that in 1983 there were 273 inhibitor patients out of a total of 4,716 patients. I won't go through each of the centres but it is fair to say that, in respect of many of them, a consideration that

was expressed to the Speywood representatives was the cost of the product.

If we could turn, please, to page 9 and something of a concluding section, "Comments on the future potential for Hyate:C". It says this:

"All of the Reference Centre Directors were of the opinion that Hyate:C is of value in treating high responder inhibitor patients and that if the inhibitor cross reactivity is favourable, it should be the treatment of choice for severe bleeds or surgery. No-one expressed any serious worries about adverse reactions, although potential immunogenicity, ie provocation of an anamnestic response was thought by most to be an important consideration in treating minor bleeds.

"Most centres thought that cost was the most significant factor in deciding which product to use for a mild bleed, and efficacy and cost when deciding for a severe bleed. The cost of using porcine [Factor] VIII relative to using high dose human [Factor] VIII was frequently mentioned (porcine being approximately 4 times the price of human) as was the cost relative to FEIBA, (which is currently 20p/unit).

"Several centres would like to have Hyate:C in stock on a 'sale or return' basis and feel that in



that case they would be more likely to use it in an emergency."

I will leave that document there, sir, but we can see the significance of cost in the market penetration of Hyate:C.

One further point which goes to the question of why Hyate:C wasn't used more widely in non-inhibitor patients is that the 1986 Speywood marketing plan records that it had to be stored at minus 15 degrees Celsius, which, obviously contrasted with storage at 4 degrees Celsius in the fridge for a factor concentrate, minus 15 would obviously require a freezer. The reference for that is IPSN0000580_001.

The company Speywood, and Porton, which took it over, had some success in marketing Hyate:C internationally. Product licences were obtained in Canada and the United States in 1986, IPSN0000477, and there was marketing in France and Germany as well, IPSN0000420, though the marketing efforts involved an emphasis on viral safety of the product, the references for that are IPSN0000133_002, and IPSN0000148_012.

Just to close this section, sir, with two further observations. If we could have IPSN0000073_001 on screen, please.



This is an article by an American haemophilia doctor, Dr Carol Kasper. You will recall that she was mentioned in the 1982 meeting in Germany in Dr Smith's note. This is an article in Hemophilia Notes, a publication by the US National Hemophilia Federation.

I won't go through the entire document. It's about porcine Factor VIII, as we can see from the title. If we could just look at the last two paragraphs beginning "Porcine factor VIII has not been known". I should say this is dated spring 1987.

What Dr Kasper wrote is this:

"Porcine factor VIII has not been known to transmit hepatitis or human immunodeficiency virus ... The pigs are raised in isolated herds in rural England. Thus, the concentrate has been especially appropriate for persons not yet exposed to hepatitis or HIV, such as patients who don't have congenital hemophilia but have developed an antibody to Factor VIII as an autoimmune disorder. Another advantage of porcine factor VIII is that some patients with hemophilia and inhibitors don't show as much stimulation of the inhibitor level after porcine concentrate use as they do after human concentrate use. A few such patients in England have used the



porcine concentrate routinely for hemorrhages for years without any rise in inhibitor level. Most persons who are treated intensively with porcine concentrate (for example, for critical hemorrhages or for surgery) develop increased levels of inhibitor to porcine and human factor VIII, and the level of inhibitor to porcine factor VIII may get as high as that to human factor VIII.

"We welcome porcine factor VIII concentrate as one more option in our array of methods of managing inhibitors."

An article by Dr Kasper from 1989 in the publication Progress in Hemostasis and Thrombosis, volume 9, pages 57-86, entitled "Treatment of Factor VIII inhibitors", recorded that, and I quote:

"There have been no reports of transmission of blood borne infections with porcine factor VIII concentrate. Therefore, it has been popular for use in patients not previously exposed to blood products such as patients with auto antibodies."

The reference to that is IPSN0000057_093, so we can see from those articles in 1977 and 1979 that porcine Factor VIII had a good record on viral safety but it was -- when we put it this way -- it was not seen as a magic bullet that could be used in all

circumstances. There were side effects and there were risks to using it, particularly where it was used in the treatment of critical haemorrhages because of the development of inhibitors.

That, sir, is all I intend to say about porcine Factor VIII and, indeed, all I intend to say about Speywood. We will be turning to the final presentation, which is about a series of companies, Abbott, Alpha and Grifols, and I wonder if that may be best done after a break.

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

**(11.13 am)**

**(A short break)**

**(11.45 am)**

**SIR BRIAN LANGSTAFF:** Yes?

**MR HILL:** Sir, just before I turn to Abbott, Alpha, Grifols, if I could just correct a reference from this morning. The Carol Kasper article in Hemophilia Notes, the reference should be IPSN0000073_003.

The final presentation of these few weeks is about a series of interrelated companies, Abbott, Alpha and Grifols. I will explain in due course how the companies interacted with one another.

The focus is going to be on the 1970s and on the



1980s and on variants of the Factor VIII product, Profilate.

As a result the concentration will be on the company Abbott, who manufactured and supplied Profilate until around 1978 and then on Alpha, who did so thereafter, although there is a period of transition in 1978.

There are also UK subsidiary companies and at least one European company that operated in the UK and they will be introduced in due course. To date, no disclosure has been provided directly to the Inquiry by Abbott, Alpha or Grifols, whether through their UK or their multinational entities. This has made the task of investigating the story of Profilate somewhat more difficult. We had less material and so we know less about it. We are often reliant on what others say about what Abbott and Alpha were doing, rather than what the company itself says.

For example, we see the DHSS's view in internal memoranda and we see what competitors are saying in their sales memoranda. So we should keep that in mind as we go through.

The approach that I'm going to take is firstly to consider the corporate structure of the companies and go into a little detail about why we don't have



disclosure.

Then to look at Profilate, the initial provision to the UK market of this Factor VIII product in unheated form, and the limited market penetration that it achieved. Then there could be introduction of the heat-treated product from 1984, and it was a relatively early entry on to the market of a heat-treated product and it had considerable success.

We will briefly look at the replacement of Profilate Heat Treatment, HT, with Profilate SD, a solvent detergent product, in and around 1989 and 1990. For each of these products we'll look at the licensing position and the communication of risk associated with the product, and we will do that chronologically rather than separating those two elements out in this instance.

Included in that consideration of the licensing position will be the thought that was given to the possibility of suspending the licence for Profilate HT in the late 1980s, due to concerns arising from a factory inspection.

We will then, after looking at Profilate, turn briefly to a Factor IX product, Profilnine, but, as this was not widely used in the UK, I don't intend to



spend much time on it. There is a period in 1984 to 1985 when heat-treated Profilnine was available and was taken up by UK haemophilia doctors because there was no equivalent heat-treated NHS product.

Finally, we will turn to the plasma sources and the donors. Here, as with elsewhere, I would remind everyone that we will be coming back in November to look at the response to risk of the companies in the US, in particular in response to AIDS, but also in response to hepatitis.

Here, we're going to use some of the information that we're going to come back to in November to try to set out what the position was in the 1970s and the 1980s before the changes were made in response to AIDS.

So we begin then with corporate structure and with Abbott. This is an American company that dates back to 1888 and Dr Wallace Abbott of Chicago. The company was incorporated in 1984 and was renamed Abbott in 1915. An office was first opened in England in 1907, and a UK subsidiary was incorporated on 24 June 1937. This was renamed as Abbott Laboratories Limited in August 1949.

Abbott's blood products, including factor concentrates, were manufactured and sold by its

Scientific Products Division and those products, of course, included Profilate.

In August 1978, Abbott US, the American company, sold the Scientific Products Division to the newly formed Alpha Therapeutic Corporation. This is the American company and I will, at points, refer to it as "Alpha US". Alpha US was, at that time, owned by the Green Cross Corporation of Japan. In a letter explaining the position to customers, regulators and other interested parties, it was stated that Alpha US had acquired, and I quote, "all the personnel, premises, plant and knowhow and expertise of the former Abbott division". So that's the Scientific Products Division. That's DHSC002197_172.

The Krever Report described Alpha Therapeutic Corporation as follows, this is the US company, and I quote:

"Alpha, owned by the Japanese pharmaceutical company Green Cross, is one of the major producers of blood products in the world. In 1981 it sold more than US$10 million worth of products in the United States. By 1988, this figure had increased to US$38 million."

That's pages 735 and 736 of the Krever Report.

Initially, the British operations of Alpha US



seemed to have been in the hands of a German company called Alpha Therapeutic GmbH. However, a UK subsidiary, Alpha Therapeutic Limited, was established in 1979. And again, the clue is the use of the word "Limited" indicating the UK company, as opposed to the US or German company.

1994 company filings, which are available at Companies House, record that the UK subsidiary was wholly owned by Alpha US, and that the ultimate holding company was the Green Cross Corporation. So Green Cross sits at the top, then Alpha US, then the UK subsidiary.

A further reference is DHSC0002197_168.

According to records held the Companies House in 1977 a Spanish company, Grupo Grifols SA, purchased a majority shareholding in the British subsidiary, Alpha Therapeutic limited and became its holding company, though Green Cross continued to be listed as the ultimate holding company. The UK company's name was changed to Grifols (UK) Limited in 1998.

Now the corporate links between Grifols, Green Cross and Alpha, on an international level, date back to the 1980s. They can be explored further if required, but for today's purposes I don't think that's going to help us.



In December 2002, Alpha US sold various assets to Baxter Healthcare Corporation. What remained of Alpha was by then owned by a company called Mitsubishi Pharma Corporation, rather than Green Cross. That sold some of those remaining assets to the Spanish company Grifols in July 2003.

Now, the Inquiry has evidence from two witnesses about the corporate structure and about the limitations on disclosure that that has resulted in. The first is Kevin Gogay, he is the UK and Ireland finance director of an existing UK company called Abbott Laboratories Limited; which is an affiliate of Abbott, which is still headquartered in Chicago. So Abbott, as you'll recall, was the first company to produce Profilate.

That statement provides an overview of the corporate relations between Abbott and Alpha in the 1970s, and he also states that the existing UK company, Abbott Laboratories Limited, had conducted searches in response to requests from the Inquiry, and believes that it doesn't hold or control any relevant documents relating to Profilate.

Mr Gogay pointed in particular to the sale of the Scientific Products Division of Abbott to Alpha in 1978. He says the then existing books and records



relating to the business were sold at the same time, and that was obviously some 42 years ago.

Further details are contained in the statement, which is at WITN4130001.

The second witness statement, or series of statements, is from David Bell. Now, Mr Bell gives statements with different hats on, as it were. He acted as an external lawyer for Alpha Therapeutic Corporation, the US company, from 1981, including as lead counsel in the US HIV litigation, and he joined the company for around two-and-a-half years from October 2000. So one of Mr Bell's statements addresses the activities of Alpha and its predecessors from the 1970s, based on, as he put it, "non-confidential information that is in the public domain". It should be noted and remembered that Mr Bell, as a lawyer, is bound by rules of professional privilege, which meant that he can't disclose privileged information without being given permission by his client.

Mr Bell also provided a letter as general counsel and chief innovation officer at Grifols. This dealt with issues concerning the way in which different parts of Alpha were divested during the 1980s and the 1990s. I won't go into the details but

the key point for present purposes is that when Grifols acquired some of Alpha's assets in July 2003, these did not include the product licences for Profilate or Profilnine and, as a result, there isn't disclosure for that company to give to the Inquiry.

The references are WITN4514001 and WITN4514002.

I don't intend to say anything more about corporate structure, sir. It's a matter that we can return to if needs be.

Profilate. We know from the documents that we have that Profilate received a product licence in 1975. It's not clear from the material that we have seen whether and to what extent it was used in the UK before then. We know that some UK clinicians were at least aware of the product, which is perhaps unsurprising. Archives from the Oxford Haemophilia Centre show that promotional materials from 1973 were obtained by the Oxford Haemophilia Centre but it's not clear whether or not those were circulated more widely in the UK. The reference is BPLL0008067.

Perhaps we could just have that on screen as it shows the way in which the product was being licensed at that time. What we can see on the first page is a compliments slip dated March 1973 saying:

"Some of the Abbott literature (selected by me)



..."

If we could then go to the next page, please, I suspect this is from -- the initials which were underneath the redaction were EB, so probably Ethel Bidwell.

Then the next page says, "From Dr Rizza", 7 March 1973. If we expand the page out, please, Soumik, we can see, bottom right-hand corner that this is literature provided by Abbott Scientific Products Division. I stress we don't know whether or not this was circulated within the UK or whether or not it just came into the possession of Drs Bidwell and Rizza. If we could have a look at page 3, please. We can see there is a picture of two young boys playing, climbing a log or a tree, and the literature says:

"Boys will be boys ...

"Even if one is a Hemophiliac."

It goes on to say:

"Hemophilia. The constant threat of haemorrhage. Now ABBOTT Scientific Products Division Antihemophilic Factor (Human) AHF offers the hemophiliac the opportunity to lead a more normal life.

"Antihemophilic Factor (Human) Lyophilized is a stable, dried concentrate, easily reconstituted in



a diluent and administered without the side effects occasionally associated with plasma. Every bottle is labelled with the number of Factor VIII units it contains. So when the individual patient factors affecting dosage have been established, the patient's average dosage can be accurately calculated and administered; even allowing the hemophiliac to be treated on an out-patient basis. It can reduce the incidence and severity of bleeding episodes, and the pack contains all the components needed -- AHF, diluent, and administration set -- for immediate use."

If we look at the next column, under the heading "Caution", it says:

"This product is prepared from units of human plasma which have been tested and found non-reactive for Hepatitis Associated Antigen. However, it is recognized that presently available methods are not sensitive enough to detect all units of potential infectious plasma and the risk of transmitting hepatitis is still present."

We can see there, sir, the way the product is being marketed as of 1973 and the advantages of concentrate that are being stressed at that time. If we could go over to the next page, please, Soumik. This is a data sheet that was provided with the



literature. I won't take you through it, at the bottom right-hand column we can see that there is a caution. That is in the same terms as the one that I have just read to you from the main literature.

**SIR BRIAN LANGSTAFF:** Where?

**MR HILL:** If we could expand, please, "This product is prepared".

**SIR BRIAN LANGSTAFF:** That's the very bottom?

**MR HILL:** The very bottom of the right-hand column.

**SIR BRIAN LANGSTAFF:** No, we got the wrong expansion a moment ago.

**MR HILL:** This product is prepared from units of human plasma which have been tested and found non-reactive for Hepatitis Associated Antigen. However, it is recognized that presently available methods are not sensitive enough to detect all unite of potential infectious plasma and the risk of transmitting hepatitis is still present."

**SIR BRIAN LANGSTAFF:** Could we just have the very bottom right-hand corner of the page where the date is of this? October 1971. Thank you. So in October '71, they were warning about the risk of hepatitis.

