Friday, 1 October 2021

(10.00 am)

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

SIR BRIAN LANGSTAFF: Yes.

MR HILL: Sir, today we turn to Speywood, and it is important to begin by noting the differences between Speywood and the other companies that we have been Speywood was a British company and was, throughout the period involved, a relatively small company. While it manufactured some blood products, these were not widely used in the UK market. It's fair to describe them as being somewhat peripheral products.

The company was also involved in a wide range of other activities, we will look at those as we go through. But there are three elements that of particular interest to the Inquiry. The first, and as we heard yesterday, is that Speywood imported Cutter product, Koate, and subsequently re-branded it as Humanate, and sold it in the UK.

The second aspect is the work that was done by Speywood on human Factor VIII fractionation through a process called polyelectrolyte fractionation. We will hear evidence about what that was in due course. The product subsequently came to be called

Mono VIII:C, but is often referred to in the documents as the human Factor VIII product, or words to that effect. The product was never widely produced and never widely used, and we will explore why that was.

The techniques developed for Mono VIII:C were, however, very important in the origins of the recombinant Factor VIII story. We will look at that today as well.

The third element of interest to the Inquiry of Speywood's work was the production of porcine Factor VIII, again, through polyelectrolyte fractionation.

As the name suggests, porcine Factor VIII was produced from pig plasma. The product that was made using that technique was called Hyate:C. It was primarily used for treating patients with Factor VIII inhibitors, and was not in general used for haemophilia patients who did not have inhibitors, and we will examine why that was.

We will hear evidence later today from Sarah Middleton, who was, among other roles, the chief scientist at Speywood for a period during the early eighties, late seventies and early eighties. We will hear her evidence after this presentation. What I say in the presentation is not intended in any way to

pre-empt that evidence. Her analysis of the documents may be different to mine, and ultimately, sir, it will be for you to decide what your analysis is.

The presentation, as with all of the presentations this week, will touch upon some of the documents. It's not exhaustive. It is not comprehensive. There are matters that we may have to return to later, if that would be of assistance to you. And as, again, with all of the presentations in the last couple of weeks, it is limited by the access that we have to the papers. We have a lot of material, but we have by no means all of the material that we would like to have in order to tell the full story.

Before turning to the products, it is helpful to have a look at the company structure and how that developed over time. A helpful way of doing that is by looking at a document IPSN00000027, please, Soumik.

We can see from the front page of this document that it is a report prepared by Deloitte, Haskins & Sells, a firm of accountants, a very eminent firm of accountants, and it is dated 9 December 1981, and the report is headed "Speywood Laboratories Limited".

The context of the report is that it was prepared ahead of a proposed joint investment in

Speywood by the National Enterprise Board, who was a Government body that's invested money in firms that were, it was hoped, going to go on and make a successful business within the UK, and also an investment by Prutec Limited, which was the investment arm of Prudential Insurance. We will return in due course to the context of that investment and what happened around it, but for present purposes, the report is a helpful way of us understanding the company and the way that it was structured as of 1981.

Could we have, please the second page.

We can see in the left-hand corner that the report is directed to DA Smart of Prutec Limited and I Burns of the National Enterprise Board. It says:

"Introduction:

"In accordance with the instructions contained in your letters of 26 October 1981, we have carried out an investigation into the affairs of Speywood Laboratories Limited and its present subsidiaries ('Speywood Group') in connection with a proposed joint investment of £4 million in Speywood Laboratories Limited ... by Prutec limited and the National Enterprise Board."

The report refers to Speywood throughout and I'm going to do the same throughout this presentation. If

we could go, please, to page 3. The "History and Business" section. The report says this:

"Speywood was incorporated on 19th November 1973. In 1974 the company purchased ethical drug products from S Maw and Sons, including animal plasma fractions for the treatment of haemophilia and Zonulysin, an enzyme for the removal of cataracts.

"By 1978, the main trading activity of the company was the sale of Koate (human Factor VIII imported from Cutter Laboratories). This distributorship was terminated by Cutter in 1980 although Speywood are still able to obtain the product through a US intermediary. Speywood continued to sell Koate in the UK under the name of Humanate, but stopped in June 1981 when the product licence was amended."

Pause there, sir, to tell you that these are all matters that, I will come on to in due course.

On to the next page:

"Over the years the company has been seeking to improve its animal plasma products. It has now developed a manufacturing process using polyelectrolytes developed by Monsanto. Porcine Factor VIII produced by this process and sold as

Hyate C is now the company's main product."

The report then goes on to list subsidiaries and former subsidiaries, and we can see at various points there have been a variety of businesses: a dietary food business, a television projection and ancillary equipment business, a business entitled Vision Medical Limited. These had all either been sold off or had ceased trading, some with losses, some sold at a profit. Then the final one is Cardio Technology Limited, and we can see that that was sold with 85 per cent of the share capital to a Mr P Hammond, who went to become the Chancellor of the Exchequer.

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

Some further businesses, retail pharmacies, and then a US company, Speywood Corporation, and a west German company, Speywood GmbH, which were intended to be outlets into those two markets. But, as the report says, the US company has never traded and the German company is intended to be used as an outlet that, at that stage, I don't think it was being used. These aren't companies that will trouble us today.

What is also clear from the report is that Speywood is based in two centres. There is an office in Nottingham, or Nottinghamshire, I should say, and, as we can see in the "Future Plans" section,

a 10,000 square foot factory on the Wrexham Industrial Estate leased from the Welsh Development Agency.

If we could go over, please, to page 7. This is a page containing details of a licensing agreement reached with the Monsanto Company. We will again come back to some details of this, but I don't intend to go through the fine detail of who had which rights. But you will see there, sir, that by 1981, there is a fairly detailed explanation of the relationship between Speywood and Monsanto. The crux of it is that Monsanto had licensed to Speywood the technique to use polyelectrolyte fractionation both in porcine and human plasma, and in return, Speywood had agreed to certain limitations on its rights use the products that resulted from them.

Although that version of the licensing agreement dates from 15 August 1981, there was a previous agreement as well.

If we could now, Soumik, please, go to page 30 of the document. Under the heading "Management and Staff" the report says:

"At the time of our review, Speywood employed 12 persons at Bingham [that's the Nottinghamshire site] and 21 at Wrexham."

So we can see, sir, a much smaller company from

those that we have been dealing with in the recent days and weeks.

"The senior staff are:-

"D Heath -- Managing director

"P Lees -- Commercial director

"D Williams -- Marketing director"

And those names, David Heath, Peter Lees and David Williams will come up as we go through the presentation today.

Then, a few names down:

"Mrs S Middleton -- Chief Scientist"

That's Sarah Middleton who will be giving evidence later today.

If we could go back, please, Soumik to page 27 -- sorry, 26. The bottom half of that page, please, under the heading "Share Capital". The accountants set out the current position as of 1981 on the shares that were owned by the different equity holders in the company. I will use the adjusted figures, and we can see that an investment trust owns 32,000 shares, so that's about 40 per cent of the company.

A finance body owns a further 21,200 shares, so that's about 26.5 per cent of the company. Mr Heath owns 18,800 shares, that's 23.5 per cent. So that's

about roughly a quarter of the company. And Mr Lees and Mr Williams have about 5 per cent of the company each. So those are the equity holders.

I merely note that Sarah Middleton is not one of the equity holders. She was the chief scientist and hence an employee of the company.

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

The proposed investment of £4 million was in fact made in 1982 by Prutec and the National Enterprise Board. Both of those entities took 25 per cent of the equity of the company, meaning that the 50 per cent that was left remained in the hands of the original investors, presumably according to the same proportions.

After that investment, a new chairman, Mr Seymour, was appointed, and Mr James Mottram became the general manager in 1983. His brief, according to the documents that we have, was to, and I quote, "reorganise Speywood into a classical UK pharmaceutical company". The reference for that is IPSN0000166_019. Mr Heath and Mr Williams subsequently left the company and we will hear a little evidence about the circumstances in which that took place, and the disputes that gave rise to it.

In 1984, the company was acquired by Porton International. It was later acquired by Ipsen Biopharm Limited.

Just for your note, Ms Middleton, from whom we will hear later, left the company in 1984, just before it was acquired by Porton.

Turning then to the importation and sale of factor concentrates. As we heard yesterday, there was an agreement, a distribution agreement, between Speywood Laboratories and Cutter Laboratories, so that Speywood could import and sell within the UK the Factor VIII product, Koate. The agreement itself is at IPSN0000139_003. It ran for three years from June 1976.

I won't take you to the agreement, sir, but it is there for future consideration should that be necessary.

A product licence, PL 0370/0004, was granted to Speywood for Koate in August 1976. The reference I have for that is IPSN0000312_036. We know, and as we heard yesterday, that Cutter had originally submitted an application for Koate, but Speywood in effect took this on. There is correspondence to that effect, which is BAYP0000020_046.

Unfortunately, sir, we don't have at present the

documents that will help to answer the questions that we raised yesterday about the level of detail that was provided before the licence was granted, to what extent further information was provided about the source of plasma and the way in which donors were selected and indeed rejected. That is something we will continue to explore. We will seek to work with others within the Inquiry, as well, to see if they can shed any light on it. But, at present, I'm afraid, I can't take that story any further.

We know that there was some further correspondence about packaging and the hepatitis warning in October 1976, a reference is IPSN0000312_040. The warning itself -- and perhaps we could bring this up, Soumik -- is at IPSN0000329_001.

Here we can see the data sheet for Koate. The product licence is there on the left-hand side. The address of Speywood and, of note, sir, is that the address given is the Bingham address, the Nottingham address, and not the Wrexham address. There may be a significance to that as we go through.

If we could -- give me one second, Soumik.

If we could go to the second page, please, the "Contra-indications and warnings", it says:

"There are no known contra-indications to Koate.

"*Hepatitis* -- Koate is prepared from units of human plasma, each donation offer which has been found non-reactive for hepatitis B antigen ... when tested by radioimmunoassay. In addition, each batch has also been tested against hepatitis by radioimmunoassay. However, despite these tests and the precautions taken in selecting donors, the risk of transmitting serum hepatitis cannot be excluded."

Thank you, Soumik.

The product was on sale from Speywood from 1 November 1976. Reference for that is IPSN0000312_038.

We have some sales figures from November 1976 to October 1977, and please can we have this on screen, please, Soumik, IPSN0000146.

Very helpfully set out per haemophilia centre with a grand total at the bottom. We can see that we're not entirely comparing like with like because the -- some of the centres have been using the product for longer than others. Bristol has been using it for a full 12 months, compared to St Thomas's just using it for five.

More than 500,000 units, and I take that to mean international units, had been sold to Oxford. Then about just over 300,000 units to Liverpool.

If we go down to the bottom Soumik, we can see that the total sales for that period, November '76 to October '77, a 12-month period, is 2.7 million units.

Those sales, sir, were achieved despite not tendering for the NHS central contract that we have seen in some of the other presentations. We will return to this matter and, indeed, the reasons why Speywood didn't tender to that contract when we come back to look at some of the evidence from civil servants and Government ministers.

A reference, so that we have it for when we come back, is DHSC0003719_098, which explains Speywood's thinking at that time.

David Williams, the marketing director, one of the names that we saw in the accountant's report, met with leading haemophilia clinicians between August 1978 and January 1979 to discuss their factor concentrate usage, and the Inquiry has considered some of the notes that he made of those meetings when examining each of the centres, so I won't take you through each one but they're helpful ways of getting a snapshot of what the Centre was doing at the time.

I will, however, just highlight one, for present purposes, which is IPSN0000334_019. We can see from the file note that this is Mr Williams's meeting with

Professor Bloom at the University Hospital of Wales on 24 August 1978.

I'm going to read through all of this note, sir. There will be some things that I focus on now, which are to do with the product sales, and some things that I will come back to in due course which in particular concerns polyelectrolyte fractionation. The initials "PE", as we will see on this note, refer to polyelectrolyte fractionation.

What Mr Williams said in the note is this:

"There are 250 haemophiliacs attached to this centre, of which 100 are regular attenders and 13 inhibitors. Until recently, human factor VIII purchases have been split three ways, Hemofil, Factorate and Elstree. They have now stopped using Armour, following the hepatitis problem."

I just pause there to note that, although it's not clear from this document, that may relate to reports in 1977 and 1978 of adverse reactions and hepatitis infection through the use of the Armour product.

"Prices are: Hemofil 11p and Factorate 9.5p."

Factorate being the Armour product.

"Bloom used to favour Immuno, but as this is now 16p, he never buys.

"He is not interested in the administration kits but prefers to make his own up in the hospital.

"I offered Koate at 10p for 50,000 unit lots and am reasonably confident that we will get some of the business. Bloom always likes to keep two suppliers, but is reluctant to make frequent changes.

"Bloom is obviously not an animal lover although he is interested in our work."

Pause there, sir. A slightly cryptic reference, I believe, to porcine Factor VIII.

"He is prepared to look at the new material when available. He referred to Rizza's suggestion that use of porcine increased the inhibitor level to human. He also felt that the present material was too antigenic and expressed doubts as to the likelihood of our reducing this to a level which he would regard as satisfactory. I think it important that we provide him with clinical evidence as soon as possible. Perhaps Jean Pierre could prepare some notes."

I pause there, sir, to say that we will be coming back to this, but Professor Bloom's reaction to the possible use of porcine Factor VIII is, I would suggest, fairly typical of the view at that time in 1978, and we will come on to see how that view changed or, indeed, whether it changed, in due course.

"Bloom would like some PE to help with new research project of his looking at the biochemistry of human factor VIII. He has a research worker starting January 1979, to work full time on this subject. We could arrange to have first option on the results.

"PPF was at one time rationed in his area, but is now issued on a first come, first served basis. There is never enough available, partly because the Health Service does not produce sufficient, partly because of the high price. Bloom felt that there was a place for commercial material, if it could be produced more cheaply. We should obviously investigate."

The date of the note is 31 August 1978 and we can see at the bottom that it was copied to Mr Heath.

As I say, sir, there are a number of other similar notes. I'm going to be give some references for the transcript so that people have those in case they are of use to them. I would point out that in one of them, which concerns Dr Stewart at Birmingham, he says that he hadn't heard about any hepatitis problem in connection with the Armour product. That is IPSN0000333_022.

The other references are IPSN0000332_021, IPSN0000334_019, IPSN0000331_008, IPSN0000333_022,

IPSN0000338_011 and IPSN0000321_026.

The prices that were offered to the various clinicians varied. Some of that variation is due to different amounts of product being offered. As you observed the other day, sir, there is generally a discount for bulk. However, there is also an attempt to negotiate with individual clinicians to try to get their business, in essence.

As we've seen in that letter, 10p was offered to Professor Bloom; 9.5p for 1 million international units was offered to Dr Kernoff at the Royal Free in January 1979; 9p was offered in a draft letter, seemingly to the whole Haemophilia Centre Directors, dated 1980. The reference for that is IPSN0000325_001.

Dr Preston was offered 9.25p in August 1979 and 8.5p by May 1980. The reference is IPSN0000322_006, and the same stem, _003.

The pattern, which you will have observed, sir, is generally a falling one.

In December 1979, an issue arose about the potency claimed for Koate on its labelling.

What appears to have happen is that, when the product was tested by NIBSC and by the individual Haemophilia Centres, they found that their assays did

not accord with the potency that was stated on the label. If we could go, please, Soumik, to IPSN0000575, we will see some of the correspondence about this. The date is 4 December 1979, and the letter is going from David Williams to Mr C Jones of Cutter Laboratories. As we will see it's not only raising the problem but also raising the point that Speywood would like compensation from Cutter for the difficulties and the financial difficulties that the problem had given rise to.

What Mr Williams says in the letter is that the:

"... situation with respect to [as he terms them] 'suspect' batches of Koate is as follows ..."

We can see there four batches listed down, and we can see, in the second column, the assigned potency, which I take to mean the potency that was stated on the label.

You can also see the quantity received, the current stock and how much had been sold.

The paragraph below, Mr Williams says:

"As you will realise from the quantity involved, we have a major problem. On the one hand, we are desperately short of 'good' stock and, clearly, we dare not sell new batches without first obtaining NIBS clearance. So your urgent help with prompt despatches

is of paramount importance. The other side of the coin is that we have two major and influential customers, Oxford and Newcastle, reluctant to trust our assay figures and insisting on their own check prior to acceptance."