**MR HILL:** Yes.

**SIR BRIAN LANGSTAFF:** Thank you.

**MR HILL:** The trademark Profilate was registered in the

United Kingdom on 31 July 1974. That is taken from paragraph 7 of Mr Gogay's witness statement. Shortly thereafter in August 1974, Abbott Laboratories Limited, so the UK company, applied for a product licence. This was considered at the meeting of the Committee on Safety of Medicines Biologics Subcommittee in November 1974. If we could have that on screen, please, Soumik. MHRA0000091_005. Top right-hand corner, we can see that this another report by Dr Duncan Thomas. It is for a meeting to be held in November 1974. The date received is 23 August 1974. I take that to be the date in which the product licence application was received.

If we go down the document, we can see at 1.3 the licence is to be held by Abbott Laboratories Limited, the UK company; the manufacturer, at 1.5, is Abbott Scientific Products Division, that's the American company; the proposed method of sale is through the Supply Division of the Department of Health and Social Security.

That's maybe a reference to the fact that, at that time, there were efforts made to purchase factor concentrates centrally by the DHSS, a topic to which we will return in due course.

If we could go to the second page, please,



Soumik, the very bottom. The section dealing with the "Collection of blood" says this:

"The Source Plasma (Human) used in the manufacture of the product is collected by the United Biologics Donor Centres, owned by Abbott Laboratories. On November 20th, 1973, the United States Food and Drug Regulations for Source Plasma (Human) became effective. As required under these Regulations, applications for licence for Source Plasma (Human) for each location were submitted to the Food and Drug Administration before this date. These locations are in California, Arizona, Texas, Oregon and Washington."

So we can see, sir, that the blood is coming from American centres. Those centres are owned by Abbott Laboratories -- owns United Biologics Donor Centre.

Further down the page "Labelling", 7.1, the application states this.

"The label and the passage enclosures will carry the following warning:

"'Single dose container for intravenous administration'

"'Discard unused contents'

"'This product is prepared from units of human plasma which have been tested and found nonreactive



for Hepatitis Associated Antigen. However, it is recognised that presently available methods are not sensitive enough to detect all units of potentially infectious plasma and the risk of transmitting hepatitis is still present'."

A similar warning, sir, to the one we have just seen.

If we could go over to the next page, please, and section 9 "The method of manufacture", "9.1 Specification of starting material", the application states:

"Plasma meets the requirement that each donation shall be individually tested, using the radioimmunoassay method, and found to be non-reactive for hepatitis associated antigen."

So RIA testing was being used.

If we could go over to the next page, please, Soumik, and section 11 at the bottom, "Selection and screening of blood donors". A quote from the application again:

"The controls applied in the collection of plasma for AHF manufacture are detailed in the copies of the forms used to collate the information of the medical history, physical examination and laboratory data of a proposed donor; the donor medical history



cards; the plasma donor list and daily donor rejection list."

Those are listed at pages 29-37 of the submission, which, sir, we don't have, or at least we have not found. But you can see there, sir, that this application includes information about donor rejection.

If we could go to the final page of this document, please, Soumik, at page 8. "Proposed shelf life". The application says:

"A shelf life of 1 year at a storage temperature of 2-8 degrees Celsius is given."

The medical comment -- this is a comment from Dr Thomas, and I quote:

"The blood used for the preparation of this Factor VIII concentrate is screened for HBAg by radioimmunoassay. Blood is obtained by plasmapheresis of commercial donors at eight centres in the USA. Insufficient information is given on the assay of Factor VIII, particularly in relation to whether or not the International Standard for Factor VIII is used in the assay.

"The manufacturer in California has not been inspected by the Licensing Authority.

"Recommendation". [This is Dr Thomas's

recommendation]:
"That a product licence be granted."
We don't, sir, as I've said, have the full set of records of this licensing process. But we do know, from a letter dated 10 December 1974, that Dr Duncan of the DHSS -- that's Dr Mary Duncan -- informed the company that the CSM -- that's the Committee on Safety of Medicines -- had advised that a licence should be granted, subject to two conditions concerning batch release and using international units as the method of describing the product. Abbott agreed to both of those conditions. The reference is MHRA0000091_012, pages 14 to 16.
An indication, therefore, that the licence is going to be granted, but the licence wasn't actually granted at that stage. There was some further correspondence -- Abbott applying for a variation to the licence to cover, as they put it, "new stages in the manufacturing process and consequent other changes". These were changes which had been accepted by the FDA. The reference is MHRA0000091_012. And at the same time, Abbott identified additional donor centres.
If we could have, please, that document, MHRA0000091_012, on the screen, please, Soumik.



Page 2. So this is a JVR Marriott, the manager of regulatory affairs at Abbott, writing to Dr Duncan of DHSS, saying:
"I would also bring to your notice that we have added the following to the list of donor centres."
You can see there is a list of nine further centres, all based in the United States. Most of them -- one of them is said to be a United Biologics Donor Centre, and that, you will recall, sir, is a company that was owned by Abbott. The other companies -- the other donor centres are listed under the heading "American blood components". No further information is provided as to whether that company was owned by Abbott, or whether it was effectively controlled by Abbott, or whether it provided the material under a contract which specified the way in which it was collected.
There seems to have been a period of delay, the cause of which is not entirely clear, but in May 1975 the company wrote again to the DHSS, again accepting the conditions that the DHSS had stipulated as Licensing Authority as a requirement of the licence. Abbott reminded the DHSS that it had already accepted these conditions in September 1974 and said, and I quote:



"We do feel this matter has dragged on for too long."
So it seems to be something of a chaser from Abbott Laboratories Limited to the DHSS. That reference is MHRA0000091_008.
It seems to have done the trick because the product licence was granted on 22 May 1975. It was granted to Abbott Laboratories Limited, and the formal document was dated 30 January 1976. The reference is CBLA0000006_009. So the product was licensed from 22 May 1975.
A data sheet for Profilate appeared in the 1976 edition of the Association of the British Pharmaceutical Industry compendium, a publication that we have looked at before. Could we have on screen, please, Soumik, ABPI0000008. We can see this is the entry for Abbott in the 1976 compendium. As we have seen, these compendiums are prospective, and so it is likely that the data sheet was inspected in the final quarter of 1975 before its entry into this document.
If we could have the second page, please, we can see in the left-hand corner towards the bottom that this is the entry for Profilate, and it contains the usual information about presentation, uses, the dosage and administration. Then if we go on to the next



page, please, page 3, in the section entitled "Contra-indications, warnings, et cetera", it states under the subheading "Warnings":
"Profilate is prepared from units of human plasma which have been tested by radioimmunoassay and found non-reactive for hepatitis B antigen. However, the methods at present available are not sensitive enough to detect all units of potentially infective plasma, and the risk of transmitting hepatitis is still present. Patients with mild deficiencies who consequently have not received multiple transfusions of blood, or blood products, are at greatest risk. Under such circumstances, the benefits of Profilate administration must be weighed carefully against the risk of viral hepatitis; single donor products are preferable whenever possible."
So a more expanded warning than the one that was contained in the product licence application.
If we could just go down to the section headed "Note". The data sheet contains the following:
"Nurses and others who administer this material should exercise appropriate caution because of the risk of exposure to viral hepatitis."
The next available data sheet for Profilate is contained in the 1978 compendium and it is in the same

terms. The reference for that is ABPI0000014.

Turning to market share of the unheated Profilate. Two DHSS documents from 1976 provide some insight into this. The first was prepared by Dr Sheila Waiter for a meeting in March 1976, and it is a memo entitled "Survey of commercially produced and NHS produced Factor VIII concentrates". It's at DHSC0100007_004. If we could have had on screen, please.

We know that Dr Waiter was the author because of the way that the document was discussed at a meeting on 11 March 1976. The reference of that is DHSC0100007_003. I needn't take you to that document.

If we could go down to the second paragraph, please, Soumik. It says this, and I quote:

"This paper is concerned with the available forms of freeze-dried Factor VIII concentrate, the advantages and disadvantages of these, and the resulting clinical preferences. As the declared intention is to make the NHS independent of commercial producers of the therapeutic agent, it is essential to produce within the NHS concentrates which are as acceptable and as effective as those made commercially."

That, sir, provides the context of this



document.

Under the next heading "Preparations of Factor VIII", this refers back to the pool method of preparing cryoprecipitate, and it states this, and I quote:

"In 1964, Judith Pool prepared a method of preparing cryoprecipitate which is still the most widely used preparation of Factor VIII. It is made in the Regional Transfusion Centres from fresh frozen plasma and distributed on demand to clinicians. Its main disadvantage is that the activity can vary considerably from Centre to Centre and from batch to batch. Unless held at suitably low temperatures and infused shortly after thawing, activity may be diminished."

If we could go over to the next page, please, and underneath the heading "Commercial services of freeze-dried Factor VIII concentrate". This is the position as described by Dr Waiter in March 1976, and I quote:

"Product licences have been granted to three overseas commercial firms, enabling each to sell its product in the UK but restricting the market available to the firms to designated Haemophilia Centres. Supplies are more than adequate to meet UK demands,



but the product is expensive.

"At present, three products are available: Hemofil, Kryobulin, and Profilate.

A fourth firm will shortly be given a product licence, and a fifth is likely to apply for one."

Likely to be references to Armour and to Cutter.

If we could go over on to the next page, there's a discussion of the NHS sources of product. And I just note, sir, for future reference, the paragraph -- the first substantive paragraph of this page where Dr Waiter says, and I quote:

"The three NHS production units make freeze-dried Factor VIII concentrate by the same process, which is that described by Newman et al, based on cryoprecipitation and purification of the cryoprecipitate by washing."

So that's describing the NHS methods which we will come back to in due course.

Then on to the next heading which is "Clinical preferences for the available Factor VIII concentrates". And as we have seen from the context, Dr Waiter is seeking to understand what the clinicians want, in part to inform the NHS about their own products so that they can meet the clinician's demand.

What Dr Waiter says is this, and I quote:



"A limited survey among users of Factor VIII concentrates (14 clinicians in 9 centres) has revealed clear preferences, usually for one product.

"Factors mentioned as being significant are:

"1. Availability;

"2. Cost;

"3. Presentation, including availability of a selection of dose sizes ...

"4. Volume of diluent required;

"5. Solubility;

"6. Activity of reconstituted product;

"7. Risk of transmission of viral hepatitis;

"8. Presence of blood iso-agglutinins;

"9. Levels of fibrinogen and other proteins."

Sir, I say now that, having read the document as a whole, I do not read that as being listed in order of importance; they are just the nine factors that have been raised by the clinicians.

If we turn to the next page, please, "Availability of the product". Dr Waiter wrote, and I quote:

"There is a more than adequate supply of commercially produced Factor VIII concentrate. Hemofil is the product most commonly bought; more Kryobulin is now being bought; there has been little

uptake of Profilate."

If we could go to the next heading, "Cost of Factor VIII concentrates", we can see the current prices are listed. Hemofil at 12p per unit, the same as Kryobulin; Profilate slightly cheaper at 10p per unit.

If we could then turn to page 6 of the document, please, Soumik.

Entry 7, "Hepatitis", and I will read an extended quotation from what Dr Waiter wrote.

"The risk of acquiring hepatitis, and in particular hepatitis B, following infusion of Factor VIII concentrates has recently been highlighted. The commercial products are prepared from large pools of fresh human plasma which may contain the causative agents of viral hepatitis.

"This is especially likely if the sources of the raw material are paid donors or donors from geographical areas where the diseases are more prevalent. It is not possible to subject the concentrate to any treatment known to diminish the risk of hepatitis ..."

I pause there. We can see that originally typed were the words:

"... since such treatments greatly increase the



loss of Factor VIII activity during preparation."

That has been struck through, that final clause, and it's not clear whether or not that was -- or why that was done.

**SIR BRIAN LANGSTAFF:** Well, the result, as it says, is you can't do it at all, whereas previously it says you can do it but you lose an awful lot of Factor VIII in doing so.

**MR HILL:** Yes.

The next paragraph states, and I quote:

"The commercial products available in the UK carry a warning that a risk of acquiring hepatitis, although small, accompanies the infusion of these products. It is now obligatory for commercial firms to test individual donations of blood or plasma for HBsAg and to batch test the final product by radioimmunoassay."

It then goes on to discuss the NHS products. It says they too carry a risk of transmitting hepatitis B. Dr Waiter says, and I quote:

"However, this risk is considerably less than that accompanying the use of commercial products."

And, of course, that reflects the understanding at the time. You have seen other evidence about what was known later.



If I could continue the quotation:

"Some clinicians accept the risk of using Hemofil, claiming that the benefits of using a high purity product outweigh the risk of transmitting hepatitis, particularly for the severely affected patient who is less susceptible following repeated and frequent treatment. Others prefer to use an NHS product, regardless of the relative inconvenience of using these products to avoid the risk."

If we could turn to the next page, please, Soumik, page 8. The summary of the users' views. Dr Waiter, after reminding the reader that only a small group of users was approached, says that there was a fairly consistent preference, which is summarised in the following way:

"1. Users like the ease of reconstitution of the commercial products and the resulting small volume of a haemostatic dose of factor VIII, even for adult patients."

Then added in handwriting:

"This is particularly true of Hemofil."

"2. For home therapy, a small volume dose is essential. Some patients on home therapy use cryoprecipitate, but the majority are on high or intermediate purity concentrates."



Added in handwriting:

"A small dose, approximately 250 millilitres of Hemofil given early often produces haemostasis."

"3. The risk of transmission of viral hepatitis, particularly following the use of Hemofil and particularly to the less severely affected haemophiliac, is recognised. All the clinicians interviewed would, for this reason, prefer an NHS product. A few consider the risk of infection acceptable as the product is effective. Some patients are reported to have refused commercial concentrates following recent publicity.

"4. The presentation is important."

I won't go through the detail there, sir.

"5. Ease of reconstitution."

And it is noted that Hemofil is, on average, the quickest and the easiest, and that the NHS products take the longest time to reconstitute.

"Conclusions", and I quote:

"Clinical preference is for the commercial product, based on ease of reconstitution and delivery, but there is every indication that NHS products of comparable solubility and ease of reconstitution and of consistently high potency would be used to the exclusion of commercial products."

If we go down a couple of paragraphs, Dr Waiter also writes:

"Costs will be an incentive, also the safety of the product, but attention must be paid to presentation."

I stress that "presentation" here is used to mean what is provided with the product so that it can be used, not just the mere external appearance or anything like that.

So that's Dr Waiter's paper of March 1976. An interesting paper more generally, but for Profilate it shows a limited market penetration at that time.