He gives some further detail on each of the batches.

The first batch, C 1090, if we look back at the table we can see that its assigned potency was 1,100. Mr Williams, in his letter, says that C 1090 was:

"Not acceptable to NIBS unless we re-label at 900 my own view is that this should be returned to USA."

So NIBS has run its tests, found that the potency figure that they can obtain using their tests is around 900, and are insisting that the product is re-labelled to show that potency, if it is to be sold in the UK. This is an example, sir, of the stop orders that we have heard made reference to. The suggestion from Mr Williams is that that product should be sent back to Cutter and, presumably, Speywood would be compensated for the cost of it.

The second lot considered is NC 8610, which:

"... has been extensively used in Oxford and Newcastle and is the subject of an attached letter

from Rizza and Jones."

We don't have that letter.

"NIBS obtained 210 and cleared at 230. Repeat assays at Oxford indicate 185."

What I take that to mean, sir, is that when NIBS -- the assigned potency, as we can see from the table on the previous page, is 230. NIBS in their tests obtained 210, the units don't matter but a figure of 210 for the potency, so about 10 per cent below that which was claimed. I read that as meaning that NIBS were content to clear the product as saying that it had a potency of 230, presumably allowing some leeway for a potential difference in testing.

But when the product was then tested at Oxford, the potency was 185, which appears to have prompted a complaint to Speywood about the product.

Mr Williams goes on to say that:

"For the present, I have supplied replacement material free of charge to both centres. Probably the simple way out financially, is to give them units equivalent to their 'loss', say 20% or 126,000 units. Obviously we will be looking to Cutter for compensation."

So the fact that the product is not as potent as claimed means that more will have to be used, hence

that figure of 20 per cent. They will build up the stockpile to replace that which these centres should have had. And as is stated in terms there, Speywood are looking to Cutter for compensation on that. So Speywood very much seeing this as a problem of Cutter's making.

"NC 8185

"This was cleared by NIBS at label declaration, although their assay was around 10% low."

Again, sir, showing that there is a degree of leeway allowed by NIBSC. But as we can see from "NC 8184":

"NIBS again got 900 and will not clear without re-label."

The claimed potency was 1130.

So the leeway only extends so far before NIBS, using stop orders, say: you can't distribute this product without re-labelling it.

What Mr Williams says about that product is:

"I originally stated that we would [re]sell to France at label strength and in fact we have sold them 200,010 units. However, in view of total problem, I feel it is not sensible to continue this policy."

I would say there is a further document, sir, at IPSN0000291, which is dated 21 February 1980, which

shows that, after further thought, Speywood had decided not to sell product to France when NIBS has said that it must be re-labelled. And one of the reasons that is given for that policy is that Duncan Thomas of NIBSC is in regular contact with his French opposite number and it would be embarrassing for the companies involved to be found to be selling with one label in one country and one label in the other country. Although I should add that it's important to note that in his letter of 21 February 1980, Mr Williams also refers to a basic moral issue that is involved as well. So it is not just a cynical attempt to avoid being caught.

The further point made by Mr Williams in his letter of 4 December 1979, a little further down the page, please -- thank you Soumik -- is:

"Of course, any recommendations on these batches could change if your technical people can resolve the matter with NIBS. I do hope you can achieve an agreement quickly."

So there is some thought that this may be a technical issue perhaps about how the different tests work.

Thank you, Soumik. We can take that down.

I leave that there, sir. It is an example of

the way in which the licensing system works its way through at different levels.

Turning to the switch of products from Koate to Humanate. The June 1976 distribution agreement between Cutter and Speywood ran for three years, and it appears that it was terminated at the end of 1979. Cutter then began supplying Koate directly to the UK market. We heard something about that yesterday.

The references are IPSN0000331_001, and MHRA0036365_018.

In February 1980, Speywood obtained a variation to their product licence allowing them to continue selling Koate for up to one year, and also allowing them to import unlicensed -- sorry, to import unlabelled factor concentrate manufactured by Cutter for relabelling and for sale under the name Humanate.

I'm afraid, sir, that we don't have the documents that accompanied that licence variation application, or at least we haven't identified them if we do have them. Our information is taken from a later licensing issue, which we will come on to. The reference is MHRA0036365_018.

MR HILL: According to company records, the last Koate batch imported by Speywood was released by the DHSS, so that's released by NIBS, in February 1980. The

reference is IPSN0000139_022. That product, of course, would have had a longer shelf life. The last time that a Speywood sale under the licensing agreement seems to have been cleared by NIBS was February 1980.

The way in which Speywood began to sell Humanate can be shown by a letter that was sent to Dr Aronstam at Treloar's Centre by Mr Williams on 30 July 1980. The reference is IPSN0000331_001.

Again, sir, I'm going to read all of the letter through. There are matters that we will come back to later, but I think it is important to show how the different strands of Speywood's work: the human Factor VIII, the porcine Factor VIII, and the sale of imported products, all work together. Although we're going to be looking at them individually for purposes of analysis, they are running alongside each other all the time.

What Mr Williams said is this, and I quote:

"Dear Tony,

"As you are aware, Speywood are the only British owned company researching new blood fractionation techniques and the isolation of highly purified plasma proteins for clinical use.

"The first successful result of our research

programme, 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 the use of porcine material can be relaxed."

I will come back to that later.

"We are now working hard to produce human VIII:C and a vWF [von Willebrand's fraction] concentrate. Initial clinical samples will be ready by the end of this summer.

"Financing this research has been a major difficulty for such a small company as ours. For the first four years, we relied on our profits from sales of Cutter's Koate to provide the cash. Cutter are now selling direct and, to fill the gap, we have arranged the supply of a high quality freeze-dried Factor VIII product under our own trade mark, Humanate.

"Humanate is not an intermediate product and has a specific activity of approximately one AHF unit per milligram of protein. It is readily soluble and ideal

for home treatment. A leaflet and data sheet giving further information are enclosed. Pack sizes are nominal 250, 500 and 1,000 units.

"Our price for Humanate is 7.5p per unit, delivered, regardless of quantity, which we hope will give you some saving over current prices.

"Administration kits are available free of charge, if required. We can normally guarantee delivery within 24 hours.

"I do hope you will be able to give us some support and use Humanate for part of your treatment programme."

He says that he is sending a copy of this letter to Brian Grundy in Southampton.

One point that I would pick up from the letter, sir, is the reference to Humanate being, and I quote "not an intermediate product". You've heard evidence about the distinctions drawn between intermediate purity and high purity product and it was Dr Kingdon's evidence in his witness statement, CBLA0000011_005 at paragraph 31, he's referring to the 1970s but this letter is 30 July 1980. His evidence was that high purity was between 1 and 2 international units per milligram.

What is claimed for the product Humanate is that

the specific activity is approximately one AHF unit per milligram, which perhaps explains the slightly odd wording of Humanate being "not an intermediate product" but it is not claimed that it is a high purity product.

Soumik, can we have on screen, please, BAYP0000021_023, at the top right-hand corner, please.

This appears to be a data sheet for Humanate and, in the top right-hand corner -- I'm afraid it's a very poor copy -- we can see that it's written:

"Humanate is prepared from human ..."

SIR BRIAN LANGSTAFF: It looks like "venous".

MR HILL: "... venous plasma"? Yes, it looks like "venous plasma".

"Each unit of donor plasma has been tested for Hepatitis B Surface Antigen by a radioimmunoassay technique and found non-reactive. However, this test does not necessarily preclude the presence of Hepatitis Virus."

That appeared to be the warning that accompanied Humanate as of circa 1980.

Two things are clear from other documents. The first is that Humanate was Koate being sold under a different name. We saw reference to that in the accountant's report that we looked at earlier, and

a further reference, should it be needed, is BAYP0000021_063.

Second, the product was not obtained directly from Cutter but through an independent company called Parlier Medical Support. Sorry, Parlier Medical Supply Company, which was based in San Francisco, the reference for that is MHRA0036365_018.

On the first of these points, can we have on screen, please, IPSN0000338_001, a letter dated 31 October 1980, a few months after the letter that we looked at a moment ago, and sent from Mr Williams to Dr Evans of the Royal Manchester Children's Hospital. The section that I'd like to look at now is the second and third paragraphs. What Mr Williams says is, and I quote:

"Humanate is manufactured for us by Cutter Laboratories, so is identical to the product which we have previously sold as their agent [that's Koate].

"I will be grateful if you can keep this information confidential."

SIR BRIAN LANGSTAFF: So what you've just told me means that that's a lie, does it?

MR HILL: No, sir.

SIR BRIAN LANGSTAFF: "Manufactured for us", because it was bought from an intermediary, not direct.

MR HILL: It was bought with the knowledge, I believe, of Cutter, so --

SIR BRIAN LANGSTAFF: So Cutter manufactured it for Speywood and sold it through an intermediary?

MR HILL: As I understand it the position to be, yes, sir.

SIR BRIAN LANGSTAFF: I see, so it was manufactured for them?

MR HILL: So far as I can ascertain from the documents. It was certainly manufactured with -- well, it was within Cutter's knowledge that Speywood were doing this.

SIR BRIAN LANGSTAFF: Well, that's a different issue. You may know that somebody is manufacturing or selling something that you actually made but you may not want them to do it.

MR HILL: You may not, I don't know, but I've seen no evidence to suggest that Cutter didn't want them to do it, and Cutter could have entered into an arrangement with the Parlier Medical Supply Company to ensure that they didn't do it, and that, at least at this stage, does not appear to have been --

SIR BRIAN LANGSTAFF: At some stage they used the word "pirate product", Cutter.

MR HILL: There is a tension which develops, and we saw some of that in some of the documents yesterday.

The --

SIR BRIAN LANGSTAFF: That's not yet this stage?

MR HILL: So far as I can tell, that's not yet this stage. But there is a tension which does develop, and we will see, shortly, that there is also a tension with licensing position --

SIR BRIAN LANGSTAFF: Yes.

MR HILL: -- with Speywood.

What I take from this document, though, is that Mr Williams is prepared to answer what appears to have been a question from Dr Evans, and say, "This is Koate and it's made by Cutter", but, as we have seen from a previous letter from Dr Aronstam, there was an opaqueness, if I may put it that way, as to what the product was. It was certainly not said to Dr Aronstam that, "This is Koate", and it was not said, indeed, that it was a Cutter product -- no, sorry, it was said that it was a Cutter product. It says -- no, sorry I apologise. It was not. It said:

"We have arranged for supply of a high quality freeze-dried Factor VIII product under our own trademark Humanate."

So no further information given there about the source of that product, but, seemingly in response to a request from Dr Evans, Mr Williams does explain

where the product was from but then asks Dr Evans to keep that information confidential.

We will come back to this letter about the porcine product in due course.

If we could go forward, sir, just a few months, this is a document we did see yesterday BAYP0000021_063, please, Soumik.

This is the board meeting of Cutter Laboratories Limited, the UK-based company, held on Tuesday 16 December 1980. As I say, Ms Richards showed us this yesterday. If we could go down, please, to the central paragraph under the heading "Koate", it says:

"It was agreed that the Managing Director, Mr BA Dyos, would put together a full situation report regarding Koate and also the Speywood parallel product known as Humanate which was in fact Koate marketed under a different label. It was agreed that this situation report was important and should receive full priority."

A little further on there's a discussion about sales, and if we pick it up three lines from the bottom, it was said:

"... it should be possible to price Humanate out of the market coupled with the fact that NIBSAC and Doctor Duncan Thomas were very concerned regarding

Humanate and the impossibility of tracing its manufacture back to its source."

So concerns within Cutter Laboratories Limited about the market position, if I may put it that way, of Koate in respect of this other product, and a desire to price it out of the market. And also an indication that the Licensing Authority was concerned. And that is the second element that I'll pick up now: the significance of the use of Parlier Medical Supply Company.

The concerns flagged there in the minutes, the specific reference to Dr Thomas, led in fact to a variation of the licence that had been granted to Speywood for Humanate, and it's helpful to examine that process in a little detail, again because it assists us with our understanding of the way the licensing process worked.

If we could have on screen, please, Soumik MHRA0036365_001.

We can see that these are the minutes of the Committee on Safety of Medicines, that's the main committee, a meeting held on the Thursday, 22 January 1981. So the first meeting of 1981, and just a month or so after the previous document that we looked at.

There's a list of attendees. I note in passing that Dr J Smith, Dr Joseph Smith, is there, from whom we've heard evidence. And among the committee secretariat, for hearing 2 only, are Dr Fowler and Dr Holgate. Hearing 2, as we will see, concerns Speywood and Humanate.

If we could turn, please, Soumik, to page 3 of that document. Under the heading "Hearings" it says:

"Humanate ... Speywood Laboratories.

"8.2. A record of the Committee's findings in respect of the above is included at appendices B and C to these minutes."

And it is appendix C to which we will turn, because that's records a discussion on Humanate.

That is at MHRA0036365_018.

You can see, top right-hand corner:

"Appendix C ...

"CSM/81/1st Meeting

"Hearing 2"

Medical assessor is Dr Fowler and the product is Humanate.

We're going to go through this document in a little detail, partly because this is the information that we have about the original variation that allowed Humanate to be sold in the UK. We don't

have further papers, or at least we haven't found further papers. We will continue to look for them, because it will be interesting to see how the original variation was granted.

"Background

"1.1. Since 1976, Speywood Laboratories Limited has sold anti-haemophilic globulin (Factor VIII) manufactured by Cutter Laboratories under the name Koate in the United Kingdom. This arrangement had been terminated by Cutter at the end of 1979.

"1.2. In February 1980, Speywood had obtained a variation to their product licence which had permitted them to:-

"a. continue selling their remaining stocks of Koate for up to one year.

"b. import, in bulk, unlabelled vials of anti-haemophilic globulin manufactured by Cutter for relabelling and sale under the name Humanate.

"1.3. The material for sale as Humanate was not obtained from Cutter, but through an independent company called Parlier Medical Supply Company of San Francisco, California.

"1.4. At the time of granting the Speywood Product Licence for Koate in 1976, a full 'stop order' had been routinely applied. This had required the

licence holder to supply samples and protocols of tests above on every batch of product and not to sell or supply material from a batch until a certificate of clearance for it had been granted by the licensing authority. Speywood had complied with this requirement for Koate by supplying samples and protocols obtained from Cutter, to the National Institute of Biological Standards and Control."

I pause there, sir. That is why we had that exchange about the potency of the products and re-labelling.

Paragraph 1.5.

"The protocols supplied to NIBSC by Speywood for their first batch of Humanate has provided results of tests done on the finished product by a British contract laboratory. These had followed very closely those done by Cutter for Koate, but the protocol had omitted material included in the Koate protocol concerning the Bulk Active Substance Used for Formulation, Formulation and Filling. The Koate protocol had also contained Cutter's statement that the product had been manufactured by them at their plant in Berkeley, California. Although the tests done on the finished product were satisfactory, the protocol had been deemed inadequate, as it was

impossible to assess the safety of a blood product by reference to finished product-testing alone. Speywood have repeatedly said that they now had no contact with Cutter, and thus had no access to information relating to the manufacture of the product they were selling."

Over the page.

"Moreover the Product Licence granted to Speywood had obliged the company to ensure that all batches of the product continued to conform to the various specifications contained in the original application. While Speywood had acted as distributors for Cutter they had been able to do this. Now that they had no contact with Cutter they were no longer in a position to guarantee that the product sold as Humanate conformed to its Product Licence specification. If in fact Cutter were the original manufacturers of Humanate as claimed by Speywood they could have changed the source, place or method of manufacture of the product and Speywood would have been unaware of this and unable to communicate such changes to the Licensing Authority.

"The scientists at the National Institute for Biological Standards and Control ... frequently had to refer back to the company for clarification or further information concerning the manufacture of the product.

Where the Licence Holder was the manufacturer or his authorised distributor, this posed no problem. Where the Licence Holder had no communication with the manufacturer, as in Speywood's case, such a dialogue was impossible.