If we could now go to DHSC0003719_118, this a document that we have seen on several occasions before. It is Mr Drew's minute from a supply department, dated 21 December 1976, sent to Dr Waiter, listing the different products that are used in the 12 months to 31 October 1976 and their value. Factor VIII is listed first. I have now, in my own time, done the maths, and Factor VIII is -- the average cost of it is 8p, if one takes the value and divides it by the number of units. As you said, sir, that is a crude way of doing it because you would expect a sliding scale with discount for bulk. But just doing it in that crude way, Armour's Factor VIII



is 8p; Hemofil, 5.2 million units, at about 12p; Kryobulin, just over 4 million units, at about 12p, and Profilate, only 383,000 units, at about 10p. So we can see the figures are consistent with that -- those which Dr Waiter included in her paper. Profilate is the least used of all of those products, even though it seems to have got to the market before Factor VIII.

The following year, November 1977, the annual DHSS purchasing guide lists a price of 12p per unit for Profilate. That's DHSC0002187_085.

That brings us to 1978, when the Scientific Products Division of Abbott was sold to Alpha US. I don't need to take you to the documents, but it appears that an agreement was struck so that Abbott continued to provide the product to the UK market for a transitional period in 1978 before Alpha took over. The reference is DHSC0002197_171.

On 10 September 1979, so the following year, the DHSS cancelled Abbott's licence and transferred it to Alpha Therapeutic GmbH, that is the German company. The reference is MHRA0000091_006, and the same stem _007. A new product licence number was issued, so same product but being sold by a different company.

That product licence was then renewed for five



years, dating from 22 May 1980. The reference is MHRA0000091_006.

If we could have on screen, please, PRSE0003437, this is a table showing the position of the different products in 1980 and 1981. We can see the first manufacturer listed is Abbott for Profilate, even though by this time it's actually Alpha who was providing the product. International units provided in 1980 is about 1.65 million, and in 1989 *(sic)* it's 1.9 million. We can see that is the lowest other than Speywood's Humanate in 1980, which is 615,000 and in 1981 is 1.5 million. It compares with the market leader, Factorate, which is 16.5 million units in 1980 and 14.6 million units in 1981. So considerably more than Profilate.

We can also see from the same table that Koate and Hemofil and Kryobulin were also more popular than Profilate. There is a reference to Interhem from Hyland, which I think may be a reference to the higher-purity product which Hyland have been -- sorry, the intermediate purity product that Hyland had been producing at that time.

So, overall, Profilate making up 1.6 million units of a 34.7 million unit market in 1980, and 1.9 million units of a 34.8 million market in 1981,



thus limited market penetration for the non-heat-treated product.

In 1982, an application was made for an alteration to the licence for Profilate in order to introduce a polyethylene glycol step in the manufacturing process. This was described by David Bell in his witness statement of 2 February 2021, WITN4514001. If we could have that up, please, Soumik, at page 6. The fourth paragraph down, beginning "In addition", Mr Bell wrote:

"In addition to the use of specific hepatitis testing for donor screening, Alpha adopted various manufacturing procedures in the late 1970s to increase the specific activity of Factor VIII in its concentrate. This was accomplished primarily by removing excess fibrinogen, which was felt to carry a large burden of the hepatitis virus. In 1981, Alpha received its licence for a more highly purified concentrate incorporating polyethylene glycol fractionation. Alpha believed that concentrate purification would offer a greater degree of protection against hepatitis transmission as a result of viral partitioning and removal."

We heard from Ms Middleton on Friday about viral separation through the use of polyethylene glycol.

Mr Bell's reference to receiving a licence in 1981, I would take to be a reference to receiving an FDA licence. The application in the UK came on 30 August 1982. It was considered by the Committee on Safety of Medicines Biologicals Subcommittee in March 1983, and Dr Fowler's medical assessment was that the variation should be granted, subject to a satisfactory pharmaceutical assessment. That assessment was carried out by Mr Betts and the assessment was that a number of points required answering before the variation could be granted.

If we could have on screen, please, MHRA0000091_004. If we could have page 23 of that document, please. So this is the pharmacist Mr Betts commenting on the document. The areas requiring further information include, at 1.1, "Source Material":

"Details of the collection and testing procedures actually used should be stated clearly.

"1.2 Information should be supplied on the control exercised by Alpha Therapeutic Corporation over the listed plasmapheresis centres and affiliated centres."

If we go to section 2, "Manufacture of the Product", 2.1:



"The size of the production batches should be stated."

There are a number of other points here, I won't go through them all. If we go down to 4, please, "Development Pharmaceutics":

"Evidence should be supplied to demonstrate the improved purity and the physical characteristics of the PEG material over the currently licensed product.

"Evidence should be provided that the upper limit of PEG is non-hazardous in man."

If we could turn over the page, please, to a "Pharmaceutical Recommendation", and I quote:

"A variation to the Product Licence should be refused until full information is received on the above points."

The Committee on Safety of Medicines Subcommittee on Biologicals followed that advice and advised in the same terms. If we could have page 1, please, on the screen -- the same document, first page -- and we can see that it's recorded that:

"On the evidence before them the Sub-Committee were unable to recommend that the product licence should be varied as indicated in the application.

"The Sub-Committee considered that inadequate information had been presented by the Company to



assess this variation."

Underneath that, we can see an extract from another set of minutes has been pasted on to this document, saying that:

"This application was considered by the Sub-Committee at their March meeting. The application was not subsequently considered by CSM as it was decided that insufficient information had been supplied in support of this variation."

The only other point I would note about this application, sir, is that a data sheet was provided -- the reference is page 6 of this same document -- and that contained a hepatitis warning in the same terms as that contained in the 1976 Compendium, which we have looked at.

So far as the Inquiry is aware, no product licence variation was granted to allow the polyethylene glycol step.

That application was made in August 1982. In October 1982, Alpha was involved in an application -- another application, this time for a clinical trial certificate, for the product Mono VIII, which was made by Speywood. We referred to this, sir, on Friday, and I would just like to show one or two documents relating to it. If we could have on screen, please,



DHSC0003949_102.

It is important to stress, sir, that this not the product that was the subject of the study by Professor Tuddenham and Ms Middleton. That was produced by BPL, and was only used on four patients, and it was using BPL cryoprecipitate. This is an application for a further clinical trial certificate, for a wider clinical trial; it would again use the polyelectrolyte fractionation technique that Speywood had developed but the source material was going to be, and I quote:

"Bulk cryoprecipitate manufactured by: Alpha Therapeutic Corporation ..."

So instead of using the cryoprecipitate taken from BPL, which would have come from UK voluntary donors, it is instead using commercially sourced cryoprecipitate from America.

If we look at this document, we can see that it is an application for a clinical trial certificate. It is received on 20 October 1982, and is to be considered at the Subcommittee on Biologicals meeting of March 1983. There is also a reference to another meeting, PSM, on 4 November 1982. I am afraid I can't assist with what that is.

It was assessed by Dr Fowler and Mr Betts, the

same team that assessed the previous application that we were looking at. The proposed certificate licence holder is Speywood. But if we expand the document, this part of the application concerns the "Bulk Cryoprecipitate manufactured by [Alpha]", and that is at 1.2, the "Product Summary".

Then if we look at the final section, 1.5.1, dealing with the "Proposed Uses", it says:

"Mono-VIII-C is to be studied for efficacy and clinical tolerance in the treatment of haemarthrose involving the knees, elbows and ankles of severe haemophiliacs."

If we could now have on screen DHSC0003949_104. We have a little more information provided about the particulars of the trial. If we could go down to item 6, please, "Patient selection", it's stated that the trial will involve:

"Up to 50 males aged 7 years to 18 years ... All will be severe haemophiliacs with hemarthroses of the knee, ankle or elbow."

If we could now have DHSC0003949_105, please. This explains a little of the structure of the application. Under the heading -- it explains a little more of the proposed trial -- "Indications":

"[Mono C] is to be studied for efficacy and



clinical tolerance", as we have seen.

"Patient election", it says:

"A total of 200 bleeds will be required for the study, of which 100 will be treated with Mono-VIII:C and 100 with intermediate purity commercial concentrate ..."

If we could turn over to the next page, page 2, and it's section 5, "Duration":

"The duration of this study is anticipated to be approximately 8 months."

Then on to the next page, page 3, section 9, the investigator is Dr Aronstam of Treloar.

**SIR BRIAN LANGSTAFF:** Could you just go back a page. Yes, the trial is -- the "Trial design", it's a random double-blind study which compares Mono VIII:C with unspecified, intermediate purity commercial concentrate.

**MR HILL:** The following page has the control products listed.

**SIR BRIAN LANGSTAFF:** Let's have a look at that.

**MR HILL:** Under section 8, it says most control products are Hemofil, Factorate, Koate, Profilate and Kryobulin. I should have stressed at the outset, sir, this is about the human Factor VIII product that Speywood was producing, not the porcine product.



**SIR BRIAN LANGSTAFF:** Yes.

**MR HILL:** As was mentioned on Friday, Dr Aronstam of Treloar was the person who was listed as participating in this trial, there had also been some indication that the Royal Free may have been involved as well.

I needn't take you to the document, but at DHSC0003949, there is an explanation that a separate application has been filed for the cryoprecipitate stage of the trial, and a separate application for the Mono C side of the trial, and the application of that to the patients, obviously to be considered together. It is stated that:

"Full details on donor selection, collection procedures, quality control and manufacturing methods are given in the product licence application."

If we could now have, please, DHSC0003949_106, this the medical report, so Dr Fowler. If we could have -- thank you, the second page under the heading "Bulk Cryoprecipitate", Dr Fowler explains the way in which the application has been structured, with separate application for the cryoprecipitate, which is one that's being considered here. Under the heading "Manufacture", Dr Fowler states, and I quote:

"There is nothing in the process which would render the product incapable of transmitting hepatitis



but some claims have been made that PE fractionation removes [hepatitis surface antigen]. As the source cryo has been screened for this, one is more concerned with [non-A, non-B] hepatitis. This is not mentioned."

If we could turn, please, to page 4, and the final paragraph. There is a reference to the fact that the company has provided a published paper by Tuddenham et al about the efficacy of the treatment. That is the paper we looked at on Friday, in which Dr Tuddenham referred to the four patients that were treated with the BPL product.

If we could turn to page 5 now, please, "Medical Comments". Dr Fowler wrote this:

"This [clinical trial] application by Speywood is dependent upon the parallel [product licence] application by Alpha Therapeutics for the importation of bulk cryo paste to be used as raw material for the manufacture of Mono-VIII:C. If the Alpha licence is not granted, this Speywood application is seriously deficient in that respect.

"The Speywood application gives no indication of the precautions taken to ensure that the Alpha bulk cryo remains frozen throughout its journey from Los Angeles to Wrexham via an un-named UK airport,

beyond replenishment of the dry ice at the UK airport. Who, in fact, is responsible for this replenishment and, possibly, recording whether the cryo is still frozen on arrival?

"PE fractionation has never before been used for any blood product licensed in the UK. It might therefore be thought essential for the company to demonstrate conclusively that their product prepared in this way was no more toxic than [Factor] VIII prepared in the conventional way."

I pause there, sir. I erroneously stated earlier that this is Dr Fowler considering the cryo aspect. It's not, it's Dr Fowler considering the Speywood application but obviously with reference to his concerns about the way in which the cryoprecipitate is going to be shipped to Speywood.

**SIR BRIAN LANGSTAFF:** Well, he's asking whose job is it to make sure it remains frozen.

**MR HILL:** That question hasn't been answered, so far as he can tell, from the application.

If we could turn to page 6, please.

**SIR BRIAN LANGSTAFF:** Just pause for a moment.

**(Pause)** Yes.

**MR HILL:** The point made in the final paragraph, sir, about the single paper. What I understand Dr Fowler



to be saying there is that, although Dr Tuddenham's paper has been presented, that product, of course, was made using UK cryo from BPL, which is different from the application which is being pursued now, which using American cryo.

If we could turn over to the top of page 6, please, Dr Fowler says:

"The proposed study poses no fundamental problems but two matters deserve consideration. Some indication of the way in which clinical tolerance is going to be monitored should be given and some restriction should be put on the number of treatments an individual patient may receive during the trial. In view of the fact that the product is effectively coming straight from bench to clinic, it might be thought that 200 bleeds in a possible 200 patients, was excessive at this stage of a product's development. A smaller number or, perhaps, an interim report to the Committee on, say, the first 50 might be desirable."

The "Medical Opinion" is:

"Subject to the grant of a product licence to Alpha Therapeutics for the imported bulk cryoprecipitate used as a raw material, a Clinical Trial Certificate should be issued. This should



reflect the recommendations made in the preceding paragraph. The company should be advised now about the amount and nature of safety and efficacy data which will be required to support any future application for a product licence."

That is the medical report from Dr Fowler about the Speywood element, obviously referring to the cryoprecipitate but not primarily focused on the cryoprecipitate. The CSM Main Committee, if we could have DHSC0003946_060, this is the Main Committee's conclusion about the cryoprecipitate element.

What the main committee, at their meeting on 24 March 1983, say is, and I quote:

"On the evidence before them the Committee had reason to think that on grounds relating to safety and quality they would be unable to advise the grant of a product licence for this preparation and directed the Secretary to notify the applicant ...

"The Committee provisionally concluded that:

"1. The bulk cryoprecipitate should be prepared by Alpha Therapeutic only from Source Plasma ... derived from their own licensed plasmapheresis centres,

"2. Evidence should be provided to show that the cryoprecipitate is at least equivalent in quality



to that used for the manufacture of Alpha Therapeutic's US licensed Factor VIII,

"3. Inadequate information was presented on the control of the material during transportation to the UK,

"4. An undertaking should be given that donor lists should be available to the manufacturer of the finished dosage form,

"5. In the event of a licence being granted for this product, the batch release procedure should apply, to include the provision of protocols and samples of bulks as required,

"6. There were inadequate details on the manufacturing process."

"Remarks" are given are, including at 2, and I quote:

"The Committee advised that special attention be given to the inspection of the Company's premises in the [United States]."

Sir, we can see that the importation of cryoprecipitate for the Speywood trial was refused with those comments made. That relates directly to the Alpha side of the application.

We looked at some documents about this on Friday and we asked Ms Middleton about it and, as far as she

was aware, the trial did not, in fact, go ahead and we have seen no documentation to suggest that it did go ahead. A further point to note, sir, is that by the time of this decision, March 1983, information knowledge had grown about the risk of AIDS. So, even if the application had been successful, Dr Aronstam and others would have had to consider the position in 1983, in light of the knowledge of AIDS, as to whether or not to continue with that trial. The fact that they made the application in 1982 does not necessarily mean they would have gone through with it in 1983.

**SIR BRIAN LANGSTAFF:** I think we may have to remember the date of October 1982 for this proposal when we look at the-- what Alpha may have known about the risks in respect of AIDS and the steps it might be taking elsewhere to deal with some of that risk --

**MR HILL:** Yes, sir.

**SIR BRIAN LANGSTAFF:** -- at the same time.

**MR HILL:** We will be looking at that in due course.

I note the time, sir, but there are just couple of documents which we may have time for before lunch about the unheated product, before turning to the heat-treated product.