"As a matter of routine, the additional conditions contained in the Schedule to the Product Licence issued to Speywood referred to protocols but no mention was made therein to the contents required in respect of such protocols. This lack of information was unsatisfactory, particularly in regard to biological products of the type in question. So as to remedy the situation, it had been proposed under Section 29(1) using powers conferred under Section 28(3)(g) of the Medicines Act 1968, compulsorily to vary Speywood's Product Licence in order to require the protocols to include evidence of the source and date of collection of the donor blood from which the product was prepared, the date of manufacture and the results of tests done during and on completion of manufacture. This would have put beyond doubt the nature of the evidence required when the term protocol was used and would have served to bring Speywood into line with the current practice of other manufacturers of anti-haemophilic globulin."

I pause there, sir, to summarise what I understand the position to be, that the use of the intermediary company meant that NIBSC were unable to satisfy themselves that there was a chain that they could follow all of the way back to the manufacturers of the product in order to understand how the product was manufactured and the -- (overspeaking) --

SIR BRIAN LANGSTAFF: Way I understand it is that, leave aside the intermediary, there was no direct link between Cutter and Speywood any more --

MR HILL: Yes.

SIR BRIAN LANGSTAFF: -- so Speywood didn't have the information.

MR HILL: Yes.

SIR BRIAN LANGSTAFF: It begs the question, going back to what I raised earlier in the letter to Evans, how one could say that Cutter was making it for Speywood.

MR HILL: Yes. I will jump, if I may, to paragraph 1.10, which records that:

"The Licensing Authority [wrote] to the company on 27 November 1980 stating their proposal to vary the product licence ..."

The wording is given, which I won't go through now, because it will come up again.

On 30 July 1980, the company had written to the

Committee giving notice that they intended to avail themselves of the opportunity to appear before the Committee to ensure that their position was fully understood.

So this the working through of the Medicines Act 1968. The Licensing Authority is proposing to vary, the company has an opportunity to put its case and this report from Dr Fowler is part of the process that then follows.

Paragraph 2, or section 2, "Additional information":

"The Company had submitted a paper giving the background to their case and why the variation to the licence should not be imposed.

"On the day of the hearing, the Company handed in a copy of the a notarised statement from Parlier Medical Supply Company which certified that bulk unlabelled antihaemophilic factor (human) shipped to Speywood was:

"(i) manufactured and sold by Cutter Laboratories,

"(ii) approved and released for general sale in the USA by the FDA (Bureau of Biologics division)

"(iii) derived from human plasma collected in plasmapheresis centres licensed by and conforming to

the regulations of the US Bureau of Biologics.

"Preliminary discussion

"The following points emerged from the preliminary discussion:

"(i) that 4% of the batches supplied for testing in 1980 came from Speywood

"(ii) that of 50% of the batches from US sources, there had been need to refer back to the manufacturers."

We understand that to mean that in 50 per cent of the cases where batches of factor concentrates are tested, there's a need to go back to the manufacturer to ask of them some questions, which shows the importance of having that chain going all the way back.

"(iii) that Speywood were merely being asked to give information which was routinely supplied by all manufacturers of anti-haemophilic globulin sold in the UK."

Section 4, the "Hearing":

"The representatives of the Company were as follows ..."

Mr Williams, the spokesman and Dr Jones, from Newcastle.

"The Company's representatives were welcomed by

the Chairman, who introduced the Committee, the secretariat, and the DHSS officials present. The representatives had no objection to the presence of any officials.

"Mr Williams referred to the affidavit from Parlier Medical Supply Company which had been furnished and with the aid of slides explained that the Cutter material was subject to Cutter in-house quality control, before submission to the FDA/BOB for clearance. The material was purchased after clearance and thus its integrity was in his view guaranteed. Following delivery to Parlier Medical Supply Company, all packaging was removed and the product shipped intact to the UK. On arrival in the UK, the (unlabelled) material was subject to quality control, carried out in the laboratories of Toxicol and the Oxford Haemophilia Centre. Samples were then submitted to NIBSC together with protocols and following approval, the material was repackaged as Humanate.

"He considered that all Factor VIII products carried a risk of Non-A, Non-B hepatitis, but that the risk was minimised by the monitoring of donors by the FDA.

"Mr Williams felt that any additional data could

be obtained from the FDA possibly by NIBSC, under the US Freedom of Information Act.

"He explained that his objective in appearing before the Committee was to seek an extension of the present arrangements to enable the company to make other arrangements if possible for the purchase of Factor VIII and eventually to remove the Company's financial dependence on this imported Factor VIII.

"Dr Jones then explained that he had come to the hearing as an independent consultant (unpaid) to advise the Committee that in his capacity as director of a Haemophilia Centre, he had satisfactorily treated patients with Humanate.

"In reply to questions Mr Williams stated that he thought that, if necessary, donors of blood might be traced from Cutter's records by means of the Freedom of Information Act.

"He had accepted that the batches he imported (unlabelled) were consistent with Cutter batches, because of the assurances given by Parlier Medical Supply.

"Mr Williams said that he did not know of any other manufacturer who was asked to provide the information required.

"Findings

"The Committee found that there was insufficient evidence of any firm arrangement which would enable Speywood to obtain the data specified in [paragraph] 1.9."

SIR BRIAN LANGSTAFF: Sorry, now, that's not coming up on my screen at the moment.

MR HILL: Section 5 of page 4 of the document.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: "The Committee found that there was insufficient evidence of any firm arrangement which would enable Speywood to obtain the data specified in ... 1.9."

If we can go back now, please, Soumik to page 2 and to 1.9, and I'll read out what that data is.

What paragraph 1.9 says is:

"Following the Licensing Authority proposals a letter had been sent to the Company on 29 July 1980 in accordance with Sections 28 and 29 and Schedule 2 of the Medicines Act 1968. It had informed the Company in accordance with paragraph 2 of Schedule 2 that the committee had had reason to think that they might have to advise the Licensing Authority to vary the Product Licence for this product" --

SIR BRIAN LANGSTAFF: The information is the last five lines, six lines, is it?

MR HILL: Yes, so it is proposing varying the product so

that the information -- so that it contains --

"... the licence holder should on request furnish the Licensing Authority from every batch of a product" --

SIR BRIAN LANGSTAFF: -- (overspeaking) --

MR HILL: -- "a sample of such amount as the Authority considered adequate for any examination ... the licence holder should if required by the Licensing Authority, furnish evidence of a source and date(s) of collection of the donor blood from which the product was prepared, the date of manufacture of the product, and an outline of manufacturing methods, protocols and results of tests done, on the donor blood, during manufacture and on the finished product."

So that's the information that the Committee accepted was necessary, and they accepted the point made to them by the Licensing Authority that there was no way that Speywood could obtain that data.

The advice that the Committee then gave, and it's important to remember that the Committee is not the decision-making body, the Licensing Authority is the decision-making body, but, under these circumstances, it must consult the Committee. The advice that the Committee gave was to vary the product licence --

SIR BRIAN LANGSTAFF: Well, let's have a look at that because we're still back on paragraph 1.10.
MR HILL: Yes.
SIR BRIAN LANGSTAFF: We need to go to paragraph 6, don't we?
MR HILL: Page 5, please, Soumik.
SIR BRIAN LANGSTAFF: Shall we go back to the previous page?
MR HILL: Page 4, please, Soumik.
SIR BRIAN LANGSTAFF: "Advice", at the bottom of the page.
MR HILL: The advice that has been given is to vary the licence to "include the following words", and that's on page 5. I quote:

"The Licence Holder shall on request furnish to the Licensing Authority from every batch of the product, or from such batch or batches as the Licensing Authority may from time to time specify, a sample of such amount as the Authority may consider adequate for any examination required to be made; and the licence holder shall, if required by the Licensing Authority, furnish evidence of the source and date(s) of collection of the donor blood from which the product is prepared, the date of manufacture of the product, an outline of manufacturing methods, protocols and results of the tests done, on the donor

blood, during manufacture and on the finished product."

So it's accepting the argument that had been made by the Licensing Authority as to the information that was required.

The reasons for the advice, if we can go back, please, Soumik:

"That, because of the risk to patients arising from lack of evidence as to the origins and provenance of the donor blood, the Committee were not satisfied as to the safety [underlined] of the product."

That was the advice given by the Committee. I don't have a document for you, sir, showing the decision of the Licensing Authority, but it is clear that there was a product variation, and that, as a result of that product variation, Speywood ceased to sell Humanate.
SIR BRIAN LANGSTAFF: You mean licence variation?
MR HILL: Sorry, licence variation, yes. The accountant's report that we looked at earlier, IPSN0000027, page 3, says in terms:

"Speywood continued to sell Koate in the UK under the name of Humanate but stopped in June 1981 when the product licence was amended."

I don't know, sir, why there is a gap between

this consideration, which is taking place in January 1981, and the ceasing of the sales of Koate in June 1981. We don't have the --
SIR BRIAN LANGSTAFF: What was it, sales of Koate?
MR HILL: Sorry, of Humanate. It's fair to say that the accountant's report doesn't cite the resources that it's using, and nor was this its principal focus. So I'm afraid we simply don't know why there is that seeming gap -- of the significance, if any, of it.

I'm going to turn very briefly, sir, if I may before the break -- because I've nearly finished the section on Humanate and Koate -- there were a number of adverse incidents in the use of Humanate.

Glasgow Royal Infirmary reported possible NANB infection in three patients in a letter to Speywood in January 1981, and later, in March 1981, expressed their view that it was "highly probable" -- those were the words they used -- that Humanate was responsible for that infection. The references are IPSN0000336_005 and IPSN0000336_002.

There were also reports from Treloar's and Bournemouth of apparent allergic reactions to Humanate in February 1981. IPSN0000323_002 and IPSN0000323_003.

It may be that these concerns prompted the

following letter which was sent by Professor Bloom in March 1981. It's DHSC0001191.

I'm afraid it's a very poor copy. It is dated 10 March 1981. It is sent to Dr Holgate at the DHSS. I will try my best to read from it.

Dr Bloom says at the start that he is writing in his official capacity as Chairman of the Haemophilia Centre Directors of the UK. And he is referring to, he says, the problem of --
SIR BRIAN LANGSTAFF: "At a ... meeting of Reference Centre Directors the problem of [something] impurities ..."
MR HILL: It is for something I'm afraid I can't assist with, but it is referring to impurities in Factor VIII concentrates, and in particular, Humanate.

If we go to the second paragraph, the first legible sentence of it:

"... the first concerns the preparation of Humanate, about which there was some adverse publicity in the National Press recently. My colleagues and I would like to be reassured that this material has been cleared for use and has passed the normal control processes for the UK. We would like to be reassured that it is possible from the protocol to trace actual batches to source in the event of an outbreak of

hepatitis etc attributable to it. Most of us are aware of rumours that this material originates with an American Company and is sold through brokerage or other means to Speywood Laboratories Ltd where it is relabelled. This seems to us to be somewhat irregular and would greatly appreciate your advice on its current status."

If we could go to the final paragraph:

"The Haemophilia Reference Centre Directors have expressed disquiet at these developments although we are aware that by virtue of plasma [brokerages] ... in the USA it may be difficult sometimes to be sure of the exact origin of plasma used in any of the currently available concentrates. These problems highlight the importance of developing a UK potential within the Health Service to supply all the needs of the British haemophiliacs. I would be very grateful for your advice."

So that is the concern that is being raised in March 1981 with Dr Holgate.

His reply is at BPLL0001351_039, dated 23 March 1981. Dr Holgate wrote:

"Dear Professor Bloom,

"Thank you for your letter of 10th March drawing our attention to the recent disturbing press reports

concerning Factor VIII concentrate and enclosing a copy of a letter given to you by Dr Savidge.

"As I am sure you are aware, one of the cornerstones of our philosophy for the licensing of 'biological' products is to have detailed knowledge of and control over early stages of manufacturing and in-process control -- this including source material. I am particularly delighted to have your clearly expressed support for this attitude.

"With regard to Humanate and Speywood Laboratories Ltd I can say no more at this stage as the matter is being dealt with at the present time."

This may reflect the strict confidentiality that surrounded the meetings of the Committee on Safety of Medicines. We can see that as of 23 March 1981, at least according to Dr Holgate's letter, the matter is still being dealt with, the process is still running. But as we know, they were aware of concerns pre-dating Professor Bloom's letter and had proposed a variation of the licence as a result.

SIR BRIAN LANGSTAFF: Well, Professor Bloom was referring to some press comment, I think, wasn't he?

MR HILL: He was.

SIR BRIAN LANGSTAFF: So the matter was out in -- at least allegations were out in the open.

MR HILL: Yes. What we don't know is what the adverse publicity in the press was, whether it was just that there had been a hepatitis outbreak or whether it was the more detailed point about the ability to trace back. But it's interesting to note that Professor Bloom, the director of Haemophilia Centre Directors -- sorry, the chairman of the Haemophilia Centre Directors -- referred in his letter only to rumours about the origins of Humanate. He does not appear to have known the exact process by which Speywood imported the product.

SIR BRIAN LANGSTAFF: If you write to someone like Mr Evans and say, "Well, you've pressed me, so I'll tell you this is really Koate manufactured -- which we buy from a broker and put a label on it, well, they make it for us, but please keep it quiet", it's bound to be at the level of rumours, I would have thought.

MR HILL: Yes. Save for the fact that Dr Evans asked and was given an answer.

SIR BRIAN LANGSTAFF: Yes.

MR HILL: Sir, the only other point I would make in respect of the importation of products is that no product licence was obtained for Konyne, which is the Factor IX product, and the Inquiry has found no evidence that Speywood sold Konyne in the UK.

Reference, should one be needed, IPSN0000139_022. I note the time, sir.

SIR BRIAN LANGSTAFF: Right, well, we will take a break now until ten to 12. Ten to 12.

(11.22 am)

(A short break)

(11.50 am)

MR HILL: Sir, I'm turning now to Speywood and polyelectrolyte fractionation. I'm going to attempt to give a very brief layperson's guide to polyelectrolyte fractionation but I'm conscious that Ms Middleton will be able to give us far more detail, no doubt more accurate detail, in due course.

My understanding is that it is a process that involves the use of a polymer, a large molecule, that when used in fractionation can act as an absorbent, meaning that it causes the adhesion, the sticking of certain protein factors, such as Factor VIII, to separate it out from other molecules, particularly lower weight molecules. It is a different method of fractionation when compared to the traditional methods based on the work of Cohn and others.

There were two potential advantages which were of particular significance to this Inquiry, sir. The first is that it could allow for a higher purity of

Factor VIII to be obtained. The second is that there was a line of thinking, and we will see how far that developed, that while Factor VIII would adhere to the polyelectrolyte, the lower weight viruses would not, which means that the two could be separated out. So it would work as a form of viral inactivation.

SIR BRIAN LANGSTAFF: Yes. I will stand to be corrected in due course, as you are, by Ms Middleton and what she has to tell us, but my understanding is that there are two steps. One is the adherence or adsorption of the protein of interest onto a substrate, which is a basically a form of polymer, and the second is applying a solvent to release it from the polymer. So it gets separated out by the process of adsorption and then released by the process of -- well, it's eluted, to use the words of the scientist.

MR HILL: Yes, that's my understanding, sir.

SIR BRIAN LANGSTAFF: Right. Well, we may both be wrong.

MR HILL: Ms Middleton will mark our homework in due course.

Speywood had begun its work on polyelectrolyte fractionation of porcine Factor VIII by 1978, before Ms Middleton's arrival. I won't go to the document but we can see that from documents including IPSN0000334_019.

On 7 May 1979, Speywood met with representatives of the DHSS to discuss the possibility of Government financial assistance. The minutes help to explain the position at that time, and if we could have them on screen, please. DHSC0003936_082, please.

We can see this is a meeting that was held on 7 May. Present were Mr Heath and Mr Lees of Speywood, and Mr Weston and Mr Buck of DHSS. The minutes record this:

"The meeting had been arranged to discuss the possibility of government financial assistance for the company."

It talks about its establishment and its specialisation of porcine blood fractionation.

The minutes go on to say that:

"The company had 3 projects under consideration."

1 is -- I'm afraid, the first word is --

SIR BRIAN LANGSTAFF: "To use", I think.

MR HILL: Yes.