**SIR BRIAN LANGSTAFF:** What do they say?

**MR HILL:** They are just showing the level of market



penetration that Profilate had as of 1983.

**SIR BRIAN LANGSTAFF:** Well, can you summarise that for us?

**MR HILL:** It's the document that we have seen on several occasions before, Dr Walford's questionnaire response, shows Profilate at approximately 5 million international units as of 1983, well behind Factorate and also behind Koate and Hemofil. So, again, showing a limited market share. That table also --

**SIR BRIAN LANGSTAFF:** Roughly what was the total market at that stage?

**MR HILL:** I'm afraid I'll have to bring the document up to see that. It's DHSC000 --

**SIR BRIAN LANGSTAFF:** I shouldn't have asked!

**MR HILL:** Haha. DHSC0002229_055. I'm afraid I don't have -- that's the one document I don't have in paper copy in front of me. If we could have the second page of that, please, Soumik.

No total figure is given but we can see Factorate is between 15 and 20 million international units; Immuno is somewhere in the region of 6 or 7; Hemofil, 8 to 9 million units; Koate 8 million units; and Alpha, 5 million units. So not as far behind as it was, but still the least used of the commercial products.

Another point to note from that table is that



there is no Factor IX product listed for Alpha at that time.

**SIR BRIAN LANGSTAFF:** Yes. It looks as though it's gone up to roughly, very roughly, 10 per cent of the market, whereas it had been just over 5 per cent, I think.

**MR HILL:** Somewhere in that region, sir, yes.

**SIR BRIAN LANGSTAFF:** Thank you.

**MR HILL:** The final document, which I won't take you to, but we'll just refer to, BAYP0000026_008. This is a marketing plan from Cutter dated October 1983, so commenting on its rivals. In respect of Profilate, it says that was making some gains due to its low price, which tallies with the table we have just seen.

The next section of the presentation, sir, deals with heat-treated Profilate and --

**SIR BRIAN LANGSTAFF:** And that's after lunch. Shall we take a break, then, until two o'clock. Two o'clock.

**(1.02 pm)**

**(Luncheon adjournment)**

**(2.00 pm)**

**MR HILL:** Sir, I turn now to heat treated Profilate, the trade name of which was Profilate HT. This was a product that was heated for 20 hours at 60 degrees centigrade, and it was heated in a suspension with



n-heptane. It may be helpful to just bring up MHRA0033388_029, please, Soumik. Page 16.

This is from the UK product licence, but it describes the process by which the product is produced, and it helps to show the difference between this product and some of the other heat-treated products that were on the market at the time.

We can see that it starts off with cryoprecipitate, which is clarified by filtration. Then there is mixed filtration with polyethylene glycol, centrifuged again, and then centrifuged with polyethylene glycol to make a final concentrate. It's then suspended in a different solution and filtrated, and lyophilised, so at that stage it's dry heated and turned into a powder.

Now, for dry heated product, that powder form was then placed in a vial and then was heated either in ovens for a pure dry heat treatment, or in the case of Immuno, the vial was heated with vapour, as we have seen in our previous presentations. So the product is still in the vial, and it's being heated that way.

With Profilate, the lyophilised powder was then suspended in heptane, so it is mixed with heptane -- not fully dissolved but mixed with it -- and then it was heated at not less than 60 degrees centigrade for

not less than 20 hours. It was then filtrated out of the suspension, dried again, freeze-dried, and that creates the final product.

**SIR BRIAN LANGSTAFF:** So this isn't dry heating. It isn't pasteurisation as it is conventionally understood. It's a sort of in-between in which a solvent other than -- a solvent is used and heat applied.

**MR HILL:** Yes. It's usually referred to as heating in suspension in some of the documents.

**SIR BRIAN LANGSTAFF:** Yes.

**MR HILL:** It's unflatteringly referred to as slurry heating, to give the idea that the solid is still there. But it's, as you say, sir, between dry heat and between what is conventionally called pasteurisation, which is fully heated within a solution.

**SIR BRIAN LANGSTAFF:** Yes.

**MR HILL:** The only product that I am aware of that underwent true pasteurisation of this form was for the Behringwerke product, but that was not, as of 1983, 1984 and 1985, available in the UK. It became available later.

**SIR BRIAN LANGSTAFF:** Yes. I mean, it had been available earlier, but it obviously wasn't actually distributed.

**MR HILL:** I'm afraid, sir, I --



**SIR BRIAN LANGSTAFF:** That's a detail we can deal with later.

**MR HILL:** Yes. Yes. But it is a significantly different process to the pure dry heat that we have seen with other products.

David Bell, in his statement dated 2 February 2021, gives some evidence about the background to this. If we could have on screen, please, Soumik, WITN4514001, page 6, please.

If we could highlight the last two paragraphs of that page, starting in early 1982. Mr Bell said this:

"In early 1982, Alpha began an additional programme to inactivate any residual hepatitis virus through heat, which culminated in a licensed product in February 1984."

I pause there, sir, to note that that reference is to an FDA licence in February 1984.

"After evaluating various inactivation processes, researchers at Alpha concluded that heating the concentrate in a liquid solvent without added stabilisers might not have the undesirable effect of stabilising any residual virus in addition to the Factor VIII protein. Unlike other entities who utilised 'dry heat', Alpha developed a procedure using 'wet heat' (a suspension in n-heptane). While this



procedure reduced the final yield of Factor VIII and was costlier to implement, it provided, in Alpha's opinion, a more robust inactivation of viruses. (A simple analogy is: dry heat is similar to placing your hand in an oven; wet heat is like placing your hand in a hot water bath -- the transmission of heat in the bath is much greater.) Alpha's protocol for this additional processing step was established in the fall of 1982 and submitted to the FDA.

"Studies conducted pursuant to FDA licensure demonstrated that Alpha's heat treatment process inactivated significant quantities of marker virus, hepatitis B and non-A, non-B hepatitis. However, both the Bureau of Biologics of the FDA and the haemophilia treatment community raised concerns about the possibility of neoantigenicity related to the heat treatment. This concern centred around researchers' and physicians' belief that heating the concentrate altered the molecular structure of the Factor VIII molecule, which could have a deleterious effect on persons using heat-treated concentrates, essentially making a treatable patient untreatable.

"Studies conducted by Alpha failed to show any evidence of neoantigenicity. However, the treatment community did not fully accept these results until the



end of 1985. Until haemophilia treaters' concerns about neoantigenicity were allayed, non-heat treated concentrates continued to be prescribed and recommended by physicians as the principal treatment of choice."

That concerns primarily the American position and we will come on to see the UK position. If I may take you to page 3 of the same document, in response to some questions by the Inquiry, and in a statement dated 6 July 2021, Mr Bell provided a little more detail. He said, and I quote:

"Alpha began its research program for factor concentrates prior to the initial reports of HIV. The program was in response to the potential risks of hepatitis and was undertaken by senior Alpha scientists including Martha Heinski and Charles Heldebrant. Prior to the work initiated by Alpha and others in the 1970s/early 1980s in response to the risk of Hepatitis, the scientific and clinical understanding was that, while heat treatment/pasteurization was utilised for viral inactivation in Albumin, it required the addition of specific stabilizers. As it related to heat treating factor concentrates, it was believed that the factor concentrates were very heat labile and, even in the

presence of stabilizers, heat would denature the proteins creating neoantigens and rendering a patient untreatable. Even today, the creation of neoantigens (inhibitors) is one of the largest problems facing patients being treated for bleeding disorders. My current recollection is that this information was based on scientific and clinical evidence as conducted by Charles Heldebrant in the laboratory of Ed Davis at the University of Washington it late 1970s where it was found that factor VIII was denatured by heat even in the presence of stabilizers and by clinical information provided by leading clinicians treating hemophilia, including Louis Aledort, who, along with recognition as one of the leading treaters of hemophilia, was also the Medical Director of the National Hemophilia Foundation."

We will, of course, sir, come back to issues about heat treatment in due course.

In the UK, we've heard from Dr Mark Winter of the Kent Haemophilia Centre, who explained that after Alpha obtained their FDA licence, which was in February 1984, he and others approached the company to request the material on a named-patient basis. The reference to that is INQY1000059, it's pages 136-40 of his oral evidence to this Inquiry on 1 October last



year.

Dr Winter's evidence is that all of his Centre's patients were transferred to heat-treated Factor VIII or Factor IX on a named-patient basis in May to June 1984. He also thought that similar changes were made at Middlesex, Sheffield, and at St Thomas's. That, of course, is his evidence about what went on there rather than direct evidence.

An indication of the move toward heat-treated products and in particular Profilate, in 1984, is available in an article from The Haemophilia Society Update from 1989. Could we have HCDO0000276_047, please.

This is an article marking "A decade of service to haemophilia" from Alpha Therapeutic UK, so the UK company. If we go to the second paragraph down, for the entirety of that left-hand column, this is what the article, which dates from 3 June 1989 says, and I quote:

"Alpha was established in 1979 under the direction of Ian Marshall and the firm enjoyed several years of steady growth in the early 1980s."

This is, of course, the UK firm, sir.

"The advent of heat-treated concentrates in 1984/5 to combat the threat of hepatitis and AIDS was



to change the company's fortunes dramatically. Following the urgent licensing of several heat-treated products in early 1985 PROFILATE was rapidly established as the market leader in the commercial sector due to its unique method of viral inactivation. Fortunately for Alpha the summer of 1984 had seen Barry Barber join the company and Alpha was able to cope with the very rapid expansion of business that coincided with the new treatment era. Ian [that's Ian Marshall] recalls:

"'The situation at Christmas 1984 was chaotic. Everyone wanted to exchange their non-heated factor VIII for the heat-treated product, which had only been used here for the first time a few months before. Barry and I seemed to spend all our time either on the telephone to the USA or in a van on the M11 driving around exchanging hospital stocks as much as possible. One local taxi firm was delighted though -- we booked their fleet of cars and vans for last minute deliveries on Christmas Eve!'."

That's the end of that quotation. Back to the article:

"In early 1988, following the decision of several major US manufacturers to stop production of dry heated concentrates Alpha was being called on to



supply [two-thirds] of all the factor VIII being used in the UK. At a time when the world, and in particular the USA was very short of factor VIII, securing enough supplies to prevent shortage was very difficult."

Back to another quote from Mr Marshall:

"'We had to introduce rationing' ..."

Sorry, not Mr Marshall; it's Barry Barber:

"'We had to introduce rationing' says Barry 'To have simply sold all our supplies to the first hospitals to ring up would have been very easy and just as profitable for us. However, that would have meant some hospitals receiving no product at all and treatment programmes would have been severely curtailed. We adopted a very responsible attitude which, on the whole, ensured everyone got enough to maintain a service and I know from the reaction of centre directors that we did the right thing."

Pausing there to note that the suggestion that Profilate HT was two-thirds of the all Factor VIII being used in the UK as of 1988 may be misplaced. It may have been intended to mean or a misstatement of the fact that approximately two-thirds, or around that figure, of the commercial market may have been Profilate, but at that time, NHS Factor VIII, from

both PFC and BPL, would have been widely used as well.

As we have heard from previous presentations, the DHSS, as of November 1984, encouraged other companies to apply for product licences for heat-treated products, and Alpha Therapeutics UK did so on 3 January 1985. We have looked at the manufacturing process from that application. The references are MHRA0033388_033, and the same stem _029. The application was signed by Ian Marshall and the applicant was Alpha Therapeutics UK. So the UK company rather than the German company.

The application documented that the product was licensed by that stage in both America and West Germany.

A warning was contained in the application. I won't take you to it, sir, but I will just read it now. It's at page 6 of the same document that we looked at earlier:

"Viral hepatitis may be transmitted by these products. Patients with mild deficiencies who consequently have not received multiple transfusions of blood or blood products are at greater risk. In this situation, the benefits found of haemophiliac factor Profilate Heat Treated must be carefully weighed against the risk of viral hepatitis. Single



donor products should be preferentially utilised whenever feasible."

So a similar warning to the unheat-treated product, sir. We will come back to some of the subsequent warnings in due course.

Following the provision of the application, there was a process of correspondence between the DHSS and Alpha Therapeutics UK. I don't think I need to take you to the detail of that. I would note that at one point the DHSS requested or required Alpha to include in its literature the fact that the product had been heated at 60 degrees centigrade for 20 hours, and it also said that it should be specified that that step had been taken, and I quote, "in order to reduce the risk of transmission of infectious agents". So, as we have seen with other products, not referring to hepatitis or AIDS, but "infectious agents" generally. The reference is MHRA0033388_018.

There is some further discussion between the company and the DHSS about the precise terms of any warnings, but I don't think I need to take you to that.

As with other applications for heat-treated products, Dr Duncan Thomas was consulted by Dr Mary Duncan, and his letter of 17 January 1985, if we could



have this on screen, please, is MHRA0033388_026. You will recall, sir, that Dr Thomas's letter about Kryobulin, Koate and Hemofil, dated 8 January 1985 formed part of our presentation on Kryobulin. This is a letter from nine days later, specifically about Profilate. What Dr Thomas said was this:

"Thank you for your letter of January 16th, accompanying the copy of the abridged application for a heat-treated product from Alpha Therapeutics. I think the submission indicates that the company has made a serious attempt to reduce the infectivity of their product. As you noted in your letter, they have used four marker viruses, including HTLV-III, and have shown that their heat-treatment step inactivates at least down to the current level of detection of this virus. I cannot see what else we can expect them to do. Their treatment of Factor VIII is of course different from that of the other manufacturers and, as far as I know, they are the only one that is treating the material with heptane, followed by heating.

"As you know, the main worry about these heat-treated products is whether evidence will emerge from long-term studies of the formation of neo-antigens and, particularly, antibodies to Factor VIII. I think the immunologists might claim



that, on theoretical grounds, one might expect evidence of neo-antigens to develop eventually. All one can say, however, is that nobody has yet demonstrated their presence and that, in some 18 months of use in other countries, the problem does not seem to have developed in patients. I suppose it is reasonable to swap an uncertain hazard of antibody development some time in the future, for a very definite hazard from unheated Factor VIII in the present.

"On balance, I think Alpha Therapeutics have made a reasonable case for their modified product. Once again, one is struck by contrast between this submission and one or two others that you have sent to me."

He then goes on in the following page to talk about the idea of a scientific meeting taking place. But that, sir, is Dr Thomas's view, and it appears that this consultation with Dr Thomas took the place of a formal referral to the Committee on Safety of Medicines.

The UK product licence for heat treated Profilate was issued on 19 February 1985, with conditions including a requirement to adhere to the batch release process. The references are

MHRA0033388_14 and 15.