"1. To use polyelectrolytes for a new blood fractionation process. The process had been developed and patented by Monsanto, who had licensed it to Speywood in March 1979 because they were concerned about their corporate image in view of the possible

link between blood products and hepatitis. Palmer Research in North Wales were making the polyelectrolyte under licence for Speywood, but further development work was needed on the fractionation process, and this work was being undertaken by Dr Johnson in New York. The potential market for the porcine product could not be met from production at their Wrexham plant and they were looking at an advance factory in Wales. £200-250K expenditure on sterile areas etc, was envisaged. About 80-90% of the £4-5m turnover from the factory would be exported. They hoped to occupy the factory in November or December 1979 and be ready for production by April 1980.

"Human blood fractionation using polyelectrolytes was a more problematic undertaking because of the implications of using human blood for commercial purposes. Speywood envisaged taking out patents and licensing overseas producers, and supplying the polyelectrolyte for the NHS to undertake their own fractionation. Dr Lane of the BPL was working on the fractionation process."

Then there are references to the other lines of business that Speywood were pursuing at the time, sets and disposable accessories and blood bags.

What the meetings record is that:

"Speywood sought assistance [this is the final paragraph] specifically with the first project."

So that's polyelectrolyte fractionation of both porcine and human Factor VIII.

"This was a new product area with considerable commercial potential but the company would have to proceed slowly and cautiously unless government support was available. The Department said that the PPDS assistance appeared to be the appropriate, and offered to consider an application, with support from STB."

PPDS is the Department of Industry's Product and Process Development Scheme. So the company Speywood are being invited to consider an application under that scheme, with some assistance from the Department. I will leave that document there, sir.

An application was made to the scheme on 12 October 1979. Can we have, please, on screen, Soumik, IPSN0000165_077.

You can see there, sir, the application title page, "PPDS Application", by Speywood. On page 3, please, Soumik. You can see the date, 12 October 1979.

If we can turn, please, Soumik to page 5.

This application gives us a picture of what Speywood was doing at that time, and what it intended to do, as of October 1979, whilst seeking a degree of financial assistance from the Government to do it.

Under the heading "Introduction":

"For over two years Speywood Laboratories Limited has been researching into the fractionation and purification of animal (porcine) and human blood fractions using polyelectrolytes. The initial work which has concentrated on Factor VIII has been very successful. Moreover, the laboratory results show that polyelectrolytes can be used for a total blood fractionation process producing purer fractions with better yields at lower capital and labour costs than can be obtained with a traditional Cohn process. This discovery could have a significant impact on the Department of Health's plasma fractionation costs, it will generate substantial foreign exchange earnings from exports and licence fees, and it will increase employment. This introduction explains the process and programme required to turn a laboratory discovery into commercially producible licensed products."

If we could go over to the next page, please, Soumik. This is under the heading "The Process". I won't go through every word, but you can see the

different stages involved: the first is production research, the second is small scale production, and the third is pilot plant production.

If we could go to the paragraph that follows. It goes on to say:

"Because of the size of the Company, its personnel, laboratory equipment and research facilities, much of the work in Stage 1 is either sub-contracted to outside laboratories, or is carried out by Speywood's staff in outside laboratories. Two laboratories are of particular importance to us:

"- Dr Alan Johnson's laboratory in New York. Dr Johnson was the first man to realise the possible potential of polyelectrolyte fractionation.

"- Dr Jean-Pierre Allain's haemostasis and coagulation laboratory at the CNTS in Paris."

And you will recall, sir, that there was a reference we looked at before the break to getting some data from Jean-Pierre. That is Jean-Pierre Alan.

"Other laboratories where specific parts of the work will probably be carried out include Dr Richard Lane's laboratory at the Lister Institute, Prof Arthur Bloom's laboratory in Cardiff and Dr Preston's laboratory in Sheffield. Proposed programmes of work in these various laboratories are

outlined in Appendix B.

"At Stage 2 [small scale production] all the work is drawn together at Speywood."

Sir, we can see there the plan is to use external laboratories as part of the research stage before bringing things back to Speywood once you get to scale matters up to production.

"The Programme", section 2:

"The Company's intention is to develop the existing polyelectrolyte fractionation process to a point where the Company can produce itself a range of animal fractions and can licence others to produce human fractions. The fractions envisaged and their stages of development are as follows ..."

If we could turn over, please, to the next page. I won't go through all of these, sir, but the point is that although Factor VIII:C is the first of the factions mentioned, there is an intention or a hope that the process can also be used to produce other products: fibronogen, albumin, animal globulins, et cetera. I won't go through the detailed plan as to how that might be achieved.

If we could turn, please, to page 10, Soumik.

This is entitled "Capital Investment", and it talks about the figures that are going to be involved.

I won't take you to each one of them, sir, but the document reveals that the anticipated capital costs are £298,000 to June 1980, £354,700 of management costs to July 1981, and £142,660 of external research costs. There are also further costs for clinical trial and licensing stages. So we can see, sir, that these are considerable sums of money.

That was the application, sir. It was discussed within the DHSS. I'm not going to take you to all of the documentation about those discussions, but there is one helpful summary at DHSC0003936_049, please, Soumik.

This is a memorandum on 30 October 1979 from D Weston, copied to colleagues within the DHSS, about the application, and it is sent to Dr Walford.

Picking it up from the second paragraph, this refers back to some of the other correspondence that has been going on in the DHSS at that time.

"Dr Waiter's earlier comments, and those received from Dr Wintersgill and Mr Sloggem, suggest that DHSS should support the application on medical/technical grounds and there are also sound commercial reasons which hinge on the prospects for import substitute and export earnings. The main problem was, and still is, that the project is

extremely ambitious for a relatively small company of limited financial and technological resources and with the first application it seemed that neither the company nor the project could be regarded as being financially viable. Some of the earlier doubts about supplementary sources of funding have been lifted a little and it is possible that once one body makes a firm offer others may follow suit. But the fact remains that this is a project not far short of £1M in value and even with grants and loans which [may] be expected to amount to something in excess of £1M the company will be hard pressed to fund the operation even allowing for the substantial sales it expects to obtain. Cash flow problems are likely to loom larger in view of the level of expenditure expected especially during the first nine months of the project.

"I have discussed the application for funds with Department of Industry and they have are prepared to consider a case for financial assistance: under the PPDS this may take the form of a cash grant of up to 25% of approved project costs but if we considered the development to be of outstanding significance and importance, 50% funding with provision for a return on sales might be recommended."

I will leave that document there, sir.

On 14 April 1980, the Department of Industry did offer a PPDS grant of up to £186,820 which represented 25 per cent of net eligible costs. So, as we have seen from Mr Weston's memorandum, that is approval for the application but at the 25 per cent level rather than the 50 per cent level which could have been given for a development of outstanding significance and importance.

Separately from the application for financial assistance from the Department of Industry, an agreement was reached between Speywood and BPL for a joint programme in developing polyelectrolyte fractionation of human blood, according to -- stress that this is human rather than porcine.

Could we have, please, Soumik, on screen BPLL0016008_151.

This is the proposal for that joint development. I will read through it. The "Background":

"Speywood Laboratories Limited, a privately owned British company, had developed unique and beneficial technology for the processing of animal and human plasma.

"The first stage of the development programme, the production of high quality coagulation factors, is

completed to production clinical scale for porcine factor VIII:C and, to pilot scale for human factor VIII:C. The feasibility of the process is thus confirmed.

"Speywood lack facilities for the scale-up of human blood processing to the next stage. That is, the finalisation of the production scale process for human factor VIII:C and the extension of the technology to the separation of albumin, immune serum globulins, etc.

"This initial proposal is confined to the factor VIII:C aspect."

Then it goes on to talk about the "Objectives of the joint programme":

"Finalisation of a production scale process ...

"Determination of the purity and yield parameters ..."

On to the next page, please, Soumik:

"Initial UK clinical trials ...

"The preparation, acceptance and approval of a UK product licence ..."

Moving to the "Benefits envisaged":

"1. A product consisting primarily of factor VIII:C purified 500 to 1000 times over plasma."

It talks about the total removal of A/B

isoagglutinins, negligible fibronogen, negligible von Willebrand's factor and Factor VIII:RAg.

"2. Improved yield, via plasma

"3. Considerably greater clinical acceptability."

The first point raised there is reduced hepatitis risk. The other points are lower incidence of protein shock, reduced liver damage and reduced injection volume.

Fourth point:

"Simpler processing procedure, requiring considerably less time."

So that is what it is hoped this method of fractionation will lead to.

The "Staff/facility requirements":

"1. Speywood Chief Scientist, Mrs Sarah Middleton, to work at Elstree."

We'll come back to that with Ms Middleton's evidence later.

"2. [Technical] assistant is to be provided by BPL.

"3. Speywood to provide all equipment, with the possible exception of [a] centrifuge.

"4. BPL are to provide cryoprecipitate ..."

So that is the proposal. Speywood would provide

the solid phase polyelectrolyte, which is said to be the key to the process.

SIR BRIAN LANGSTAFF: We're missing that, I think.

MR HILL: On to the next page, please, Soumik. Point 5. My fault, sorry.

Then reference to the space requirement.

SIR BRIAN LANGSTAFF: Can you assist with this, I've just noticed the date of this, 31 July 1979 --

MR HILL: Yes, sir.

SIR BRIAN LANGSTAFF: -- and the application for the PPDS scheme was made in October '79.

MR HILL: Yes.

SIR BRIAN LANGSTAFF: In that, it was said that there were three stages. It wasn't suggested that they were already at and had completed, stage 2?

MR HILL: No.

SIR BRIAN LANGSTAFF: But they are suggesting that in this document, aren't they?

MR HILL: There does -- the wording between the two documents is not precise, but this document certainly suggests that they are further down that route. Yes.

SIR BRIAN LANGSTAFF: It says, "We're ready to roll it out commercially", as I read it.

MR HILL: I don't think it's quite saying that. It is saying that they need to finalise a scaling up of the

process.

SIR BRIAN LANGSTAFF: Yes. So they've done the first two steps?

MR HILL: They have done the production of high-quality coagulation factors, completed to production clinical scale for porcine and to pilot scale for human.

There has been some production, according to this document, of human Factor VIII but, in contrast to the document that is to come, which says that there will be a -- Speywood will bring in to house future production. This proposal is actually saying that Speywood don't have the facilities to do that and, hence, that has to be done with the assistance of BPL.

SIR BRIAN LANGSTAFF: The date of their suggesting this agreement, was this at about the time that the sales agreement with Koate ended?

MR HILL: The sales agreement with Koate ends a little later, at the end of 1979.

SIR BRIAN LANGSTAFF: Yes. So it's '79?

MR HILL: Yes, but there is, from the documents that we -- the letter that we saw earlier, the way that Speywood explained the position to clinicians was that they were using the importation business to finance their research --

SIR BRIAN LANGSTAFF: Yes.

MR HILL: -- to these areas, and --

SIR BRIAN LANGSTAFF: But the importation business was ending?

MR HILL: The agreement with Cutter was ending and there was then an attempt to --

SIR BRIAN LANGSTAFF: I see. So the importation business is separate, the one where they secure it from the intermediary?

MR HILL: Yes. So looked at from the outside, there would continue to be an importation process which would allow for sales which would allow for money to keep coming in to the company which could then fund the research that they were undertaking.

As we will see, in due course, when that supply of money ceases, there is a need to find funding from elsewhere. That's when we get on to the National Enterprise Board and Prutec.

I won't go through the commercial arrangements, sir, at heading E, but they are there should they be of relevance later. But there is -- this, it should be remembered, is the proposal.

The agreement, which I won't take you through, is BPLL0016007_013. The agreement was formally for a 6-month period but, as we will see, it continued in practice into 1981. Reference for that is

DHSC00003936_005.

Jumping forward about nine months to one year, we have some optimistic predictions of the future which come from Mr Heath. The reference, please, is IPSN0000257_059.

This document is called "Polyelectrolyte plasma fractionation 10 years on", and it is signed by Mr Heath and dated August 1980 in the bottom right-hand corner. The purpose of this document isn't clear, but it shows what Mr Health was saying as of August 1980.

Sir, he's projecting ten years into the future and saying what the situation will be.

"By 1990 the Cohn and cryoprecipitate fractionation techniques will have been replaced by polyelectrolyte ion-exchange process.

"The effect on the plasma donation programme, the plasma fractionation industry and clinical application will be dramatic.

"Extra high yields of the coagulation factors will enable the donor programme to keep pace with the increasing demand with only a minimal increase in plasma collection. The imbalance between the requirements for Factor VIII and the other plasma proteins will vanish. Donor centres will be

responsible for the first stage of the fractionation adsorbing the labile fractions directly onto the polyelectrolytes.

"Elution and further processing will be completed by a local fractionation unit, which, due to the simple, low cost nature of the polyelectrolyte process, will be viable for a much smaller plasma throughput. This spread of technology coupled with the increased yields will allow most countries to conform with the WHO ideal of 'self-sufficiency' in plasma products. Paid donor collection will decrease rapidly in the United States when export demand declines.

"There will be no risk of hepatitis infection from polyelectrolyte fractionated materials, prophylactic treatments will increase and new fractions will provide a wider range of therapeutic treatments probably via the intramuscular route."

That's his vision of the future, as it were. I stress, sir, now, that we are dealing here with a businessman who is talking about a product and a process that his business is promoting. This is a very different thing from looking at data sheets containing detailed information about individual products.

I will trace through in some documents the development of polyelectrolyte fractionation, a topic that we will return to with Ms Middleton later. Some of the documents can helpfully be introduced now.

By November 1980, Dr Edward Tuddenham, at the Royal Free, had begun work on a clinical sample of human and porcine Factor VIII provided as a result of the BPL/Speywood/Monsanto collaboration. Reference is BPLL0016008_125, and IPSN0000156_034.

At some point in 1981 he gave a lecture in Toronto on his initial laboratory results. It is a document that Ms Richards took Professor Tuddenham to when he gave his evidence in October last year. I won't go through it all, but I will just bring it up and refer to certain sections of it.

IPSN0000156_101, please.

The lecture begins:

"It was at the 1976 World Federation of Haemophilia Conference in Kyoto that Dr Alan Johnson of [New York] University first outlined a new fractionation process using solid-phase ion exchange resins known as polyelectrolytes".

So that's where the technology dates from.

Professor Tuddenham goes on to say:

"After almost 5 years of further intensive

research and scale up we can now report that polyelectrolytes do indeed offer a viable alternative to conventional processes, giving extremely pure fractions at high yield."

I note, sir, that the "5 years" is where we get the date of 1981, because the date isn't on the document itself.

If we could just expand out, please, Soumik, we can see that there are references to slides, which don't help us because we don't have the slides, but what I will do is take you to page 2 of this document, please.

Towards the bottom of that page, Dr Tuddenham says:

"The operation has significant advantages over current fractionation methodology.

"1) Higher yields -- 35% from cryo, 50% from plasma."

That is referring to the source material that is used in the polyelectrolyte fractionation. So if you use cryoprecipitate, your yield is 35 per cent. If you use plasma, it's 50 per cent.

"2) Ultra high purity fractions."

Not just high purity, but ultra high purity.

"3) Simple process, less labour, energy and

capital required."

Go on to the next page, please, Soumik.

"4) Operates at room temperature.

"5) Can be performed at small scale, 1 Kilo cryo or 1 litre plasma.

"It is thus an entirely feasible process for individual blood centres or small Governmental fractionation units."

Some more detail is given in the page that follows. I will just pick out the point that the specific activity of human Factor VIII is ten units per milligram. We were talking earlier about high purity being between 1 and 2 units, as defined by Dr Kingdon. So this is what is meant by ultra high purity.

The final paragraph of that page, please, Soumik.

"Both products [so that's the human Factor VIII and the porcine Factor VIII] have now been used clinically and some of the results have been presented here and in Toronto. Half-life is of the same order as present [Factor]VIII products, ranging between 8 and 16 hours, depending on individual patient response."

Go over to the next page. I won't read the

section about porcine Factor VIII. We will come back to that. The paragraph starting "In vitro tests", I understand this is about human Factor VIII:

"In vitro tests have demonstrated that Hepatitis B surface particles do not bind to the E5 polyelectrolyte under the conditions used for the production of FVIII:C.

"In trials, using heavily infected cryo, simple washing of the polymer reduced hepatitis B below detectable levels, leaving the Factor VIII:C intact. There is the encouraging possibility of concentrates with a reduced risk of hepatitis transmittal. It has also been hypothesised that the immunogenic character of [polyelectrolyte] [Factor] VIII:C may differ from that of the conventional [Factor] VIII agglomerate. Antibody response may be changed.

"Only further clinical experience will prove or disprove the latter points but, despite this, we feel that a higher purity Factor VIII concentrate at a yield significantly above the conventional, offers excellent prospects for the treatment of haemophilia in the 1980s."

So an optimistic assessment but, as that final paragraph shows, the need for clinical experience being required to test whether or not these laboratory

results will be replicated.

Dr Tuddenham was also the author on a paper considering response of patients to infusions of polyelectrolyte Factor VIII. Ms Middleton was the co-author, so I will ask her about that in due course. There is a further paper from October 1983 from Ms Middleton on the clearance of hepatitis B surface antigen during polyelectrolyte fractionation and, again, I will ask her about that in due course.

As I mentioned earlier, alongside these developments, there was thought being given to the need for further investment in the company, no doubt in part prompted by the disappearance of the importation business, as a result of the variation of the product licence.

I won't go through all of the documents, but I will take you to one which is of significance from July 1981. It is DHSC0003936_019, please, Soumik. Again, from the front page we can see the Speywood group's title. On the second page, please, Soumik, "Human Protein Plans", the title of the document, and the date -- sorry, Soumik, if we could just go back one page, bottom right-hand corner, and handwritten on "July 1981".

If we could turn, please, to the third page

electronically of the document, "Introduction:

"Over the past seven years Speywood Laboratories have spent large sums of money researching and developing new protein fractionation techniques. Approximately two-thirds of the funds have been expended on animal plasma fractionation, the remaining third on human plasma processes. In the last few years a new technique, the 'polyelectrolyte process', has emerged as a practical and exciting alternative to the 40 year old Cohn process.

"Whilst the polyelectrolyte animal fractions have far less eventual potential than the human fractions, they are unique to Speywood and offer an ideal base for a small, highly specialised business. To maximise on their potential, Speywood have committed to a new 10,000 [square foot] facility for production and research purposes, and a comprehensive and costly development programme for the next five years. This plan does not allow for any major expenditure in the human fractionation area.

"The human polyelectrolyte process has not been practised on the same scale as the animal process. However, recent production yields, clinical trials and hepatitis tests have adequately demonstrated that the major protein, Factor VIII:C, can be produced

economically, is very efficacious and is most probably free of hepatitis infectivity. Other human proteins, which have a vast therapeutic potential and cannot be produced via the classical Cohn fractionation process, have also been successfully isolated. To exploit these developments Speywood originally planned to license this technology and the products thereof to a major American plasma fractionator. In the light of these recent findings and in view of a new EXCLUSIVE licence from Monsanto, Speywood now proposes to raise the necessary finance to fund the advance of 'human proteins' through a new venture."

Go over to page 2, please, Soumik. We can see the "Outline plan" for that new venture, which is:

"To form a new division adequately financed to undertake the following:

"1) The establishment of a new manufacturing unit for the production of human biologicals, using polyelectrolyte fractionation technology and continuous centrifugal electropheresis.

"2) A research and development programme aimed at providing further therapeutic proteins from plasma and servicing the development of fractionation/purification skills.

"3) An external research and development

programme, designed to investigate the viability of producing therapeutically proven proteins via the recombinant DNA route.

"This highly specialised company will have a base of products from the outset. It should become one of the leading protein fractionation companies in Europe with unique technology that can be applied to natural or synthesised product separation. The research and development plan is intended to provide a second generation of products which do not rely on the finite source -- plasma.

"Financial Support:

"£4-5 [million] will be required to fund MBL through the first 4 years."

That's Molecular Biology Limited, which is the proposed name of the new company:

"The National Enterprise Board, Prutec and Celltech [an American firm and we will come back to their role later] are evaluating Speywood's proposals with a view to providing this requirement in the form of equity and loans."

Turning to page 3, I won't read through all of this, but we can see that the manufacturing unit is proposed for Wrexham and, by the end of the year, it's proposed that this will employ 61 people. The section

headed "Raw materials", if we look at the second paragraph of that:

"A supply of cryoprecipitate has been arranged direct with a United States plasma collection company, on a long term contract. Each shipment will have full donor information and the plasmapheresis centres will be open to inspection by the UK Medicines Inspectorate."

So this, sir, just so that we are clear, it's not about importing finished Factor VIII product but the raw material that will be used in polyelectrolyte fractionation.

If we go over to page 4, please, "The products".

"Factor VIII:C

"For the treatment of haemophilia A.

"-- 20 times purer than any competitive product.

"-- Substantially free of hepatitis."

Various other claims made including a greater yield than conventional Factor VIII.

Then he goes through the other products that is intended to produce a von Willebrand's factor, fibronectin and fibrinogen. Then it says:

"The Factor VIII:C and [von Willebrand's factor] are fully developed products. The Fibronectin and Fibrinogen still require considerable development

effort to scale up to commercial production scale."

If we turn to page 5, we can see various programmes set out, but the first is research and development programme. Then item 3, the genetic engineering programme, which talks about the need to have academic institute studies and then scale up, and the pilot plant and then industrial production. That, as I understand it, is a reference to recombinant.

On page 6, you can see the academic institute studies that have been instigated by that stage, so there's a team in Oxford, and a group at the Royal Free Hospital and the Hallamshire Hospital. The objective is:

"Investigational studies to produce the gene clones and the laboratory expression of the following proteins", which includes Factor VIII:C.

Thank you, Soumik, we can take that off the screen.

As of July 1981, that appears to be the Speywood plan.

This plan seems to have prompted considerable concern at BPL, who, at that stage, were still collaborating with Speywood on their work. We see correspondence from BPL to Dr Tuddenham, urging him to take steps to protect intellectual property. I won't

take you to those letters, sir, but they're at BPLL0016008_075, and the same stem _066.

There are minutes from a meeting on 12 July 1981 between BPL, the DHSS and Speywood, concerning the ongoing collaboration and the future of the collaboration. That is at DHSC0003936_005. That's a need there, to formalise what other arrangements are going forward and it is revealed at that meeting that BPL had entered its own talks with Monsanto, which created a further layer of complexity and tension.

Those minutes also record that a lead time of three years is estimated for a product licence.

I am going to take you to two documents though, which show the nature of BPL's concerns and the terms in which it is expressed.

Could we have, please, BPLL0016008_068, please, Soumik.

This is a letter from Dr Lane to Dr Walford. It's dated 17 August 1981. From the context of the letter, we can tell that Dr Lane is referring back to the human protein plans document that we have just looked at. What Dr Lane says is this:

"Dear Diana,

"I am sure you have seen this document [that's the human protein plans] which has presumably been

presented to NEB, Prutec and Celltech among others, including DHSS. On page 4, I hope the attention has been drawn to these organisations of the highly spurious nature of the claims made on three of their principle four products. I have coloured these in.

"The claims are either without substance, ie 'At greater yield than conventional factor VIII', or meaningless, for example, 'Substantially free of hepatitis'. There are also substantial contradictions as in 'Fibronectin for the treatment of traumatic septic shock' followed by 'A fibronectin therapeutic concentrate has never been produced before' ...

"I am well aware of Speywood's enormous needs to generate funds for their operation but I would be disturbed if financial backers in this country were so ill-advised that they could not see some defects in the claims that are being made in this document. I would be pleased to have your comments.

"Our experience of polyelectrolyte indicates that its development has not reached the point set out in the attached document and is not appropriate for onward process of the fresh plasma into immunoglobulin, albumin and other fractions which are needed to make the overall economies."

Dr Walford's reply is at BPLL0016008_ 064.

I won't take you to it, sir. Suffice to say that Dr Walford thinks that those involved in potentially backing this project have got sufficient information and sufficient expertise to be able to make their own -- form their own judgements. But she acknowledges Dr Lane's concerns.

One further document, BPLL0016008_065, please, Soumik.

This is dated 26 August 1981, and it is from Dr Smith in BPL, who is writing this memo to Dr Lane and Dr Harvey.

He makes explicit reference to the human protein plans, and he says these confirm:

"... ambitions which had been reported to me by third parties but denied by employees of Speywood. These intentions are incompatible with BPL's aims, the national interest, and my interpretation of our contract. They are entirely compatible with my assessment of Speywood's reliability as partners. It is obvious that if Speywood's interpretation of our current contract is taken with this document, BPL lose control of the main issues."

And he goes on to say that he is unwilling to proceed with the next stages of preparation for polyelectrolyte for clinical trial until the interests

are safeguarded. He sets out the reasons, or the safeguard that he requires.

Point (d) is:

"a firm understanding that BPL is not a training ground for Speywood employees. I will have Sarah Middleton in CF Department [I understand that to mean cold fractionation department] for the 'cryo' part of the work, and no one else, on present evidence."

So we can see Dr Smith there deeply disturbed by the human protein plans.

A further document to which I will give a reference but not go is BPLL0016008_072. This is a more technical minute in which Dr Smith expresses his reservations about the technical challenges involved in scaling up polyelectrolyte fractionation, echoing some of Dr Lane's's concerns that the document is presenting too optimistic a picture.

Despite those reservations of BPL, in December 1981 a £4 million-pound investment was announced into Speywood. The reference is BPLL0016007_048.

I won't take you to the document sir, but I will read one quote from Mr Heath, which is a press release, and Mr Heath is quoted as saying:

"Not only will this extra investment create new jobs but it will add momentum to our existing lead in fractionation technology and bring nearer the exciting possibility of producing valuable blood proteins through genetic engineering. If this becomes reality, as I have every confidence it will, then by the year 2001 we may never need to collect plasma from donors again."

So Mr Heath, at that stage, is emphasising the prospect of recombinant technology. And although, as we will see, events didn't transpire as Mr Heath would have hoped, you may feel, sir, that there is some prescience in that statement.

In the same month in which the £4 million investment was announced -- and as we know that's from Prutec and the National Enterprise Board -- the cooperation between Speywood and BPL effectively ended. The reference is BPLL0016008_053. And although there is some contact going forward, there is an end to the previous arrangements that had been made between Speywood and BPL.

If we jump forward to 24 April 1982, the document is BPLL0016008_034.

We can see this is a minute from Dr Smith to Dr Lane, an internal minute from BPL concerning

a Speywood meeting at Uberlingen on 24 April 1982.

Dr Smith said that:

"The meeting seemed to be designed to present the merits of porcine factor VIII to influential German clinicians, and to associate the PE technology for porcine factor VIII with projected production of human factor VIII."

The first page concerns porcine product. I'm going to take us to the second page, if I may. I won't go through everything that was said but it is perhaps captured by the third paragraph down.

"Pending the millennium (which incidentally sounds like a marketing nightmare), Speywood hope to make human factor VIII pay the bills. It is therefore very disappointing to find how little progress has been made since we parted company.

"Speywood would appear to have abandoned the plasma route ..."

He gives the reasons for that. So it is no longer, in Dr Smith's understanding, trying to use polyelectrolyte fractionation on plasma, but it is instead using it on cryoprecipitate.

He goes on to discuss further down the document how Speywood are:

"... concentrating on a commercial (probably US

frozen cryo source. JP Allain ... and JJ Morganthaler ... are the only people working along similar lines to Speywood, if one neglects Alan Johnson's contribution which always seems to be difficult to substantiate. The following problems continue to plague this work ..."

He goes through those problems: the frozen cryo is difficult to redissolve; the yields are low; the polyelectrolytes "is accused of being variable"; Morganthaler has not produced a non-pyrogenic batch yet and has filtration problems, which echoed by BPL's experience. And:

"(e) the lack of hard results after more than a year underlines the lack of professional control over Speywood's multi-centre efforts."

He goes on to say:

"The low yield remains the most important feature of the method."

I will leave that document there, sir, but Dr Smith's view, as of April 1982, is that very slow progress is being made and very large problems remain. It should be noted, of course, that Dr Smith is not a dispassionate observer and has some hostility towards Speywood, as we have seen from the other documents.

It should also, however, be noted that this is an internal BPL document, Dr Smith reporting to his colleagues.

I won't take you to these documents but correspondence from Mr Heath in May 1982 confirms the impression of progress being slower than anticipated. The reference is IPSN0000402 and IPSN0000232_001.

Studies were ongoing to demonstrate that the product was "free from hepatitis infectivity", but these were in vitro studies, in the laboratory, and Mr Heath, in a letter dated 2 April 1982 to the Reverend Tanner, accepted that only a full year's clinical trial in what he described as patients with clean livers would provide proof that the product was indeed hepatitis-free.

The reference is IPSN0000252_001. There is some evidence that a research project was being designed by Dr Howard Thomas at the Royal Free at this time.

Can we go, please, Soumik, to IPSN0000249.

This is a letter sent by Mr Heath, dated 7 July 1982, to the British Technology Group, which, as I understand it, the National Enterprise Board had been absorbed into, so it's to one of the financial backers and, indeed, equity holders of Speywood.

If we look at the third paragraph down, what

Mr Heath says is this:

"Producing 'Pure Factor VIII:C' for clinical use, is not going to be a commercially viable proposition and therefore will probably never generate any monies for the inventors, but, we feel it will be a useful factor in the patent protection built around biosynthetic factor VIII production."

What I interpret those words to mean is that the focus is now on the recombinant product, and the polyelectrolyte fractionation of Factor VIII is no longer being considered as a commercially viable proposition in the long term, but it's being done for reasons of patent protection in respect of recombinant product.

SIR BRIAN LANGSTAFF: This is from Heath?

MR HILL: This is from Heath. 7 July 1982.

I am a little wary, sir, that I may be reading too much into one paragraph of one letter, but it does seem part of a picture that, during 1982, there is a more pessimistic view of the prospects of the polyelectrolyte fractionation of Factor VIII.

SIR BRIAN LANGSTAFF: Well, it's gone from being a Europe-beater to being a commercial failure.

MR HILL: Yes.

SIR BRIAN LANGSTAFF: In the space of how long?

MR HILL: The --
SIR BRIAN LANGSTAFF: About a year?
MR HILL: -- protein plans was July 1981. This is July 1982.
SIR BRIAN LANGSTAFF: Yes. And what is now the enthusiasm is the recombinant, the biosynthetic.
MR HILL: Yes. Now that was always part of the protein plans.
SIR BRIAN LANGSTAFF: Yes.
MR HILL: But the emphasis has shifted to the recombinant product.

There was an application made for a clinical trial certificate for the Factor VIII product produced as a result of polyelectrolyte fractionation. That product is now known by the name of Mono C. It's not entirely clear when that trial certificate was applied for, but there is a report on the second quarter of 1982 made by Mr Heath, which says that a submission had been made at that stage. That's IPSN0000232_001.

We have other documents to indicate that the trial was intended to be established at Lord Mayor Treloar School and at the Royal Free. IPSN0000398, for those.

Can we go now, please, Soumik, to IPSN0000230. This is a letter dated 26 November 1982. It is

from Mr Heath and it is to Mr Seymour, who has been appointed as the chair. If we could -- sorry, Soumik -- if we could just take that off the screen, please.

Could we just go down a little further, please, Soumik? Thank you, yeah, we'll take it off screen.

Sir, I note there was an address that was left on that document which should not have been left on that document.
SIR BRIAN LANGSTAFF: I see.
MR HILL: I will ask in due course for a restriction order to be made.
SIR BRIAN LANGSTAFF: Yes, well, no one should reveal the -- any details which have come from looking at that letter online.
MR HILL: I'm grateful, sir. Thank you.

I will read from the letter rather than --
SIR BRIAN LANGSTAFF: Please.
MR HILL: -- show it, as a result of that.

The context of this letter, I'm afraid I cannot fathom. But the relevant section for the current purposes is this, it refers to concerns that Mr Seymour either has or has reported about how some form of conversation between somebody representing Speywood and somebody representing the DHSS may have

jeopardised Speywood's prospects of -- in the licensing process. But we can't really work out what that conversation was.