In a letter dated 10 April 1985, Alpha UK explained that it would continue to supply the product on a named-patient basis until the labelling and packaging had been approved and was available. That reference is the same stem _008.

If we could have on screen, please, MHRA0033388_006. If we could have page 4 of that document, please. This is the proposed label for the heat-treated product, as part of the discussions that went on between the DHSS and the company. We can see, under the "Caution", it says:

"This product is prepared from human plasma of donors who have been individually tested at each donation and found nonreactive to hepatitis B surface antigen by approved test. However, it is recognized that presently available methods are not sensitive enough to detect all units of potentially infectious plasma."

That's the draft label. A draft data sheet, as of 13 March 1985, is at MHRA033388_007.

I'll try that again MHRA0033388_007. Thank you.

This is the -- I said data sheet, sorry, actually this is a package insert. Underneath the "Description", we can see that the same warning is



given about hepatitis. Then the third paragraph down, we can see that it says:

"The process used in the manufacture of Profilate Heat-Treated includes a step designed reduce the risk of transmission of hepatitis, Acquired Immune Deficiency Syndrome ... and infection by other viruses. However, no method has been shown to be totally effective in removing hepatitis, AIDS, or other viral infectivity from Antihaemophilic Factor (Human)."

Sir, I note that the reference to the step being taken to reduce hepatitis and AIDS is one that the DHSS picked up upon and asked to be changed and, in later versions of this document, it is changed.

There follows a section on clinical pharmacology. I'm not going to take you through it, sir. I think it can be fairly summarised as saying that it describes the newly recognised retrovirus that had been implicated as a possible causative agent of AIDS, and it goes through how that has been tested in Profilate, and the -- the chimpanzee studies and the viral load studies that have been conducted. If we could go over onto the next page, please.

In the warning section, a bit further down, again, we have a warning about hepatitis in similar



terms to the one that we have looked at before and, on AIDS, the warning section says, and I quote:

"The causal factors of Acquired Immune Deficiency Syndrome ... have not been fully defined. However HTLV-III/LAV virus has been implicated as a possible agent of the disease. It is not presently known if other transmissible agents are involved. Alpha uses screening procedures to eliminate high risk plasma donors and a heat-treatment step of the manufacturing to reduce the risk of transmitting AIDS. However, despite the careful selection of donors, it may be possible that the AIDS causative agents may still be present in and be transmitted through this product."

In November, we will come back to the steps that are taken.

Thank you. If we could take that down, please, Soumik.

So those are some of the documents that were provided with the application to the UK authorities for the product licence and the correspondence that followed it.

An internal Alpha document, which is a UK inventory dated 31 August 1985, records that the company had 2.5 million units of heat treated



Profilate at the time. The same inventory notes that the company had about 735,000 units of what was termed standard concentrate, which was presumably non-heat treated. But the fact that those units were present doesn't mean that they were actually being sold at that time, nor indeed that any customers would have been willing to buy them. And that is August 1985, the reference being CGRA0000565.

**SIR BRIAN LANGSTAFF:** It also means that neither had they been junked nor returned.

**MR HILL:** No. They were within the --

**SIR BRIAN LANGSTAFF:** And it amounted to roughly 20 to 25% of the -- from the figures you've given me -- of the available stock.

**MR HILL:** Yes. But what that stock was available for is -- isn't expressed in the document.

Turning to market share. A letter dated 18 March 1986 shows the approach that Alpha was taking to marketing heat treated Profilate at that time. NHBT0096602_005, please.

This is sent to Mr Rhodes of the north western Regional Health Authority, and it's thanking him for an enquiry of 12 March.

It refers to two alternative preparations that are available, the first being Profilate heat treated

wet method, and this is the product that we have been talking about so far. It talks about the presentation of the heat treatments step. Then, in terms of virus inactivation data, it says this, and I quote:

"A study in conjunction with the Centre for Disease Control in Atlanta was performed where the product was deliberately spiked with live HTLV-III virus. The number of logs of HTLV-III virus and other viral markers was assayed before and after heat treatment. A full report of this data (which formed part of our product licence application to the DHSS in the UK) is attached."

So product information on that study.

"Hepatitis:

"A clinical study was undertaken in the UK to determine the effect of this unique heat treatment step on transmission of all viruses but particularly non-A, non-B virus. The preliminary results of this study were contained in a letter to The Lancet (copy attached)."

We'll come on to that letter in a second.

"A full report with patient data collated up to 1 February 1986 is available from clinical trial coordinator Dr Kernoff."

Underlined is the following comment, and I



quote:

"The results show significant reductions in the incidence of post transfusion NANB hepatitis in 'virgin' haemophiliacs. To date, this is the only product that has published evidence to substantiate a claim to a significantly reduced incidence of post-transfusion NANB hepatitis."

Then it says:

"Further safeguards. Product imported into the UK is produced exclusively from plasma donors who are both negative for HTLV-III antibody and also less than twice the upper limit of normal for ALT."

The price is stated to be 16p per international unit.

I stress, sir, that this letter is 18 March 1986, so we have progressed about a year in time where those additional donor screening tests have been taken. But the importance is the claim that the product has been shown to make significant reductions in NANB hepatitis as well as inactivating AIDS.

Before I turn to The Lancet article, and because we have the document on screen, we will see that underneath the description of the Profilate HT that we have been talking about there was also a dry heat treated method that was available. I won't go into



details as, so far as I'm aware, this was not a product that was widely used in the UK. There is a data sheet at BPLL0002217, but I don't think, sir, I need to take you to it. That product was being at least referred to in a letter to an interested person, and it seems to have been a response, which is why, even though available on a named-patient basis, this information could be provided.

The Lancet letter, which is about the suspension heated Profilate, is at RLIT0000186. If we could have that on screen, please, Soumik.

The letter is signed by Drs Kernoff and Miller of The Royal Free, Dr Savidge of St Thomas', Dr Machin of Middlesex Hospital, and Drs Dewar and Preston of the Royal Hallamshire in Sheffield. And thanks is also given, if we could just go above the signatures, to Dr Aronstam, Professor Mannucci, Dr Mitchell, Dr Robbins and Dr Winter for contributing patients to the study.

And the letter from 28 November 1985 states this:

"Sir, after a first exposure to large donor pool unheated Factor VIII concentrates of either commercial or volunteer origin, acute non-A, non-B hepatitis is a virtual certainty, implying the invariable



contamination of these products. Although heat treatment probably eliminates the risk of HTLV-III transmission, the most commonly used heating process (heating in the lyophilised state, dry heating) seems to have little or no effect in reducing the risk of NANBH. Such infections may have serious long-term consequences. Preliminary results from a prospective multi-centre clinical study indicate that heat treating Factor VIII concentrate before final lyophilisation (wet heating) is more effective in reducing the risk of post-transfusion NANBH.

"The product used in this study (Profilate heat treated; Alpha Therapeutic UK) is prepared from American commercial plasma pools [and I note, sir, this for your note] (5,000-32,000 donors per batch). The study protocol is similar to that previously described."

I won't go through those details there, sir, but the letter goes on to describe 18 patients who had been admitted to the study and had been followed up for 42 weeks. All were treated in England, apart from one Italian. Nine different batches of Profilate had been used. The authors say this, and I quote:

"None of the patients [halfway through the second paragraph] has shown serological evidence of

acute infection of hepatitis virus A or B, cytomegalovirus, or Epstein Barr Virus, and all have remained seronegative for anti-HTLV-III. However, acute NANBH has developed in 4. All 4 were treated with the same batch of Profilate, and they were the only patients of the 18 to have received this batch. In none of these patients was the hepatitis symptomatic. Incubation periods were 2, 2, 4, and 8 weeks, respectively. Possible reasons for the apparent persisting infectivity of this single batch are being examined. At this stage of the study, however, the absence of NANBH after administration of other batches suggests that the product carries a lesser overall risk of NANBH transmission than either unheated or dry heated concentrates."

As I say, sir, that is September 1985 in The Lancet.

While the publication came in September 1985, there is considerable evidence that the results were being discussed among haemophilia clinicians before that date, and that, as a result, Profilate had quickly established a strong market position among the heat-treated products, despite selling at a price, 14p, that may have been higher than some of its competitors.



A Cutter report from January 1985 noted that Dr Wensley in Manchester had switched to Profilate heat treated and appeared, and I quote, "To believe in the wet heat treatment process," though he was reserving judgment until liver function studies were known. Reference to that is BAYP0000024_070.

In March 1985 in Newcastle, Dr Jones wrote to his pharmacy department that, and I quote:

"Overall, the best product presently available for clinical use is probably the Alpha one, Profilate. This is the only product in which heating of wet material occurs, and preliminary results of a clinical trial being mounted by the company suggest that it is free of non-A, non-B hepatitis, as well as AIDS."

That reference is TYWE0000014.

On 12 April 1985, Professor Bloom in Cardiff wrote to his chief pharmacist, and if we could perhaps have this on screen. It's CVHB0000002_028. Dr Bloom wrote that he was -- and this letter concerns ordering Factor VIII -- he says -- he complains about the Koate product, and then says, and I quote:

"In addition, the heat treatment process is not as effective as that applied by Alpha to Profilate HT. I appreciate that the latter is 2p a unit more expensive, but even so, I think that clinical



considerations must be the overriding factor, and I therefore think that we should restrict our factor VIII orders to Profilate HT until such time as one of the other manufacturers can compete. I hope that you will find this course of action acceptable."

I note here, sir, that by October 1985, this preference was reflected in the treatment guidelines at the Cardiff centre, which can be found at WITN0000029003. Profilate HT was seen as the second safest product after 8Y, the BPL product.

A Cutter memorandum of 20 May 1985 recorded that Dr Savidge had presented his own Profilate HT trial results and that they supported what was described as Alpha's claim that Profilate HT was free from non-A, non-B hepatitis. His results were said to support those of Dr Kernoff and Dr Wensley. And according to the Cutter memo, some haemophilia directors were now saying, and I quote, that it was "unethical to use anything but Profilate HT, especially on virgin haemophiliacs and children." Reference is BAYP0000024_230.

A further Cutter memo from September 1985 reports that various other directors, including Dr Preston, have reached a similar view. Although Dr Mitchell in Derby dissented after one of her



patients seemed to develop non-A, non-B hepatitis, having used Profilate. That reference is BAYP0000007_113.

The preference for Profilate HT amongst clinicians such as Dr Jones, Dr Kernoff, Dr Savidge and Professor Bloom continued into 1986.

If we could have on screen, please, BAYP0000008_059. This is another Cutter memorandum in which it's recorded -- this is 16 January 1986:

"I have been told by Dr Peter Jones that Newcastle are now using only Alpha material."

His reasons were explained as follows:

"With the increased number of haemophiliacs developing AIDS or pre-AIDS, he must give them the safest known material available. He mentioned the work of P Kernoff et al (attached), and I challenged him on the grossly over-presumptive interpretation of the data that Alpha material is NANB safe. He agreed that the results were not conclusive in any way but said that Alpha were the only company with clinical data that he had seen which shows any indication of success in eradicating NANB transmission in Factor VIII concentrates. Dr Jones will express his opinions at the AIDS meeting in February. He will meet with support from three other major centres who

also only use Alpha material -- Sheffield, the Royal Free, and Cardiff."

The author of the memo goes on to describe the major blow of losing Newcastle.

So we can see, sir, a march is being stolen by Profilate HT in the heat treated product market.

An application was made to vary the licence and change the labelling in November 1986, and it was seemingly approved on 15 January 1987. The references are MHRA0033387_010, and same stem _011, and the same stem _012.

We can see some of the labelling that was being used at the time. If we could have on screen, please, MHRA0033387_014. As part of the application, the company provided the copies of the vials that were being -- copies of the packaging that were -- was being used at the time. And we can see that this is used on the small vial. The warning says:

"This product is prepared from large pools of human plasma which may contain the causative agents of non-A, non-B hepatitis, hepatitis B and other viral diseases. See package insert.

"Each unit of plasma has been tested and found non-reactive for HB surface antigen and HTLV-III antibody by FDA-approved tests."



So that's the small vial. If we look now at MHRA0033387_016, this is the large vial concentrate. The warning is different. It says:

"This product is prepared from human plasma of donors that have been individually tested at each donation and found non-reactive for hepatitis B surface antigen by FDA required test. However, it is recognised that methods presently available are not sensitive enough to detect all units of potentially infectious plasma, and the risk of transmitting hepatitis is still present."

Different warning, depending on the size of the product that you were providing.

These are the packets that are to be replaced, and we can see the proposed text for labels and cartons at MHRA0033387_017. And that text, sir, contains no warning on it, although it does refer the reader to the package insert, and we will come on to that in a second.

The application -- sorry, there was a further application on 30 July 1987, which was for a rationalisation and update of the text, including incorporation of new information about non-A, non-B hepatitis, that's at MHRA0033389_049.

The data sheet helpfully sets out the present



text and the proposed text, and if we could have that on screen, please, at MHRA0033389_050. If we could go to page 2, please.

We can see on the left-hand side, in the left-hand column, is the present text as of July 1987, and the proposed text is on the right-hand side. If we could go, please, to page 3 and the section on warnings. I should say sir, that the comparison is slightly confused by the fact that some of the text in the proposed warnings is placed elsewhere on the -- in the package inserts so it's not -- the fact that it's not present next door to the existing wording doesn't mean that it has somehow been cut.

If we look at the present text, it states this, and I quote from left-hand column:

"This product is prepared from pooled units of human plasma which have been individually tested and found nonreactive for hepatitis B surface antigen and antibody to human T-lymphotropic virus type III (HTLV-III). Other screening procedures are used to eliminate high risk plasma donors and the heat-treatment step of the manufacturing process is designed to reduce the risk of transmitting viral infection."

I note, sir, that that is the request that the



DHSS have made and that has been followed. The proposed text says, again, that:

"[The] product is prepared from pooled units of human plasma which have been individually tested and found nonreactive for hepatitis B surface antigen and antibody to Human Immunodeficiency Virus (HIV). The plasma used in the preparation of this product has been screened for Alanine Aminotransferase (ALT) levels in an effort to reduce the transmission of non A, non B hepatitis. Each unit used in the manufacture of this product has been found to have an ALT level less than 2 times the upper limit of normal for the test. Other screening procedures are used to eliminate high risk plasma donors and a heat-treatment step in the manufacturing process is designed to reduce the risk of transmitting viral infection."

If we could go over to the next page, please. Some detail is given about the testing of the product with spiked HIV and the reduction of 3.25 logs of HIV, and about the chimpanzee studies. Although we can see there is no equivalent text in the left-hand column, that material was actually contained a little earlier in the old version of the document, so it's not new.

If we go down to the third paragraph, this is

new:

"The incidence of post-infusion non-A, non-B hepatitis in patients receiving a first exposure to unheated and Factor VIII concentrates approaches 100%. In contrast Profilate Heat Treated has been shown to be effective in reducing the risk of transmission of non-A, non-B hepatitis."

Various references are given to literature in support of that. In bold, and I quote:

"However, testing methods presently available are not sensitive enough to detect all units of potentially infectious plasma and treatment methods have not been shown to be totally effective in eliminating viral infectivity from this product. Despite all precautions taken by the manufacturer it cannot be assumed that this product is totally free of HIV or hepatitis virus. As with all drugs the risks associated with use must be weighed against the benefits of therapy."

So sir, the warning against hepatitis infection and AIDS infection remains -- or HIV infection remains.

Among the new information about NANB infection that was provided with this product application was a paper by Drs Kernoff, Savidge and others, which is



worth looking at for a number of reasons, and it's NHBT0042403, tab 76. You well recall, sir, that the letter to The Lancet gave evidence in September 1985 of a study of 18 patients, and this paper, in the British Journal of Haematology, 1987, volume 67, pages 207-211 takes that study forward.

I'll try again NHBT0042403, thank you. The study is entitled "Reduced risk of non-A, non-B hepatitis after a first exposure to 'wet heated' factor VIII concentrate".

The summary states this, and I quote:

"The risk of post-infusion non-A, non-B hepatitis ... in patients receiving a first exposure to unheated or conventionally 'dry heated' factor VIII concentrates approaches 100%, implying invariable contamination of these products. Amongst 18 patients who received a first treatment with a 'wet heated' concentrate, five (28%) developed asymptomatic NANBH, suggesting a more sufficient inactivation of NANBH agent(s) by this process. 2/9 (22%) of the batches of concentrate used in the study were implicated in NANBH transmission. One of these two batches, responsible for NANBH in four patients, had been prepared from a plasma pool containing an unusually large proportion of donations with high alanine aminotransferase (ALT)



levels. A resulting high level of viral contamination in this batch may have been sufficient to overwrite the effects of the sterilisation process. All patients remained anti-HIV seronegative at 17-28 months of follow-up."

So, sir, I note there is one additional patient from The Lancet letter in September 1985 who has now been identified as having been infected by NANB, but it is still 5 of 18 patients, as opposed to the usual 100% of patients.

If we could just go down on that page to the "Patients and Methods" section. It states that:

"The patients were admitted to the study between September 1984 and August 1985, and followed for at least 40 weeks ..."

If we could go over to the next page, please. The second paragraph down, this refers to the product used. It says, and I quote:

"Factor VIII concentrate was bought from Alpha Therapeutics UK Limited and had been manufactured from US-derived commercial plasma pools obtained from approximately 5000-32 000 donations, none of which had been screened for ALT or anti-HIV. Nine different batches of concentrate were used."

I pause there, sir, to note, again, that figure



of 5,000 to 32,000 donors is given.

Because the patients were selected between September 1984 and August 1985, that pre-dates the screening of the donor pools with ALT testing and HIV testing, which, as we've seen from the documents we've been looking at, came in a little later.

If you can turn to the "Results" column. It talks about the five patients (28 per cent) who developed acute NANB, and then it goes on to say that:

"In three of the five patients who developed hepatitis, transaminase abnormalities were resolved within the 40-week follow-up period. In the other two, abnormalities persisted beyond 40 weeks, indicating the development of chronic hepatitis. Two additional patients (3 and 5) developed mild, transient, ALT abnormalities which did not fulfil the criteria for diagnosis of hepatitis."

If we go over, we just see at the bottom of that page it says:

"Two of the nine batches of concentrate (22%) were implicated" --

If we go over to the next page underneath the diagrams:

"Two of the nine batches of concentrates were" --

If we go to the text just beneath these diagrams:

"Two of the nine batches of concentrates ... were implicated in transmission of NANBH. One of these batches [batch D] caused hepatitis in all four recipients, suggesting a batch-related rather than process-related problem."

We will pick up what happened with batch D shortly.

If we could go over, please, to the final -- the penultimate page, page 4, in the "Discussions" section. If we pick it up about halfway down the left-hand column, commercial Factor VIII concentrates. The authors write:

"Commercial factor VIII concentrates subjected to 'dry heating' at 60°C for 30-72 [hours] have been found to transmit [non-A, non-B] to 84-100% of recipients [papers are cited] attack rates which are similar to those associated with unheated concentrates, whether derived from commercial or volunteer plasma ... The lower transmission rate found in this study suggests that the method used to prepare the concentrate, which included heating at 60°C for 20 [hours] while the material was in a slurry with n-heptane, was more effective than conventional 'dry



heating' and resulted in a lesser degree of viral contamination of the final product. This conclusion is reinforced by the course of patient 2, whose lack of evidence of NANBH during the first 11 months of follow-up is clearly unlikely to be attributable to host resistance factors. Reduced transmission rates have been found by other investigators using both the same and another 'wet heated' concentrate ..."

References are given to other texts. If you could go over to the next column, please, in the first full paragraph in, starting "The risk". This, sir, goes back to batch D, the batch that gave rise to four of the infections:

"The risk of ... [non-A, non-B hepatitis] by factor VIII concentrates depends not only on the efficiency of any sterilization process, but also on characteristics of the source plasma. In the absence of any reliable serological markers for [NANB hepatitis], interest in donor screening as a means of reducing viral contamination of concentrates has centered on the possibility of using 'surrogate' tests, including [anti-hepatitis B core antigen] and ALT. There is good evidence that ALT screening, in particular, is likely to result in a reduced risk of NANBH in non-pooled products ... and plasma used as



source material for US-derived commercial clotting factor concentrates is now invariably derived from ALT screened donors. This was not the case in 1984/85, when the concentrate used in the present study was manufactured, and examination of the product history of one of our two implicated batches [batch D] suggested that its propensity to cause [non-A, non-B hepatitis] might have been at least partially related to an unusually high level of NANB viral contamination in the plasma pool from which it was derived.

"The plasma used to prepare batch D was collected in the USA in early 1985, and some was provided by independent contract plasma suppliers. In 1985 the West German Health Authorities ruled that all plasma products destined for use in that country should be derived from donor plasmas which have been individually screened for elevated ALT levels. This was not, and still is not, a requirement in the UK. Without the knowledge of the manufacturers, one of their contract suppliers diverted plasma which had failed to meet the German requirements, and this was used to prepare batch D. The source plasma pool is now known to have contained a much higher than usual proportion of high ALT plasma, and it seems possible that this resulted in a high level of viral



contamination which was sufficient to override the effects of the sterilization process. The asymptomatic course of the patients who developed NANBH may be indicative of a partial neutralization of NANB agent(s), since hepatitis associated with unheated commercial concentrates is usually symptomatic ... All concentrates now manufactured by the company are derived from plasma donations which have ALT levels less than twice the upper limit of normal, and have been screened for anti-HIV. Whether or not such screening will eliminate or reduce the risk of post-infusion NANBH can only be assessed by a second clinical study, which is currently in process."

A couple of things to pick up from that, sir. First is the general point made that there has been some success in inactivating NANB hepatitis by use of Profilate HT methods, although there have been some instances where it has still been transmitted.

The second point relating specifically to batch D is the fact that the plasma was supplied under contract to Alpha, rather than from one of Alpha's own plasmapheresis centres and, in this instance, it seems that the plasma for batch D had failed the test put in place by the West German authority relating to ALT

levels and had, unknown to Alpha, been included within its manufacturing process for Factor VIII for elsewhere in the world.

A third point -- sorry, just on that second point, sir, you may recall that when we were looking at Hyland there was some reference in Hyland, in an internal document from Hyland Travenol that said that they never used any batch which failed the ALT tests in any other product, unlike some of their competitors, and it may be that that is a reference to this.

A third point for your consideration, sir, is that the ALT tests that the American companies carried out were carried out in response to a requirement made by the West German Licensing Authorities. Now, West Germany may have been a bigger market for blood products than the UK but it shows that American companies were responsive in their practices to requirements that were placed on products by European regulators, not just by American regulators.

Moving on, sir, from this document, if we could take it off the screens. In May 1988, the United Kingdom Haemophilia Centre Directors Organisation issued some product recommendations, which included Profilate HT as the third choice of



product behind BPL's 8Y and the Behringwerke product Haemate P, which was, by that stage, available in the UK. The reference is NHBT0000037_014.

At a meeting of the Haemophilia Society Reference Centre Directors in February 1989, Dr Bloom noted that Profilate HT had the largest share in the commercial market. That reference is HCDO0000432. The emphasis is on the commercial market because, obviously, significant amounts of product were being produced by NHS sources at that time, as well.

By 30 January 1990, Professor Bloom was seeking to prevent the use of Profilate HT in Cardiff because he had adequate supplies of 8Y and of Haemate P.

The reference is CVHB0000002_071. I won't bring it up, but what Professor Bloom wrote there was that, and I quote:

"The Alpha product Profilate, which was our previous commercial choice, does sometimes transmit hepatitis, and we have only used this on previously exposed patients. I do not like having it in the storage refrigerator in case it is used by junior staff after hours. However, I appreciate that it is too expensive to destroy unless you feel the budget could meet this."

Sir, we can see from those documents that



Profilate holds its position as the market leader into the late 1980s, but it is being seen as a product which does still have -- carry a non-A, non-B risk, unlike 8Y and, it seems, Haemate P as well; at least a greater risk from those products.

Profilate itself sought in October 1989 to vary its licence to allow for a new product which was a solvent detergent product, Profilate SD. So a new generation of products replacing the old heat treated version.

That variation was approved in March 1990. The references are MHRA0033386_023, same stem _021, and the CSM(B) report from Dr Rotblat and Mrs Sylvester is at MHRA0034913_003. I don't think, sir, that I need to take you to any of those documents, or indeed to the data sheet, save to know that this application is being considered from October 1989 until March 1990.

And that is of some relevance to the next section that I'm going to come to, sir, which is about a discussion which was taking place at roughly that time about the possibility of suspending the licence for heat treated Profilate because of concerns about the manufacturing site at which it was produced. I don't know, sir, if you would like me to start on that now, or whether you would prefer a break before



we return.

**SIR BRIAN LANGSTAFF:** Well, you will have quite a lot to go through there, I suspect, so shall we take a break now and come back at 3.40. Twenty to four.

**(3.09 pm)**

**(A short break)**

**(3.40 pm)**

**MR HILL:** Sir, I'm going to turn now to the issue that I mentioned before the break, which is the consideration that was given to suspending the Profilate HT licence in late 1989. The most convenient way to tell the story is to go to a document DHSC0001349, please. If we could go to page 3 of that document.

This is a note of a meeting held on 13 November 1989. The meeting is of a body called the Inspection Action Group, which is within the DHSS. We can see a list of those who were present, Dr Fowler is one of those, Mr Sloggem, some other names that are familiar as well. If we go over to page 4 of this document, this is item 5 of that meeting, and what I propose to do, sir, is read this document through because it provides the background to this issue as well as the proposals for what should be done next.

This item is headed "Alpha Therapeutics

Corporation -- USA". The minutes record this:

"Alpha Therapeutics is a subsidiary of the Green Cross Corporation of Japan. A comprehensive range of blood products is made at the Los Angeles site. The site was inspected on 6-10 October 1989. The inspection which covered the manufacture of Blood Products, the sterilization and filling into dose form containers, and the pasteurisation of those finished products, revealed that the Company had failed to correct a major deficiency found at a previous inspection in February 1988, in spite of indicating that they would do so, in order to ensure the production of viral-free Factor VIII 'Profilate'.

"Dr Kavanagh, (Principal Medicines Inspector] explained that the company in common with other commercial blood products manufacturers, employed a viral-inactivation procedure at a bulk intermediate stage, rather than a terminal pasteurisation step. A consequence of using such a method was that the product then had to be protected from possible re-contamination during the remaining stages of processing. This was generally achieved by handling virus-inactivated material in specially-constructed, isolated areas, equipped with their own independent air-supply, dedicated equipment and dedicated staff



clothing. Alpha-Therapeutic had built such an area where they prepared their Factor VIII product for the US market.

"The Profilate material for the UK, however, was made differently. The virus-inactivation step involved heating a slurry of freeze-dried Factor VIII in heptane; the equipment for this and the area in which it was sited made it extremely likely that heat-treated Factor VIII would be re-contaminated with untreated Factor VIII and/or albumin, with the concomitant risk of possible viral contamination.

"Dr Kavanagh described the process and conditions as detailed in the Inspectorate report, and explained that, following the February 1988 inspection, the company's response was that they would investigate ways to isolate the area and fit an independent air-supply system; also that they would be submitting imminently a UK [product licence] application for the USA-type product which was made in the viral controlled area.

"The inspection in October 1989 showed that nothing had been done; in fact the situation was worse in that the amount of untreated Factor VIII powder present in the heat-treatment room was much greater. In addition, the [product licence] application for the



new product had not been submitted. (Received since the inspection report).

"The company's response to the 1989 inspection remained unsatisfactory; the changes to procedures, while an improvement, were mainly cosmetic and did not address the main problems of a shared air-supply, absence of air pressure barrier and the open handling of treated and untreated Factor VIII powder in the same room. The company acknowledged that the UK product was inferior to that marketed in the US. The Inspectorate recommended withdrawal of the [product licence] for Profilate as the method used to produce it did not ensure a virus-free product.

"The Group then discussed whether the removal of the licence would cause a supply problem since the Company had indicated that they supplied well in excess of 80% of the UK commercial Factor VIII requirements.

"Mr Burton, [of the Procurement Department] explained that Factor VIII was a licensed hospital only product. He had investigated the Company's claim and established that the Blood Products Laboratory ... supplied about 70% of the UK requirements, and the [remaining] 30% of the commercial marked was supplied by Alpha and Miles-Cutter. The situation was, that



Alpha only supplied 80% of 30% of the commercial market. Therefore Mr Burton considered that there would be no supply problem. However, he referred to earlier problems at BPL and asked whether they were in a position to meet the shortfall. Dr Kavanagh stated that he understood the deficiencies at BPL had largely been resolved and production procedure had improved, and it was likely that no difficulties would be encountered in this respect. Miss Reenay indicated that this was also HS1 understanding of the supply situation. Other suppliers mentioned were Baxter, Immuno and Speywood.

"Mr Sloggem (Principal Pharmaceutical Officer) confirmed that there would be alternative supplies in the near future. Two [product licence] applications for Blood Products using the solvent detergent system, Monoclate P were to be considered by the Committee for the Safety of Medicines ... in November 1989, and were expected to be approved. A Koate HS product licence application was to be submitted to the Biological Sub-Committee and CSM in January 1990. A clinical trial exemption was in being for the new detergent system. The variation application from Alpha for Profilate which had been received in early November 1989, was to be submitted to the CSM, possibly in

January 1990. The Medicines Inspectorate commented that if the variation was approved the GMP [that's Good Manufacturing Practice] for the product was likely to be acceptable."