But this is a letter from Mr Heath reassuring Mr Seymour that's not the case. And he has spoken -- Mr Heath has spoken to Dr Keith Fowler at the DHSS. Mr Heath reports that:

"Dr Fowler concluded our conversation by assuring me that the Mono VIII:C application which was on his desk would go on the fast track as soon as the Alpha cryo application was received."

I pause there to say this I take to be a reference to the clinical trial application. So by 26 November 1982, that application was on Dr Thomas's desk, but he was awaiting what is described as the Alpha cryo application, and I understand that to be a further application that the cryoprecipitate from Alpha be allowed into the country so that it can be used as the raw material for the production of the Mono C *(sic)* polyelectrolyte fractionated Factor VIII.
SIR BRIAN LANGSTAFF: Thank you.
MR HILL: I add this now for future reference:

"However, he also added that we were doing entirely the right thing to go for a full product licence for Hyate-C."

That's the porcine product.
SIR BRIAN LANGSTAFF: Yes.
MR HILL: So clinical trial for the human product, full product licence for the porcine product.

Mr Heath goes on to say:

"On reflection, I think it was entirely wrong of me to condone Paul's request to speak to the DHSS."

That's a reference to Paul Joaquim or --
SIR BRIAN LANGSTAFF: -- Joaquim. We have a statement, have we not, from his wife?
MR HILL: That's right, which contains an extract from what appears to be a memoir, from Mr Joaquim. He was a director of Speywood and he was on the board at the behest of the British Technology Group:

"I feel that the Medicines Inspectorate in particular are anxious to be truly independent of any outside pressures, either governmental or business-wise. If anything, Speywood will get a hard ride because the BTG owns 25% equity."

I will leave that document there, sir.

The CSM main committee considered the clinical trial application on 24 March 1983, and it was rejected. If we could have, please, DHSC0003950_016. We can see that this is the minute of the main Committee of the Committee on Safety of Medicines. It

is dated 24 March 1983. So some four or five months after the previous correspondence:

"The advice that the main Committee gave was, on the evidence before them, the Committee had reasons to think that on grounds relating to safety and quality it would be unable to advise the grant of a clinical trial certificate, the preparation ... and directed the secretary to notify the applicant in accordance with the Act."

That product, as we can see, is Mono VIII:C. So a rejection of clinical trial certificate. The reasons are given. I won't go through them all. The first six relate to the use of bulk cryoprecipitate, which is obtained, as we can see, from Alpha Therapeutics. The following five reasons relate to the technical details of the product Mono VIII:C.

Remarks on page 2, please, Soumik.

"By product licence stage:

"1. Evidence should be provided to show that the manufacturing process yields a consistent product.

"2. Evidence should be provided concerning the long termed toxicity of a product and its possible contaminants.

"3. Evidence of clinical pharmacology of a product would be required."

So, that is what it's saying in the remarks to give the company further information about where it should be going.

It also, I note, at paragraph 12, just above that -- this is among the reasons for rejecting the certificate -- it says:

"In the event of a clinical trial certificate being issued the study should be limited to ten patients and to no more than one bleeding episode in each patient."

Which is, as I understand it, a more confined trial than the one that had been proposed.

So no clinical trial certificate. There was a meeting on 2 June 1983 between the DHSS and representatives of Speywood, as we have seen, this is fairly common after licensing rejections, an opportunity for the company to speak to those involved in the licensing process to understand what they have to do.

It is a meeting that was attended by Ms Middleton, as a result I will come back to that later.

It's not clear from the documents that I have seen whether a further application for a clinical trial certificate was made or whether a clinical trial

certificate was ever granted. That's something we will pick up with Ms Middleton, but I note that we are getting towards the end of her time with the company as well, so we're not sure how far we will be able to take that.

In 1983, Speywood underwent a significant change of direction. By April of that year, Mr Heath had become the non-executive deputy chairman, Mr Williams had lost his seat on the board, IPSN0000260_024. Mr Heath resigned from Speywood in September 1983, reference for that is IPSN0000442_042.

There was a significant change in business plan. If we could have, please, Soumik, IPSN0000021. You can see this is a corporate plan for 1983 to 1985. It is produced by Mr Seymour, who is the new chairman. He may also be chairman and managing director, I'm afraid I'm not entirely sure of all of his titles. It is dated 19 April 1983.

If we could turn over, please, to the next page. It sets out the original plan of the company and then, in the second paragraph, some fairly harsh words, and I quote:

"The majority of the Board now recognise that the original plans were unrealistic and that the rate of sales growth projected was unattainable whilst the

resources required to establish production, technical support and marketing were underestimated. In 1982 management priorities were poorly selected with funds being diverted to prestige projects, whilst inadequate attention was devoted to the necessities of technical support [data, I think] for Product Licences, essential product plant and facilities.

"During the first quarter of 1983 priority has been given to correcting the matters indicated above. A reappraisal has also been undertaken to ascertain whether the original plan for Speywood is still viable but on an extended timetable, or whether the company must change its direction and concept in order to ensure future profitability.

"There is little doubt that with standard management practice a radical improvement can be achieved so that a loss in 1982 approaching £1.5 million need not reoccur."

I won't take you through all of the plans, sir, but if we could go to page 6, please, Soumik. We have a comment -- sorry, electronic page 7, internal page 6. My fault.

A section on the production of human material. Mr Seymour says this:

"The fundamental reason for Speywood failing to

achieve a breakeven in the next 12 months is the absence of any revenue from products resulting from the processing of human cryoprecipitate.

"Such products are considered to be uneconomical due to a high price of imported cryoprecipitate, and impracticable due to the inevitable licensing problems that would arise in employing USA plasma raw materials, and their association with viral diseases.

"Experience to date has also indicated that the [Factor] VIII content of this material and the yield achieved after this processing is so variable that no reliable commercial forecasts are possible."

In short, a commercially unviable proposition.

I will leave that section there, just to note the door wasn't being closed completely on polyelectrolyte human factor concentrate, but severe doubt being cast upon it.

SIR BRIAN LANGSTAFF: Well, it goes on to make observations doesn't it, at the bottom of the page --

MR HILL: Yes, I will read through if that would help, sir.

SIR BRIAN LANGSTAFF: -- which suggests that "Well, it might be possible to do it but not the way we were trying".

MR HILL: Yes, yes. If we go over to the next page, as

well, please, Soumik.

It talks about some of the possibilities considered, including a contract processing human plasma or cryoprecipitate from third parties, but that also appeared to be uneconomical. It notes the DHSS's concern about the risk of AIDS, and they are now no longer prepared to permit a multi-function plant. So you can't have a plant which is doing both porcine and human Factor VIII. Then it says:

"No firm proposals are made at this time, but obviously the Board of Speywood must consider the future handling of human blood products most carefully."

So the door isn't shut but nor is there much optimism.

If we could go, please, Soumik, to page -- electronic page 12, internal page 11, of the document. The section "Final summary and conclusion", I will pick it up from the second paragraph there, and I quote:

"The company that evolves from the proposed re-organisation will, however, fall short of the aspirations of the original management. It is unlikely to have a significant role in the supply of high purity Human [Factor] VIII:C and certainly will

be unable to fund university research at a seven figure level as was originally projected. An interest can be maintained in genetically engineered [Factor] VIII:C however, providing this is progressed as a co-operative venture."

That is the recombinant product, sir.

I will come back to the recombinant product after lunch, but I will just say this now, sir. There is a dispute that then generates between the original management of the company, Mr Heath and Mr Williams, and those who are now in control, Mr Seymour and his colleagues. It's played out in a New Scientist article in March 1983, IPSN000426_036. There's an article in Business Magazine, IPSN0000442_042.

There are questions in Parliament, RLIT0001486 and 1487 and 1488, and private correspondence, IPSN0000260_024.

I won't go through all of those documents but the fundamental battle lines, as it were, are between Mr Heath and Mr Williams, who saw a lack of investment in research and a prioritisation of short-term profits leading to a failure to exploit the technological advances made, and in particular, a failure to exploit work in recombinant technologies which later comes to fruition. Mr Heath from the Business Magazine article

said:

"It's a tragedy, a disillusioning ten years of my life went into Speywood, wasted because the British didn't get the best out of it."

In contrast to that, and we can see it from the business plan we've just looked at, is the view of Mr Seymour and his colleagues which is in essence that the previous management were too ambitious, too disparate, lacking focus in their funding, and not sufficiently orientated on running a conventional pharmaceutical business. That had led to the problems that Speywood had in 1983. I don't seek to resolve that argument there. I just draw out the outlines of it for you.

I note that Speywood was acquired by Porton International Limited in July 1984.

I will come back, sir, to recombinant porcine Factor VIII after lunch, and we will also hear from Ms Middleton then. I am conscious that whereas I can continue the presentation on Tuesday if necessary, Ms Middleton must give her evidence today and I --

SIR BRIAN LANGSTAFF: Well, yes, we will obviously want to hear Ms Middleton in full, without any pressure of time, on her or on you.

MR HILL: Sir, I suggest, then, that I -- directly after

lunch, I introduce just a couple of very quick documents about recombinants, and then we hear from Ms Middleton, and then I return to porcine Factor VIII at a later stage.

SIR BRIAN LANGSTAFF: Yes, well, let's take a break now, shall we, until five past two, and expect to hear from Ms Middleton sometime around about quarter past two.

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

(1.07 pm)

(The luncheon adjournment)

(2.06 pm)

MR HILL: Sir, after further thought, it may make sense to call Ms Middleton straight away, just to avoid the difficulties of moving equipment around between presentation and witness evidence.

SIR BRIAN LANGSTAFF: Let's do that.

Ms Middleton, would you like to come forward and Lauren will swear you in.

MS SARAH MIDDLETON (affirmed)

Examination-in-chief by MR HILL

SIR BRIAN LANGSTAFF: And it is, I think, Ms Middleton?

THE WITNESS: Yes, thank you.

MR HILL: Ms Middleton, you provided the Inquiry with a statement dated 14 April 2021. I'd just like to ask you one or two things about your qualifications and

your early career. If we could have on screen, please, WITN5666001, please, Soumik.

We can see from the statement that you did a BSc in biochemistry at the University of Saint Andrews between 1966 and 1969; is that right?

A. Yes.

Q. Then if we go over to the second page, please, Soumik. The outline of your career, I'll come back to fill in some more detail on this in due course, but from 1969 to 1976 you were at the Protein Fractionation Centre in Edinburgh as a biochemist; is that right?

A. Yes.

Q. So was that your first job after university?

A. That was my first job, yes.

Q. 1976 to 1979, you were at the Department of Medicine University of Glasgow, again as a biochemist?

A. Yes.

Q. Then 1979 to 1987 it says here, "Speywood Laboratories Ltd: Chief Scientist"?

A. Yes.

Q. Is the 1987 date correct?

A. I think that includes consultancy work that I did subsequently.

Q. I understand. 1987 to 1996, another firm, Delta Biotechnology Limited?

A. Yes.

Q. Working on recombinant human albumin in yeast?

A. Yes.

Q. 1986 to 2001, "Andaris Ltd: Director of Targeted Therapeutics"?

A. Yes.

Q. Then 2001 to 2016, you founded Haemostatix Ltd, as CEO and CTO; is that right?

A. Yes.

Q. You haven't, as I understand it, given evidence previously to any Inquiry about the infected blood?

A. No.

Q. But you were interviewed with respect to a US class action. Without giving away any confidences that you can't give away, what were the circumstances of that interview?

A. I have very little recollection, actually. I was called to London, and interviewed by American attorneys, and I thought that is a class action on behalf of haemophiliacs in the United States. And I was interviewed twice, but nothing ever came of it, and there were no written papers or anything.

Q. Do you know on whose behalf the attorneys were acting?

A. I suspect they were acting on behalf of the haemophiliacs.

Q. Plaintiffs in the action?

A. Yes, the plaintiffs.

Q. Thank you. I'd like to begin, if I may, by asking you a few questions about the protein fractionation centre in Edinburgh, and your time there.

A. Yes.

Q. As we have seen, you joined in 1969, directly after university?

A. Yes.

Q. Who was your line manager, if such a thing --

A. Jim Smith. Dr Smith.

Q. Which department were you in?

A. Well, we were one big department, or one little department, in the bowels of the Royal Infirmary in Edinburgh, and we were just -- there were a group of us, about 15 of us, I guess, fractionating, learning to fractionate blood.

Q. Under the guidance of Dr Smith?

A. Yes. Well, Dr Smith was my immediate boss. The organisation was run by Mr John Watt, who was a vet.

Q. How --

A. And then he was, I suppose, reporting to -- it wasn't John Cash, it was the predecessor. I'm sorry, I can't remember his name.

Q. I understand.

A. Head of Blood Transfusion Service.
Q. You say there were about 15 of you?
A. Approximately.
Q. What kind of gradations were there in terms of the different work that was being done, in terms of the seniority of --
A. Well, I was first employed as a technician, and was promoted to biochemist, but mostly we were technicians. They were technicians.
Q. When you say you were promoted to biochemist from a technician, can you recall when that happened?
A. After about a year, I think, about a year.
Q. Should I understand from what you said there that you weren't in any policy formulating at that time?
A. No, no. I was doing what I was told.
Q. By Dr Smith?
A. By Dr Smith.
Q. Thank you. So we are clear, that's the same Dr Jim Smith --
A. Yes.
Q. -- who later moves to BPL and with whom you --
A. Yes.
Q. -- worked at BPL?
A. Yes.
Q. And if we could have page 1 of your witness statement

back onscreen, please -- sorry, page 2 of your witness statement back onscreen.

The description that you give of the different processes involved, if I could just ask you to expand a little and explain, in layperson's terms, insofar as is able, the different elements of your work there, the first being:

"Purification of Factor IX, for human plasma ..."

A. Yes.
Q. "... using ion exchange resin."
A. Yes.
Q. Could you explain what you were doing, when you were doing it and what the product was?
A. The purification took the supernatant from cryoprecipitate, which was cryosupernatant, and was then diluted and passed over an exchange resin in order to prepare a concentrate of factor II, IX and X. There was no Factor VII, which was in some concentrates.

The issue for Factor IX is that it can be thrombogenic, in other words it can actually promote clotting outside of the action of Factor IX, so you want it to be controlled and not produce clots when you're not expecting it. And this Factor IX was very

clean, and didn't appear to activate clotting factors, as some concentrates did. So it was a very -- regarded as very safe.
Q. Is this a forerunner of the products that became Defix?
A. No, that is Defix.
Q. It is Defix?
A. Yes.
Q. So the first bullet point there we should understand to be working on the production of --
A. Defix, yes.
Q. And was that the first time that it was being produced?
A. Yes.
Q. 1969 time?
A. Yes, it was.
Q. Could we have onscreen, please, Soumik, PRSE0003648, please.

This is a document that we provided you with. We have provided two sets of documents, it's in the second set.

A. Yes.
Q. And it is an article from Vox Sang, volume 24, pages 441 to 456, from 1973, entitled "A Therapeutic Concentrate of Coagulation Factors II, IX and X from

Citrated Factor VIII-Depleted Plasma"?
A. Yes.
Q. And you're listed as the lead author there.
A. Yes.
Q. With Ida Bennett and JK Smith, presumably Dr Smith?
A. Yes.
Q. If we could look at the abstract, please, Soumik:

"Abstract. A simple procedure is described for large-scale absorption on to DEAE-cellulose of coagulation factors II, IX and X from citrated, factor VIII-depleted plasma. The coagulation factors are eluted frontally from the exchanger in a high yield and in a form suitable for therapeutic use, without further fractionation. The lyophilised concentrate is very stable without the addition of heparin and, when redissolved to iso-osmolar solution ..."

Forgive my repeated butchering of pronunciations as we go through!

"... contains approximately 30 U/ml factors II, IX and X, 250-300 times purified from the starting plasma. The effectiveness of the concentrate in the treatment of haemophilia B is discussed."

A. Yes.
Q. So that's the abstract of the article. Should I take

it that this article is describing the process that you have just described to us?
A. Yes.
Q. This is the formulation of Def --
A. Yes.
Q. To the best of your knowledge, was this article from 1973 the first publication of the Defix product?
A. Yes.
Q. If we just look at the introduction section, there are a couple of points to pick out from it:
"Until 1967, only fresh-frozen plasma could be offered in Scotland for correcting deficiencies of coagulation factors II, VII, IX and X. Such treatment was frequently inadequate to maintain haemostatic levels of factor IX in patients with severe haemophilia B during major bleeding episodes or surgery."
A. Yes.
Q. "Since 1967 the Protein Fractionation Centre has made approximately 1,100 doses of 'PPSB' from blood collected in EDTA, by the method published by Soulier ..."
What was PPSB?
A. That was a full factor concentrate which contained Factor VII in addition to factor II, IX and X.

Now, I can't actually remember how PPSB was made, but obviously it started off in blood collected in EDTA, which is rather different because none of the other fractions can be collected from that blood.
Q. Could you just explain EDTA to us?
A. Ethylenediaminetetraacetic acid.
Q. I won't try and repeat that!
Going back to the article:
"This product represented an important advance in the treatment of haemophilia B, and its use has been extended to a number of other deficiencies of the prothrombin complex of coagulation factors. The demand for PPSB for use, eg, in liver disease and the reverse of anticoagulant therapy, at times threatened to exhaust the stocks required for emergency treatment of haemophilia B, and prompted us to look for new methods of recovering factor IX or prothrombin complex from normal citrated plasma. A large increase in the production of PPSB was considered uneconomical of limited fresh blood resources, because cellular components and factor VIII are not readily recovered from blood collected in EDTA. It was hoped that an alternative method could be devised to improve the yield of factor IX (only about 30% in large scale production of PPSB) and end our dependence on

procuring batches of tricalcium phosphate with the appropriate absorbtive properties."
If I just pause there for a moment, am I right in understanding that to mean that your work in trying to create Defix was a response to the need for more product and concerns about running short of the existing product?
A. More product, and more efficient use of blood.
Q. Going back to the article:
"This report describes the absorption of factors II, IX and X from large batches of citrated Cohn supernatant ... on DEAE-cellulose, and their selective elution in a form suitable for freeze-drying and administration to patients without further purification or stabilisation."
A. Yes.
SIR BRIAN LANGSTAFF: That's "supernatant I", I think it is said there, isn't it?
A. Yes, Cohn supernatant.
MR HILL: Sorry, my printed version is not --
A. It's actually cryosupernatant.
Q. I'm not going to go through the technical detail of the article but, if we could please go to electronic page 11, which is internal page 451, the section dealing with "Transmission of serum hepatitis". What

is written is this:
"More than 20 batches, each made from 200 to 600 donations of plasma, have been used since May 1970. In Scotland the screening of all donations of blood for Australia antigen by immunodiffusion or immunoelectroosmopheresis became routine during 1971. Using such methods, which detect probably less than 50% of Australia antigen carriers, the incidence of antigenaemia among blood donors in Scotland has found to be about 0.07%. All batches of the factor II, IX and X concentrate have been tested for Australia antigen by the methods used for donor plasma, usually in five-fold concentration. Australia antigen has not been found in any batch, nor has any recipient developed hepatitis or Australian antigenaemia following treatment with the concentrate alone.
"Since the methods used to detect the agent causing serum hepatitis were very insensitive and since no systematic attempt has been made to assess the incidence of sub-clinical hepatitis among the recipients, it would be prudent to assume that the concentrate could be infective if made from infective plasma, but it seems likely that the concentration of the infective agent is substantially reduced by the preparative procedure."

A couple of things to pick up from there. First of all, the batch size that is cited there, which is 200 to 600 donations of plasma, am I right to understand that that was -- those were the batch sizes that were used in the work that you were doing at that time?

A. Yes.

Q. Do you know why there was such a variation between 200 and 600 donations?

A. Well, I suspect that, at the time, we were -- well, I'm fairly sure we were -- we were making it and scaling up as we went along.

Q. Scaling up to use --

A. Scaling up to use more plasma and bigger columns.

Q. Do you know how the batch size developed in terms of the Factor IX product produced at PFC, during the remainder of your time there -- to 1976?

A. Err ... I'm actually not sure what size it went up to.

Q. Do you recall what discussions were taking place within PFC about batch size around this time?

A. No.

Q. The article here clearly demonstrates an awareness of the risk of what is described as Australia antigen --

A. Yeah.

Q. -- serum hepatitis, at the time.

A. Yeah.

Q. Do you know whether there was discussion, recognition, of whether or not that risk increased with a larger batch size?

A. No, I don't know whether there was. But it's likely, isn't it, that it would have been?

Q. Do you think you would have been involved in those discussions?

A. I was only a lowly technician at the time. I wasn't involved in those discussions.

Q. Those would have been matters for whom?

A. Er ... probably Jim Smith, um ... and/or the director of the Blood Transfusion Service, whoever that was. I don't think it was John Cash. It was --

Q. The predecessor --

A. The predecessor.

Q. Do you remember what information you were given, what training you were given, about the risk of hepatitis from such products at this time?

A. We were -- yes. We were aware of hepatitis as a potential problem but, I have to say, I don't think we took a great deal of precautions for it, at the time. We weren't that aware of it. I suspect Scottish plasma was thought to be a fairly clean plasma, so I can't really answer that question, but we

did actually have a technician in the Blood Transfusion Service who did have an accident with a positively -- a positive hepatitis B donation, and she subsequently died. So there was definitely an awareness.

Q. Are you able to say approximately when that occurred?

A. Well, it was probably in the first couple of years, I think, that I was there. Maybe a bit longer.

Q. Early 1970s?

A. Yeah, early '70s.

Q. Are you able to -- this is a very difficult question thinking back all these years -- are you able to recall what kind of journals and learning that you would have been keeping up to date with at that time?

A. Well, obviously Vox Sanguinis was one of them, Blood, Thrombosis and Haemostasis, those are the ones I sort of remember. Vox Sanguinis was very much the one to do with fractionation. Obviously Blood. No virology journal specifically, but hepatitis would have been discussed in some of those -- in those other ones that I've mentioned.

Q. Were they made available to you at the PFC or did you have to find them off your own back?

A. No, they were available.

Q. I'd like to just again pick up a couple of more things

from that section. There's a reference to the testing that became routine during 1971. Should we understand that, before that, there was no routine testing for hepatitis?

A. Possibly not. The assays, as they say, were rather insensitive at the time.

Q. That's what I was going to ask next.

A. Yeah.

Q. There's a figure of probably less than 50 per cent given.

A. Yes.

Q. An awareness, then, that testing wasn't going to catch everybody?

A. Yes.

Q. The figure that is given about the blood donors in Scotland being found to be about 0.07 per cent --

SIR BRIAN LANGSTAFF: I think we've lost it on the screen.

A. Yes -- (overspeaking) -- on the screen.

MR HILL: Apologies. If we could highlight the middle paragraph, "Transmission of Serum Hepatitis". Thank you.

A. Yes.

Q. Sir, we can see that figure there given of 0.07 per cent --

A. Yeah.

Q. -- for instance, among blood donors in Scotland. How much faith should we put in that figure, given the limited sensitivity of testing at the time?

A. I can't answer that question. I won't answer that question.

Something just in, sort of, qualification of all of this. There was insufficient Factor IX available, and very much the emphasis with everything I did at PFC, and subsequently, really, was with the aim of getting a product out there to treat haemophilia because there were problems, obviously, for haemophiliacs who didn't get treatment. So bleeding was regarded as the first problem.

Q. The question of the risk and benefit of those products, was that a question for you to consider as biochemist and previously a technician, or is that for others?

A. That was more for others, I think. But it was definitely very important.

Q. The conclusion of that sentence says:

"... it would be prudent to assume that the concentrate could be infective if made from infective plasma, but it seems likely that the concentration of the infective agent is substantially reduced by the preparative procedure."

A. Yes.

Q. Do you know the reasons why it was thought that the procedure --

A. Well, the agent -- the factors II, IX and X clotting factors were absorbed to the resin. It was very likely that the infective agent wouldn't be absorbed, would remain in the supernatant and, therefore, it could be concluded, possibly, that there would be a reduction, in any event, of virus.

Q. What was the basis for thinking that the virus --

A. Well, the virus is very big and I don't think -- I think it wouldn't -- it subsequently turned out to be the case -- it wouldn't absorb or be bound to a positively charged resin.

Q. That is, you think, the reason for that final clause in the final sentence?

A. Yes, yes.

SIR BRIAN LANGSTAFF: May I just ask, who was it who first had the idea of using electrically charged resin to attract certain proteins and not others?

A. Well, it was Jim Smith's, the method. The method actually did come, I think, from the Dutch -- I think it the Dutch, or was it the Swiss? Somebody in Europe, who was already using this cellulose method. Other manufacturers were using similar resins but not

the same, positively charged resins, and getting full factor concentrates.

At the end of the day, the difference between the resins and the products made was going to be probably the amount of activation of clotting factors that you got between the different products, and that was really the difference between them.

MR HILL: Do I understand the start of that answer to be that this idea --

A. Yes.

Q. -- insofar as it was exploited in PFC --

A. Yes.

Q. -- was that of Dr Smith?

A. Yes, that of Dr Smith within PFC, but it was being used in other places, other facilities.

SIR BRIAN LANGSTAFF: So the inspiration, the basic idea, scientifically, was somebody else's in Europe, you think --

A. I think it came from somebody else in Europe --

SIR BRIAN LANGSTAFF: -- and roughly --

A. -- because it's quite common, people were using cellulose or sepharose, I think. One was more highly charged than the other, and Oxford, the Haemophilia Centre, they, I think, were using the sepharose product, but I might be wrong, the full factor.

SIR BRIAN LANGSTAFF: Yes.

A. So it was fairly well known to use a positively charged resin.

SIR BRIAN LANGSTAFF: Thank you.

MR HILL: If I could go, please, to electronic page 15 of the document, internal page 455. This may follow from the answers you've given already, if we look at the second paragraph there, it is stated -- this is in the concluding section:

"There is no reason to believe that the concentrate cannot transmit serum hepatitis; however it is probably better in this respect than alternative sources of factor IX, including plasma."

Do I understand from your previous answer that the reason for that is the technique that was used was thought to have a degree of viral inactivation?

A. Yes, well, viral separation.

Q. I'm going to take you to another article now, if I may. It is again, one of yours. If we could have PRSE0003799.

A. Oh, right, yes.

Q. This is the Journal of Laboratory and Clinical Medicine from 1976 --

A. Yeah.

Q. -- volume 88, pages 91 to 101, "Removal of hepatitis B

surface antigen ... from plasma fractions".
A. Yes.
Q. We can see the authors are Dr Johnson and his colleagues from New York, and you and Jim Smith from Edinburgh.
A. Yes, yes.
Q. You refer in your statement, the second of your bullet points was -- sorry, third your bullet points -- was "Clearance of Hepatitis B from Factor IX concentrate using polyethylene glycol precipitation".
A. Yes.
Q. Am I right in thinking that this article covers that aspect of your work?
A. Yes. Yes, it does.
Q. Before we delve into it, could I ask you again for a quick potted guide of what polyethylene glycol precipitation is?
A. Polyethylene glycol is a large, molecular weight polymer and you can add it to solutions of protein when it would cause precipitation of proteins in a selective way, depending on their charge. And you can, by adjusting the pH of the solution, adding the polyethylene glycol, you can get selective precipitation of certain proteins. So size and charge.

Q. Size and charge. If we could look at the abstract, please:
"Endogenous or deliberately added hepatitis B antigen was removed and concentrated for assay from albumin, and from coagulation factor II, VII, IX and X concentrates as model plasma fractions. The concentrates carry considerable risk of causing hepatitis in transfused patients. The amount of antigen remaining in the fraction was estimated to be less than 1/10,000 of that detectable by the Ausria II radioimmunoassay and 1/100 of that found to be infectious when highly contaminated human sera were diluted and injected in chimpanzees. Batch fractionation methods with polyethylene glycol were used. The yield of albumin was 96 per cent and of the coagulation factors about 90 per cent."
That's an overview there of the article.
Going to the first paragraph, it says:
"The high incidence of hepatitis from the administration of blood and plasma fractions remains a serious problem despite governmental requirements to pretest donors for the hepatitis B antigen ... Use of the counterelectrophoresis (CEP) assay for screening donors has reduced the overall incident of serum hepatitis by nearly 30 per cent, and most

investigators feel that use of the more sensitive radioimmunoassay ... has reduced it by about 50 per cent. However, pretesting has failed to achieve further reduction because of possible contamination of the blood by infectious agents capable of causing non-A, non-B hepatitis, and insufficient sensitivity of the assay."
Just pausing there for a moment, two factors mentioned. One is the same as with the previous article, there's a lack of sensitivity in the testing, and the second is a reference here in this article from 1976 to non-A, non-B hepatitis.
A. Yes.
Q. So plainly you were aware, at that stage, of non-A, non-B hepatitis?
A. Yes, which is now hepatitis C.
Q. Yes. Can you recall how serious non-A, non-B was considered to be, as a risk to potential patients at that time?
A. Well, once again, at this time, the overall objective was to stop the patients from bleeding. And while we were doing this work, obviously to try to improve the situation as far as the hepatitis was concerned, that's all I was, sort of, aware of. Obviously, we were aware of hepatitis. We had the agent -- we

developed these agents to try to stop bleeding first. Second, we wanted to try and address the hepatitis problem.
Q. So that everybody is clear, your role as a biochemist was to work on those projects --
A. Yes.
Q. -- not to decide whether or not the treatment that resulted from it should be given to a patient?
A. No. I mean yes.
Q. You agree with the proposition?
A. Yes. [Laughs]
Q. Do you recall what discussions were taking place at around that time about other pathogens or potential pathogens in blood products?
A. In the 1970s?
Q. Yes.
A. No.
Q. If I could turn, please, to electronic page 7 of the article. Forgive me, I think I miscounted. Electronic page 8, please, internal page 98. This is in the "Discussion" section. In the second paragraph down, it says:
"Our purpose has been to reduce the antigen level in selected model plasma fractions, albumin, and factor II, (VII), IX and X concentrates, to 105 or 104

particles per millilitre and then inject the material in chimpanzees to determine its infectivity."

Am I right in saying this was a spiked sample that would then be inserted into the chimpanzees?

A. Yes.

Q. It goes on:

"Albumin is normally heated to 60°C to prevent hepatitis, but since this temperature would cause inactivation, and factor II, (VII), IX and X concentrates, they cannot be heated and carry a strong risk of causing hepatitis in recipients."

So albumin, it was known at that time, could be subjected to a heat treatment at 60 degrees C.

A. Yes.

Q. But, according to this article Factor IX and the other factors couldn't be?

A. That's what was considered at the time: they couldn't be.

Q. Do you know why that was considered so?

A. Well, they were both -- they're all quite labile proteins, which is subject to denaturation, whereas albumin is known to be a very robust protein and can be heated, and it was heated at 60 degrees for 10 hours, originally to remove bacteria.

Q. Do you know if any work was going on within PFC at

that time about heat treatment --

A. No.

Q. -- of those factors?

A. Not in those, no. Not at that time.

Q. No, the work wasn't going on, or, no, you don't --

A. No, the work was not going on. I'm not even sure that -- in those days, we all believed what is said here, that they can't be heat treated, and that was what was believed at the time.

Q. Received wisdom, as it were?

A. Sort of received wisdom from what we knew about those proteins.

Q. But were there any discussions, as far as you recall, about the --

A. It was --

Q. -- possible --

A. It was dismissed at the time as being unlikely to be possible, which is why we looked at this precipitation method.

Q. If we could go on to the next paragraph.

"In collaborative studies with Dr Hoofnagle, two chimpanzees were injected with PEG-fractionated II, (VII), IX and X concentrates which were known to be infectious ..."

I'm afraid the copy isn't good here:

"... and contained at least 1011 antigen particles per millilitre prior to PEG fractionation."

That's polyethylene.

A. Yes --

Q. -- glycol fractionation.

"But these concentrates were prepared by an earlier version of the PEG procedure, which" --

I am afraid I can't --

SIR BRIAN LANGSTAFF: "Utilised", I think.

A. "... which utilised 0.15 M [sodium chloride] and could not quantitatively remove the HBsAg below levels of ..."

10 to the 8th.

SIR BRIAN LANGSTAFF: 5th, I think.

A. It couldn't, anyway.

MR HILL: 105.