I pause there to note, sir, that in a subsequent memorandum dated 23 November 1989, Mr Sloggem corrected some of the information contained in this paragraph, which he said didn't accurately reflect what he had said at the meeting. The reference for that is MHRA0033386_019. I don't think I need to take you to that document.

Returning to the document that is in front of us from the Inspection Action Group:

"In view of the critical nature of the problem the Group discussed the possibility of suspending the [product licence] immediately. Mr Freedman's (Solicitor) view was that a serious threat to life would justify immediate suspension of the licence under paragraphs 10 and 11 of Schedule 2 of the Act, with concurrent [Section] 28 action to follow. This was required under paragraph 13 of Schedule 2 to provide the company with appeal rights and to suspend the licence for a further adequate period until the variation was approved. Dr Fowler supported the proposal, pointing out that the product was an extreme



patient hazard as it could be potentially AIDS contaminated material. The Medicines Inspectorate added that the Company had admitted the UK product was inferior to the US product. Miss Hepburn queried why formal action had not been taken after the 1988 inspection. It appeared that the Company's activities had been condoned for almost a year. The Inspectorate pointed out that the company's assurances of improvement had been accepted and they had given the Company time to put their house in order, but the recent inspection revealed that the problems that not been sufficiently addressed. The situation had in fact deteriorated and was now unacceptable. The Group agreed on immediate suspension of the product licence.

"The Chairman explained that in taking this action it may be necessary to effect a recall of all available material. He reminded the Group that the licensing authority could require a product to be withheld from sale only for a period of 6 weeks. In the absence of other withdrawal powers this would call for the co-operation of the manufacturer. He invite the Group to consider. There was general agreement that, in light of the information available such action was appropriate. Dr Kavanagh did not foresee any problems in this sphere.



"Miss Reenay expressed concern about the publicity which a Drug Alert would attract. She asked for HS1 to be involved in drafting the Alert message. They were likely to consult legal advisers. She confirmed the understanding that, while the product was 'hospital only', haemophiliac patients would have received supplies from consultants and stored these in home refrigerators. It would be possible to identify patients by registration.

"The Chairman reminded the Group that, in addition to the normal procedure whereby the proposals would require clearance with the top of MCA, this particular case was likely to be referred to Ministers before action took place.

"The Group agreed:

"i. To recall all Factor VIII material manufactured by Alpha. Medicines Inspectorate to seek manufacturer's agreement.

"ii. The immediate suspension of the [product licence] under paragraphs 10 and 11 of Schedule 2 to the Act.

"iii. A proposed suspension of the licence for a further period of 6 months until the [product licence] variation application had been approved.

"iv. To liaise with HS1A [that's a department



within the DHSS] at all stages."

That, sir, was the conclusion of that meeting which as we can tell from the content, refers to heat-treated Profilate.

I won't take you to the inspection report from October 1989 but the reference for it is DHSC0002412_093. That contains the detail of the point of concern that has been raised at this meeting. There was also some correspondence between Alpha and the DHSS in relation to that report, which can be found at DHSC0003567_086 and _087. Again, I won't take you to that now.

On 14 November 1989, Mr Wilson of the Medicines Control Agency circulated a memo identifying his concerns about the group's reasoning and the proposed actions that came out of that meeting. If I could take you to that, please, it's DHSC0001351. We can see that the minute is from Mr Wilson, nominally sent to Mr Franks but also a number of people copied in, including a number of those who were present at the meeting, such as Dr Fowler, and other individuals within the DHSS who had an interest. I pick out the name in particular of Dr Rotblat there, who will be referred to. Dr Rotblat being one of the scientists who was responsible for considering product licence

applications. We also saw her name raised in respect of the Speywood purification of Factor VIII and Dr Tuddenham's work on isolating Factor VIII and the gene sequencing.

Mr Wilson referred to a minute of 13 November which summarised the meeting of the Inspection Action Group, and then he says that he has several concerns, as set out below, that relate to the case for action proposed and, if the action were to be endorsed, the steps necessary for implementing it.

What Mr Wilson wrote is this, under the title "The action proposed". He says:

"The major deficiency, as set out in the inspector's report, existed in February 1988 at the time of the earlier inspection. We did not then apparently consider the process to be so unsafe as to warrant regulatory action. Mr Booth's minutes refers to the situation having deteriorated since then and to it now being considered critical. I see from the inspector's report that the heat treatment room was worse than at the time of the previous inspection. This may be so, but does this make the process materially less safe than in 1988? Is there some other aspect which has got significantly worse? Further, the company list in their letter of



2 November that a number of steps have been instituted which appear at least partially to address the alleged critical deficiencies. Nothing is said in Mr Booth's minute about whether these steps are regarded as materially meeting the critical deficiencies, and if not, why not. Can we have further written comments from the Inspectorate and medical advice on this aspect urgently?"

Paragraph 4:

"Mr Booth does not state under what provisions in section 28 regulatory action is proposed. But I gather it is probably section 28 [I'm not sure if that is an eight, I think] ..."

**SIR BRIAN LANGSTAFF:** Probably (e) I would think.

**MR HILL:** Possibly an (e):

"... relating to unsuitable manufacturing premises. But essentially the concern relates to safety, and I would like to know what medical advice was available to the IAG and what that advice was. Given that this product has been available in the UK for a long time and has, I understand, a high reputation for product safety, is there any evidence at all from clinical use to suggest that the risks of contaminated products identified by the inspectors may be actually leading to cases of viral infection in



patients? Does the present process lend itself to that possibility, and what is the nature of the risk to patients?

"I understand that Dr Rotblat has not had opportunity to comment on the papers, and I think it would be helpful if she saw them urgently, both in respect of this and other aspects, and if we had her comments available in writing. Generally, I think we need her views as to whether, on the basis of the evidence, there is an immediate hazard to health, and if so, what it is. Could Mr Booth please provide her with a set of the papers urgently?

"Nor am I clear from Mr Booth's report what legal advice was given to the IAG. Given the potential significance of the recommendations proposed, I would also like written confirmation from [and this is the legal department within the DHSS] that from the legal angle, they consider that the evidence to the regulatory action proposed would stand up to scrutiny, e.g., if the company used their rights to apply for a 'person appointed' hearing. Please also clarify on what provisions of section 28 it is proposed to rely.

"Implementation.

"I note that it is said that supply branch and



HS1 say that BPL could meet the gap created by suspension of Alpha's product licence. Before we go ahead with suspension, I think we would need to have some formal assurance on this point from a senior level in BPL, including assurance that they could do so without delay so that no one would be at any risk of being unable immediately to replace their stocks of Factor VIII. Can HS1 or PD [procurements division] confirm that this is BPL's view (making any discreet inquiry necessary). (Incidentally, if BPL can fully meet this requirement, why are they not doing so at present, given that their product is much cheaper for the NHS than the imported commercial product? Perhaps HS1 can say?) As to the 'other suppliers existing or shortly to be approved', what are they, and could we have a gap where unlicensed commercial products would be substituted for the alpha product?

"If we were to take the regulatory steps as proposed, the plan of action needs to be worked out. Immediate suspension and recall of stocks from hospitals and patients, especially in the present highly charged public and political atmosphere regarding haemophiliacs and HIV infection, is likely to lead to much publicity and questioning. HS1 need to advise on any advanced and confidential

consultations they would think necessary with, for example, the NHS haemophiliac reference centre and with the Haemophilia Society so as to ensure that, as far as possible, key people are prepared before any announcement.

"I note in any case that HS1 are concerned about the publicity if action as proposed goes ahead. We need to have a considered view urgently on how they see this matter and on any preparatory arrangements, as outlined in paragraph 7 [the previous paragraph].

"Finally, before any decision to take regulatory action on this issue, we will need to consult ministers to get their endorsement for what is proposed, i.e., both the action itself and the proposals for its implementation (on which, of course, ID [that's information division] would need to be brought in). In any submission to ministers, I think we would need to bring out why we were now proposing regulatory action (i.e., what had materially changed since February 1988) and to explain why such action was not thought necessary in February 1988. Can I have further advice on this point urgently? For example, how does this present hazard differ, if at all, from the hazard perceived in February 1988?"

He then goes on to propose a further meeting and



notes that he has provided these papers to Dr Jones. That is from Mr Wilson of the Medicines Control Agency.

Two memoranda were prepared in response to this, which I need not take you to, sir. They dealt with the ability of BPL and commercial providers to make up any shortfall. They can be summarised as showing that -- as saying there was an expectation that any shortfall could be met. Though it should be noted that Dr Rotblat, in a minute of 15 November 1989, cast some doubt on the availability of commercial product. The references are DHSC0001357, DHSC001350, and DHSC0002412_074.

If we could have DHSC001363 on the screen, please. This is from the National Biological Standards Board, so NIBSC, and it is a minute written for the attention of Mr Wilson of the Medicines Control Agency, the author of the previous minute, and it comes from SL Jeffcoate.

What it says is this:

"Following our telephone conversation this morning and an analysis of the data and commentary faxed by Mr Booth, we have come to these conclusions:

"1. There is no evidence suggesting that the product is unsafe. Batches of Profilate have been



tested here in accordance with the product licence, found to meet specifications and released to the market. This testing has included tests for antibodies to HIV and for presence of HBsAg on both the final product and the plasma pools.

"2. The inspectorate has made pertinent criticisms of the manufacturing process that reveal breaches of good manufacturing practice. However, we feel that the company are responding to the criticisms made (as evidenced by the letter of 2 November) and that the IAG is perhaps over-hasty in its recommendations.

"3. We feel that your own commentary dealt with the essential points extremely clearly."

That is directed to Mr Wilson and refers to the previous minute we looked at.

"4. Dr Duncan Thomas has had a lengthy discussion with Frances Rotblat. We don't feel that it is necessary for us to be present at your meeting tomorrow."

There is some marginalia on this document, referring to the HIV tests.

This states -- if we could just load that top section up. It's hard to decipher, but the word "Incorrect" is underlined. And then written "Is not



found as HIV," and then there is an "A is in other fractions."

**SIR BRIAN LANGSTAFF:** That must be "antibody".

**MR HILL:** I think that's "antibody", yes. "HIV antibody is in other fractions."

**SIR BRIAN LANGSTAFF:** "As in other fractions," is it?

**MR HILL:** I think I read that as "is in other fractions".

**SIR BRIAN LANGSTAFF:** There are two propositions there which I don't quite interpret. Anyway.

**MR HILL:** Then there are the words [something] "found virus".

**SIR BRIAN LANGSTAFF:** "May find virus"?

**MR HILL:** I think it may be "May find virus". The marginalia in respect of Duncan Thomas's conversation with Frances Rotblat is "No clinical data". I'm afraid, sir, I can't assist in interpreting those.

**SIR BRIAN LANGSTAFF:** There's a line from "HIV" to that, so it'll be in relation to that, one thinks.

**MR HILL:** Yes, that is -- the first piece of marginalia is related to the HIV testing that NIBSC says that it has done. There is some further marginalia in respect of point 4, Dr Thomas's conversation with Dr Rotblat, and that says, I think, "No clinical data". I'm afraid I can't assist any further than that.

So what we can see, if we take stock at this

stage, is that the inspectorate action group argued for immediate suspension of the product licence and recall of the product. Mr Wilson from the MCA casts some doubt on their reasoning and raised concerns about how such a process would be implemented. NIBSC have written, in essence, in support of Mr Wilson's position, and we have also had some memoranda which express a view that any shortfall would be made good by a combination of BPL and commercial products.

The next stage -- there is other documentation around this, but the next document I am going to --

**SIR BRIAN LANGSTAFF:** That document is 15 November.

**MR HILL:** Yes, sir.

**SIR BRIAN LANGSTAFF:** Right.

**MR HILL:** The next document is 24 November. This is the submission that was made to the Minister of State. It is DHSC0001368, please. We can see that this is from Mr Wilson. It's dated 24 November 1989. It is sent to a large number of people, including Dr Metters, Dr Jeremy Metters and, if he agreed, to the private secretary of the Minister of State for Health. The Minister of State for Health at that time was Virginia Bottomley. We can see it's also sent to the private offices of the Secretary of State of the -- and the Parliamentary Under-Secretary of State, the junior



minister.

What Mr Wilson wrote in this submission to the minister is this:

"Summary:

"This submission informs the Minister of State for Health of an adverse inspection report relating to manufacturing standards for a commercial factor VIII blood product, Profilate, marketed in the UK by a US-based firm, Alpha Therapeutic Corporation. The potential risks to health are not considered by officials to warrant any immediate regulatory action, e.g., to suspend marketing or withdraw stocks, but it is proposed to take steps to persuade the company to discontinue to supply Profilate made by the process currently used for the UK market."

So that, sir, is the summary, and we can see that the thinking has developed from the initial Inspection Action Group to this submission.

I'm going to take you through the entirety of this document, sir, because it's important to the decision making to understand the terms in which the decision was put to the minister.

"Background. The product.

"Profilate is marketed by the Alpha Therapeutic Corporation based in Los Angeles and owned by the



Green Cross Company of Japan. It has been licensed in the UK since 1985. The Blood Products Laboratory now provides about 70% of the market in England and Wales, and Profilate possibly about 20%. In recent years, before BPL facilities were developed, Profilate supplied a larger proportion of the UK market. It has also been widely marketed internationally. It has a good 'track record' for quality and safety."

Go over to the next page, please:

"Inspections.

"In February 1988, the medicines inspectorate of the department carried out an inspection of the plant facilities used for Profilate. They listed four major deficiencies which the company assured them would be dealt with. These included deficiencies relating to the risk of recontamination of heat-treated Factor VIII powder by untreated powder because of inadequate arrangements for the separation of the different stages in the treatment process. At the time of this inspection, the heptane heat treatment process used by Alpha was considered to be the best of available methods then in commercial use. The deficiencies identified related to the way the company operated the process, not the process itself. It seems most probable that these deficiencies had



existed at least since the product was licensed in the UK in 1985.

"Subsequent monitoring of the situation indicated that whilst the other deficiencies had been dealt with, the situation giving rise to the risk of recontamination had not. A second visit by the inspectors in October 1989 confirmed that the deficiency still remained and that conditions had deteriorated. On receipt of a further adverse report following that inspection, the company say they have instituted a number of changes which should reduce but will not eliminate the risk.

"Alternative process:

"Profilate marketed in the US is now produced using a new method different to the heptane treatment method still used for the product marketed in the UK. The new method is claimed to produce a superior -- i.e., safer -- product. The company have recently applied to have their UK product licence varied so as to market the US version in the UK. The US version is made in separate new facilities. It seems likely that the company have been reluctant to spend substantial sums on upgrading the heptane process when they planned to switch production to the new facilities."

I pause there, sir, to note that this seems to

be a reference to the new solvent detergent method.
"Risk assessment:
"Profilate used by the heptane treatment process has been widely used in the UK and elsewhere for a number of years. The deficiencies in that process revealed by the inspection report are of similar longstanding.
"If any of the heptane treatment Profilate has been contaminated as a result of processing deficiencies, the theoretical risks include: hepatitis B, non-A, non-B hepatitis, HIV.
"The data about infections in haemophiliac patients is relatively well documented because of the comparatively small numbers and the specialised hospital centres dealing with them which means that treatment can be closely monitored. Relative risks of different products used by haemophiliac patients can accordingly be assessed with more confidence than in other areas.
"Hepatitis B:
"There is no clinical evidence in the UK of hepatitis B transmission from Profilate. Most patients are immune due to previous infection or vaccinations, so the 'at risk' pool of patients is small. All donor blood is tested for hepatitis B



virus as well as for HIV antibodies.
"Non-A, non-B hepatitis:
"Profilate produced by the heptane treatment method is a first generation factor VIII product, and all these products are associated with some risk of transmission of non-A, non-B. But there is no evidence to suggest any higher risk from Profilate than from other first generation products. Indeed, a study (at the Royal Free) on patients previously untreated with factor VIII suggests that Profilate has a very low transmission rate for non-A, non-B hepatitis.
"HIV:
"The theoretical risk cannot be ruled out, but there is no evidence of any HIV transmission in the UK by this product, nor of any such case outside the UK.
"Reference Centre Directors:
"We have been in touch in confidence with Dr Rizza, director of the Oxford Haemophilia Reference Centre (who is also chairman of the directors of the UK Haemophiliac Reference Centre). He has confirmed that heptane treatment Profilate has performed relatively well and was regarded often as the preferred option for patients starting on factor VIII treatment. He was not aware of any clinical evidence



that heptane treatment Profilate is or has been less safe than other Factor VIII products. He was most concerned to avoid any additional pressures on haemophiliacs and their doctors at this time and hoped there could be a low profile resolution of any perceived problem.
"Regulatory action:
"The company has failed over a period of some 20 months to deal effectively with a major deficiency in their manufacturing process which could affect the safety of their product. In spite of the lack of evidence to suggest that heptane treatment Profilate has been associated with any abnormal levels of infection, MCA have considered whether regulatory action should be taken. This would involve suspension of the product licence if necessary with immediate effect. If we immediately suspend, it would be logical also to arrange a recall of stocks from hospitals and patients (some will have stocks in fridges at home). Indeed, such a step would be virtually inevitable."
Next page, please.
"Such action would remove very quickly any prospect of further exposure of haemophiliac patients to heptane treated Profilate. It is likely that BPL



could, at least for some months, meet the shortfall in supply, though it is also likely that there will be increased use of other commercial products, some not yet licensed, and some may have a less good clinical safety record than Profilate.
"14."
And the first sentence is emphasised and underlined:
"However, the clinical record of heptane treatment Profilate does not suggest that, on safety grounds, the evidence is there to warrant immediate suspension. Such action would give rise to [underlined] great anxieties amongst the haemophiliac community, a very high percentage of whom will have used Profilate at some stage. It would not be possible to assure them that the problem related only to the recent production. Many would also currently be using Profilate. There would be much attendant publicity. Questions would be asked as to why, if suspension is necessary now, the action was not taken when our inspectors first became concerned in February 1988, insofar as the deficiencies then found have not fundamentally changed."
"No immediate suspension would provide the company with time to exercise their right of appeal

before the decision becomes public and took effect."

There is a footnote which explains that the company would have a right under the Medicines Act -- go down to the bottom, please, Soumik, thank you:

"The company would have a right under the Medicines Act to make representations to a 'person appointed' by the Licensing Authority. These are formal hearings in private, followed by a report of the proceedings to the Licensing Authority. The hearing would be in private unless the company wished otherwise. The report is private."

Going back to the main body of the text.

"This appeal would probably be in private but knowledge of it could become public."

**SIR BRIAN LANGSTAFF:** Just stop there for a moment. We've got a highlighted box, which shouldn't be highlighted, I think, should it?

**MR HILL:** It is, sir. If we see the footnote, that is the footnote to which I just took you, which explained that about the right of appeal.

**SIR BRIAN LANGSTAFF:** I see, right.

**MR HILL:** Then back to paragraph 15, and "This appeal" --

**SIR BRIAN LANGSTAFF:** Very well.

**MR HILL:** -- picking it up from there:

"This appeal would probably be in private but



knowledge of it could become public. The final decision whether or not to confirm the suspension would be for Ministers as the Licensing Authority. If the product were suspended following an appeal, the attendant publicity might be less than with immediate suspension but the difficulties could be of the same order with questions also as to why, if there were safety concerns, action had not been taken earlier.

"Alternatives to regulatory action

"The company is known to want to switch production for the UK market to its new process. It cannot market Profilate made by this process in the UK until its product licence has been varied. However, it is possible that the company could be persuaded to begin withdrawal of the heptane treatment Profilate ahead of marketing of the new process product here, for commercial reasons. Whilst not making any deal with the company we could also expedite processing the application to vary the UK licence (though it may take some months even so). The company might be helped in reaching its decision if they believe that regulatory action might be taken against their licence if they do not act voluntarily."

"Conclusions

"MCA and HS1, with their medical and legal



colleagues and the Procurement Directorate, have considered the issues.

"As noted above, they have concluded that, whilst the process deficiencies revealed by the Inspectorate are a cause of concern, the clinical record of heptane treatment Profilate does not suggest that these apparently long-standing deficiencies are such as to warrant immediate regulatory action against the product.

"They concluded that a better alternative would be to open discussions with the company with a view to securing early withdrawal of heptane treatment Profilate, plus action to speed up consideration of the company's application to vary its Profilate licence so as to market the newer version of the product now sold in the US.

"MS(H) is invited to note these conclusions and to say whether she endorses them."

That is from Mr Wilson, the date of that document is not -- sorry, 24 November 1989. The response from the Minister is at DHSC0001366. It is dated 6 December 1989, and sent to Mr Wilson from the Minister's Private Office. It says:

"Thank you for your submission of 24 November. Mrs Bottomley has considered this and is not happy



with the line proposed. She would prefer regulatory action to be taken and would welcome advice on the consequences of this."

The response from Mr Wilson comes in a document of 15 December 1989, which is at DHSC0001375. We can see again copied to a large number of individuals including Dr Metters, the Deputy Chief Medical Officer, and the Minister of State for Health's private office.

What Mr Wilson says is this:

"[The Minister of State] has indicated, via your minute of 6 December, that she would prefer 'regulatory action' to be taken against the Factor VIII product PROFILATE. This was in response to my submission dated 24 November. She asked for a note on the consequence of such action. Advice to that end is set out in the Annex.

"Briefly, regulatory action could involve

"a. Immediate suspension of the product licensing for which we have to be satisfied that this is necessary in the interests of safety;

"[or] b. A proposal to suspend, giving the company appeal rights provided they give notice within 28 days. Any suspension would not then take effect until the appeal rights had been exhausted, which

could take several months.

"The Annex refers to the consequences of taking either course, for the company, for patients and for the Licensing Authority.

"Immediate Suspension

"Professional advice is that, on balance, we do not have sufficient evidence to support immediate suspension. This position was reached taking into account the theoretical risk posed by the deficiencies noted by the inspectors, the lack of problems in the batch release of the product from NIBSC and the fact that there is no clinical evidence about the use of a product which gives rise to concern. On the basis of that advice, immediate suspension would cause unwarranted concern to the many patients who are or have used PROFILATE. Such action has to be seen also in the context that (having studied the company's dossier) we now think it most likely that the Licensing Authority will be able to agree their application for a variation to their existing licence before the end of January. (The Committee on Safety of Medicines will consider it on 25 January). Once that variation is agreed it will no longer be possible for the company to market further supplies of the heptane treatment PROFILATE in the UK. The company has, we



understand, ample stocks of the new (solvent detergent treated) PROFILATE and will wish to supply it to the UK market without delay.

"So immediate suspension is now likely only to cut short cessation of supply of the product by a matter of a few weeks. With that in mind and given the lack of clinical evidence of any abnormal safety hazard, the concern immediate suspension would cause to the haemophiliacs and the serious public questions to which it would give rise, our advice to Minister must remain strongly against such action. It is true that we cannot say that there is not a potentially greater risk of infection from Profilate because of manufacturing deficiencies. But that risk has to be assessed as very remote given the usage of Profilate in recent years.

"Proposal to Suspend

"As an alternative, we could however inform the company that we propose to suspend the licence (but not with immediate effect) unless they are willing voluntarily to cease to market the heptane treatment product. A proposal to suspend would leave the company in no doubt that we were dissatisfied both with their lack of progress in putting right the deficiencies and with the present situation regarding



the production process. It would seem fully warrantable. Such action by the Licensing Authority would not be made public. The company could then choose to exercise its 'appeal' rights but we think this is unlikely. The company must indicate whether or not it wishes to do so within 28 days. Any such action would in practice be likely to be overtaken by the grant of the variation before [the] end [of] January and the company will no doubt take that into account in deciding how to respond.

"We should seek in discussion with the company to press them to exchange existing heptane treatment PROFILATE held by health authorities in the UK for the new product. We believe that the company may be receptive to this approach and will be anxious to co-operate.

"Conclusion

"If the Minister wishes regulatory action to be taken we would accordingly advise that this should not be with immediate effect.

"Is the Minister content? If so we will proceed urgently with action as at [paragraphs] 5 and 6 above. We would be happy to discuss if she wishes."

That is signed by Mr Wilson and I remind you, sir, that is 15 December 1989.



The annexes to the document are at pages 4 to 6. I'm not going to take you all of the way through those. I would point out -- sir, if we could go to page 4, please, Soumik. We have the consequences for the company set out, and that discusses some of the possibilities that have been raised in the main minute. Then the consequences for people with haemophilia, including the need to switch to a different product. At the top of page 5, underlined:

"We cannot say that patients switching from PROFILATE to other commercial products would necessarily be transferring to a potentially less risky product. Indeed we suspect that in some cases the reverse might be the case;

"there may be in the order of 2,000 patients currently using PROFILATE."

The consequences for the Department. If you look at paragraph 4, we can see that it's noted that:

"Any announcement of immediate suspension would give rise to public/Parliamentary questions about the basis for the action ... which could receive considerable media attention ..."

I quote from the document:

"It would not be easy to explain why action was being taken now when it could not be shown that the

problem was a new one. Attention might rapidly switch to that issue with accusations of negligence by the Licensing Authority. It would be possible partially to answer this by reference to the fact that when our Inspectors first identified the deficiencies (February 1988) the BPL could not have made up the then considerably bigger share of the UK market held by PROFILATE and that we could not be confident that more acceptable products would have been available. Clinicians could have chosen, on a named-patient basis, to prescribe products without a UK licence, with a possibly greater risk than PROFILATE. But that response would in turn raise concerns about other products and would be an admission that we had regarded the product as potentially unsafe for nearly 2 years.

"If the decision were that the licence should be suspended but without immediate effect the consequences would be ..."

Itgoes on to discuss the consequences for the company.

Then if we turn over to the next page, for people with haemophilia, if I read from that section, paragraph 6:

"if the company, facing suspension, decided to



cease supply, then some would need to switch to other products when existing stocks available to them were used up. By then it could well be the case that the 'new' PROFILATE (not the heptane treatment product) would be available. If the company ceased to supply the heptane treatment product ahead of the availability of the new product they would be likely to indicate that this was for commercial reasons;

"b. The prospects of causing serious concern amongst haemophiliacs and hospital specialists would be much reduced as compared with immediate suspension and there would be less likelihood of patients being switched to other commercial products which might not be any safer ..."

The consequences for the Licensing Authority of not suspending immediately:

"the Licensing Authority would not be obliged to publicise either the proposal to suspend or any final suspension. But we should need to tell the EC Committee on Proprietary Medicinal Products of the suspension (Community obligation).

"b. We would not be obliged to tell directors of haemophiliac reference centres but once the suspension had been given effect we would wish to do so on the expectation that they would not then seek to



publicise the matter.

"c. If the company, facing possible suspension, ceased to supply the product, there would be no action required of the Licensing Authority."

Those are the annexes to the submission of 15 December.

The supply to that submission came on 19 January 1990. Could we can have on screen, please, DHSC0001374, sent to Mr Wilson. Again, sent to a number of others as well, from the Minister of State's Private Office. The decision is this:

"Thank you for your submission of 15 December. As I previously confirmed to your secretary, Mrs Bottomley has considered this and is content to accept your advice, and to act as set out in paragraphs 5 and 6."

That is the proposal to indicate to the company that they proposed to suspend the licence but not take any immediate action on the licence.

It appears that that was then acted upon, because we have a letter dated 26 January 1990, which comes from Alpha Therapeutics UK, from JP Betts, the Regulatory and Technical Affairs Manager, and it was sent to Mr J Bewley at the Committee on the Safety of Medicines at the MCA. What it says is this, in



respect of Profilate Heat-Treated:

"This is to confirm our telephone conversation of today concerning the above product."

Sir, it's MHRA0033386_009. Apologies, Soumik. I should have said that. Sir, this is the letter that the company sends to the Committee on Safety of Medicines:

"This is to confirm our telephone conversation of today concerning the above product. The last batch of Profilate Heat-Treated to be imported into the UK was in the middle of December 1989. We do not intend to import into the UK any further batches of this product. As you may know, a variation application to allow the use of solvent-detergent Profilate-SD is currently outstanding with MCA.

"I would like to emphasise that the decision not to import further batches of Profilate Heat-Treated has been made on the basis of the heavy demands on our manufacturing facility in the USA and also the current market situation in the UK."

As predicted, sir, the company is explaining it by reference to commercial matters, rather than safety matters.

I will finish this section, sir, by noting a memo dated 11 January 1990, in which it was reported

that the new facility for the manufacture of Profilate Solvent Detergent method, Profilate SD, had been inspected and found to be acceptable. The reference to that is MHRA0033382_007.

That, sir, concludes the section on the consideration of the suspension of the Profilate HT licence. The outcome appears to be that the company was warned that there was a proposal to suspend and, in response to that warning, the company voluntarily agreed not to import any further products into the UK.

I note the time, sir. We have left a very short section on Factor IX and then a slightly longer section on the donors used by Abbott and Alpha. I suspect that you may wish to return to that tomorrow.

**SIR BRIAN LANGSTAFF:** Well, you certainly don't have time to present that tonight. Not least because it's now 4.35.

So we'll take a break until ten o'clock tomorrow when you can continue and deal with the -- those two remaining matters, at least those matters that remain for the moment, in respect of Abbott Alpha. So 10 o'clock tomorrow.

**(4.35 pm)**

**(The hearing adjourned until 10.00 am the following day)**



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