A. Yes, they didn't get a very good result.

Q. It says:

"... one of the two injected animals" --

A. Yes, "became infected".

Q. -- "while the other did not ..."

A. Yeah.

Q. Could you just talk us through that aspect and the significance, both of the previous method being used and the fact that one of the chimpanzees became

infected?

A. Actually, I can't, because I'm not quite sure what this actually meant, now, going back 40 years. I apologise for that. I'm not quite sure what the procedure was that was different.

Q. But you say they didn't get a very good result, whatever that procedure was?

A. Was, it didn't seem to work.

Q. Hadn't inactivated -- separated the --

A. No, it hadn't separated it out.

Q. I am just going to take you to see if we could perhaps get some assistance from Peter Foster's evidence to the Penrose Inquiry.

A. Yes.

Q. You're aware of Dr Foster?

A. Yes.

Q. He became a colleague of yours --

A. Yes, he did.

Q. -- in due course.

A. Yes.

Q. If we could have on screen, please, Soumik, PRSE0003349, this is one of the documents that you were provided with. If we could have page 3 -- sorry, just leave it there for one second, we can see this is the witness statement of Peter Foster to the Penrose

Inquiry, or one of his witness statements.

If we could turn to page 3 of that, please, and paragraph (f). It says -- Dr Foster said this:

"Factor IX preparing experimentally in the USA by this procedure, from plasma known to contain hepatitis B infectivity, was tested by Dr Johnson in chimpanzees. The chimpanzees developed hepatitis B, demonstrating that hepatitis B infectivity had not been fully removed ..."

Then there is citation to the article which we have just seen.

A. Yes.

Q. So, leaving aside the reference to whether or not it was one chimpanzee or two chimpanzees, it became infected. Dr Foster's take from the paper, as it were, is that the process hadn't been successful?

A. Yes.

Q. Or I should say wholly successful?

A. Well --

Q. It may have reduced --

A. Not really successful -- it wasn't successful.

Q. Yes, and that's a conclusion you would agree with?

A. I would agree with that.

Q. If we could just go to (g), then:

"Dr Johnson's subsequently refined for

precipitation parameters (the revised method being known as the mark II method) to remain greater removal of the hepatitis B virus. However, he told me that his application for funding for another chimpanzee study, to discover if the removal of hepatitis B infectivity had been successful, was rejected by the USA National Institute of Health (NIH) because they considered that [and he quotes] 'hepatitis is no longer a problem'."

A. Oh, that's interesting.

Q. Is that something you were aware of or can assist us with?

A. No, I wasn't.

Q. We will leave that for Dr Foster, then.

If we could continue on as we are here, to:

"h). Another issue that arose with factor IX prepared by the first (mark I) version of the method was a thrombogenic reaction in dogs [Dr Cash is cited] suggesting that the product might be harmful to patients. Alternatively, this may have been a consequence of the very high dose of factor IX ..."

SIR BRIAN LANGSTAFF: Sorry.

MR HILL: Sorry.

"... consequence of the very high dose of factor IX that had been administered in this study, as

the product was more concentrated than established Factor IX concentrates."

Were you aware of or involved in the Cash work which led to the production of that article?

A. Yes. We supplied the concentrates for it. Actually, I was surprised because I didn't recall -- and I have read Peter's submission -- but I was surprised because I -- it could have been because it was a very high dose of Factor IX that was administered. That's all I can conclude from that.

Q. Yes.

A. And that -- because a lot of Factor IX, a lot of Factor II, a lot of Factor X, that could be the result of -- that could be resulting in this thrombogenicity that I referred to.

Q. Yes, yes.

A. But that was the Defix.

Q. That was the Defix that you supplied Dr Cash --

A. Yes.

Q. -- for that article --

A. Yes, yes.

Q. So a slightly different stream of work?

A. No, that was Defix. And what -- well, I think it was -- I think that's what he's referring to. If you go back to the page before, can you just ...

Oh, I'm apologising, sorry. He wasn't referring to Defix.

Q. We will pick this up with Dr Foster in due course.

A. Yes, because when we went on to use the polyethylene glycol process that Dr Johnson had developed, we did a parallel, not -- we did it with no, obviously, hepatitis added in, we did it just to look at the fractionation of Factor IX, through this polyethylene glycol process. We actually got a reduction in thrombogenic material by tests that were introduced later, which was again one of those publications that we had.

Q. I am just going to take you back to the 1976 article of which you were a co-author.

If we could have on the screen, please, Soumik, PRSE0003799, internal page 99.

So I think page 8 of the electronic version. I'm afraid I don't have a marked copy. Sorry, page 9.

A. That's 98.

Q. Thank you. I just want to take you to the final paragraph:

"Although the clinical value of the PEG method for removing [hepatitis B] must be confirmed by further studies in chimpanzees, we fully expect that its application to selected, clinically useful blood

fractions will reduce or even eliminate post-transfusion hepatitis due to hepatitis B antigen contained in these administered fractions."

Could you just explain the basis for that thinking?

A. Um ... well, I think ... there was only two chimpanzees. The method was refined, and I think he felt that the use of a precipitation method to precipitate out the virus, which is obviously very big and very heavy, it -- theoretically, it would be a good method.

Q. Shall we read this as being that although there has been infectivity with the mark I method --

A. Yeah.

Q. -- Dr Johnson is already thinking about the mark II methods and is optimistic for the results that may be obtained?

A. Yes, yes.

Q. We see an express reference to the need for further chimpanzee studies.

A. Yes.

Q. We can tie that back to what Dr Foster said in --

A. Mm.

Q. -- and pick that up with him in due course. Thank you.

One further article from your time at PFC -- or, published after your time, but referring back to while you were there.

If we could have, please, WITN2235010. The second page of this, please.

An article from British Journal of Haematology in 1981, volume 47, pages 91-104, an article by Dr Prowse and Dr Cash:

"The Use of Factor IX Concentrates In Man: a 9-Year Experience of Scottish Concentrates in the South-East of Scotland."

You are not an author of this paper.

A. No.

Q. It is published after you have left the PFC but would include periods that you were at the PFC if it's a nine-year study; is that fair?

A. Yes.

Q. Did you have any role in the study to which this article refers?

A. No.

Q. I will leave it there.

Returning to your witness statement, you also say that while you were at the PFC, you were involved in purification of Factor VIII from human blood using purified cryoprecipitate fraction. Could you just

briefly explain what that involved, please.

A. Well, it was well known and was used, single donor cryoprecipitate, which means that plasma was thawed very slowly to not more than 5 degrees, and the precipitate that was Factor VIII and fibrinogen, in large proteins, was recovered.

This is a very slow process but it was single donor, which was the advantage from the hepatitis point of view. But it was very slow, and if a patient was bleeding, it was not a particularly useful thing to do. So what I did, again with Dr Smith, was to make bulk preparations of cryoprecipitate, which essentially involved taking large amounts of plasma, thawing it out very slowly, with mixing, to get a cryoprecipitate which would then be dissolved and -- essentially dissolved and formulated to make a bulk product, which could be freeze-dried.

And that was the first Factor VIII to be made by that method at -- in Scotland.

Q. Very difficult question but can you remember the time span in which you were engaged in that work, and particularly when it came to -- (overspeaking) --

A. Well, I did it almost when I first started my first -- in the first couple of years.

SIR BRIAN LANGSTAFF: From 1969 to 1971?

A. Yes, I guess so. Yeah.

MR HILL: How -- may I ask a broad question: how successful was the product that was created?

A. Quite successful.

Q. Was it used by clinicians in the --

A. Oh, yes.

Q. -- (overspeaking) --

A. Yes, it was. In fact, after I left PFC, which was for reasons of -- I had a husband who moved to the West Coast of Scotland, and I went to Glasgow and worked with a haemophilia director there, and was involved in some of the treatment of patients -- for the first time, really.

And they were using some of that concentrate, and it just made such a difference to -- for the patients to be able to have a freeze-dried concentrate used immediately out of the fridge for immediate use.

Q. This concentrate, shall we understand that it was essentially a freeze-dried cryoprecipitate?

A. Yes.

Q. Rather than what became known as freeze-dried factor concentrates at a later stage, rather than pooled plasma?

A. It was -- I'm not sure I understand your question.

Q. I'm sorry.

A. It was a freeze-dried -- it was freeze-dried cryoprecipitate, but made in bulk. So you got several hundred vials from a batch.
Q. I see.
A. That were freeze-dried.
Q. So what was the pool size of the cryoprecipitate?
A. Well, I know initially it was about 20 litres but I can't remember how many units that -- how much that made, but ...
Q. Obviously obtained from more than one donor at that size?
A. Yes, it was.
Q. You said initially. Do you remember about --
A. I don't know how high because it was being done in a small facility, and using small scale equipment, and therefore we were somewhat limited to about 20 litres. Now, I'm sure it went up to about 100 litres, subsequently, about that's what I recall doing.
SIR BRIAN LANGSTAFF: Can I just tell you, the -- we've had a conversion factor used in the course of the last week or so of somewhere around 600 ml a litre of whole blood is plasma.
A. Yeah.
SIR BRIAN LANGSTAFF: So if that is so --
A. Yes.

SIR BRIAN LANGSTAFF: -- then a donation of plasma is about 600 ml?
A. Yes.
SIR BRIAN LANGSTAFF: So 20 litres would give you somewhere between 35 and 40 donors.
A. Yes, yes.
SIR BRIAN LANGSTAFF: Or donations, I should say, because they might be the same donor giving a couple of pints.
A. Most likely single at that point. Yes. That would be right.
SIR BRIAN LANGSTAFF: That would be right?
A. Yes.
MR HILL: Same question as earlier. Were you involved in any discussions about the potential risk of --
A. No.
Q. -- increasing the donor size?
A. No.
Q. Again, a decision made at a higher level?
A. Yes.
Q. The final bullet point you gave through PFC is the:
"Evaluation of Plasma Fractionation using solid phase polyelectrolyte based on Ethylene Maleic anhydride (EMA PE)."
A. Yes.
Q. Now with some trepidation, given that I attempted an

explanation earlier, could I ask for your explanation of what polyelectrolyte fractionation is, please?
A. Well, essentially it was just a novel polymer, positively charged polymer, that was -- I can't remember its original use from Monsanto but it was being evaluated for plasma fractionation. And there were variations on the degree of positive charge that could be introduced into it.
So there was one called E100, which was a 100 per cent substitute with positive charge, which was used -- potentially which was developed to purify albumin and gamma globulin away from each other. And then there was -- the one that -- when I first evaluated those polyelectrolytes, I went to New York. There was no -- from my recollection, and I think this was true, there was no polyelectrolyte at that point that was very useful for Factor VIII. I don't know whether it was because the Factor VIII wouldn't come off the polyelectrolyte. I suspect that was the case. But at that time, there wasn't one.
So I ended up -- from PFC, I went over and learnt about albumin and gamma globulin.
Q. Was that at Dr Johnson's --
A. That was in Dr Johnson's lab.
Q. You mentioned Monsanto.

A. Yes.
Q. That was the company providing the polyelectrolyte?
A. Yes.
Q. Yes. And that's the same company as later provided --
A. Yes.
Q. Well, even at this time as was providing Speywood, and you would --
A. Yes. Yes.
Q. Other than those areas that we've discussed, were you involved in any other viral separation or viral inactivation work in PFC at that time?
A. Um ... no, only the creation of Supernine, which we've talked about, the PEG precipitated.
Q. We will come back to Supernine perhaps with Dr Foster or with others.
A. And I did actually -- yes. I did actually look at separation of viruses with polyelectrolyte with immune globulins. But that's not -- that was never published, so I am not quite sure -- but there obviously was an awareness there of ...
Q. Who was directing the areas in which R&D would be aimed, in the PFC at that time?
A. Um, Jim Smith. Dr Smith.
Q. What resources were available to him?
A. Plasma.

Q. As in laboratory and human resources?
A. In PFC?
Q. Yes.
A. Um ... we had laboratory, we had equipment. We had plasma.
Q. How many people?
A. Doing research, or doing this development work?
Q. Doing research.
A. Well, there was me and I guess there was a couple of others, but it was mostly me doing coagulation factors.
Q. Fair to say then that there had to be a fair degree of prioritisation on the work which you were doing?
A. Mm.
Q. We know that in 1981, after you had left, some five years after you had left, the Medicines Inspectorate gave a critical report of the PFC.

In your experience, up until 1976, did the PFC meet the standards that you would have expected of a laboratory and fractionation centre.

A. Well, I didn't know any better. They -- we were -- well, we were obviously trying to work as cleanly as possible. The Medicines Act had only just really come into play in 1969, so I think we were sort of -- it sounds terrible but it isn't meant to -- making it up

as we went along. We had to keep out bacteria, we had to keep out pyrogen in particular, and these were the things that drove us to work as cleanly as possible and that's what we did.

But the facilities in PFC at the time -- and this is before it moved into its new facility out at Liberton -- we were in the bowels of the Royal Infirmary in Edinburgh, and in fact -- which was not a particularly desirable place to be making clean blood products, but it was all we had.

Q. How did it compare with your later experience of Speywood?
A. When I first went to Speywood the conditions were not great. We were working in a Portakabin -- and a garage, actually. So I got used to that sort of thing, and, amazingly, made pyrogen-free products out of -- in some of these facilities.
Q. Is it fair to say that then both your initial work in Speywood and the work that you did at the PFC, your burdens were added to by the need to work hard to make pyrogen-free product in the --
A. Yes, it adds quite a lot of problems, and cleaning equipment, and water quality, and those sorts of things. So yes.
Q. Moving to your time in Glasgow in 1976 to '79, you

said something of it originally, but what kind of interaction, if any, did you have with haemophilia patients?
A. Well, I, having moved to Glasgow, I was involved with -- we were collecting blood samples from patients to check on their Factor VIII levels after treatment, and looking at things like half lives and those sorts of things.
Q. The half life of a Factor VIII product that they'd been given?
A. Yes, yes.
Q. Did you conduct any other routine blood tests on those patients at that time?
A. No. Just factor assays.
Q. Would you actually draw the blood yourself?
A. No, no, it was drawn by a nurse or a doctor.
Q. And are you able to assist at all with what the consenting process was that the patient went through before giving that blood?
A. There wasn't -- as I recall, there was no consenting process.
Q. So the blood would be taken from the patient without the patient being told what the blood was going to be used for?
A. It might have been. It might have been.

Q. You personally weren't involved in those discussions --
A. No -- no.
Q. -- with the patient?
A. No. I can't tell you if there were bits of paper signed or whatever was done. It wasn't that apparent, because the number of patients within a haemophilia unit -- the whole haemophilia unit is very much sort of like a family. And patients were coming in all the time to get their treatment and knew the haemophilia directors and the nurses intimately, because they were there quite often, and I don't think -- I don't know what consenting processes would have been involved.
Q. What, other than checking the blood for the effect of the Factor VIII products, what other roles did you undertake at Glasgow at that time?
A. Well, I actually looked at the Factor IX concentrate that -- the Defix Factor IX concentrate, and the Supernine concentrate, and looked at using different assays to look at that thrombogenicity.
Q. That was research work that you were doing --
A. Yes.
Q. -- on the products rather than -- (overspeaking) -- the patients?
A. Yes, on the products, yes. While I was there.

I also did things to do with Factor VIII assays, recoveries after exercise and various other things. I worked with who is now Professor Lowe at the time and we did some work with recovery of Factor VIII with exercise, and things like that, physiological effects.

Q. What links did you have at that stage with your former colleagues at the PFC?

A. Well, I was still working -- Peter Foster was there at that time. I suspect Jim Smith had left, I think. And he knew what I was doing, because we subsequently wrote the paper about Supernine and PEG concentrate. So he knew what I was doing.

Q. Did you have any links with pharmaceutical companies at that stage, while you were at Glasgow?

A. No, the only reason -- the only pharmaceutical company that happened while I was in Glasgow was that David Heath, who you've heard mentioned, came into the lab while I was working to speak to my boss, Dr Prentice, who was the haemophilia director, and started to talk about polyelectrolytes. Within my hearing. So that's how it came about that I ended up working for Speywood.

Q. You've pre-empted my next question.

A. Right.

Q. It was how you were recruited to Speywood in 1979.

Was it from that --

A. Essentially I heard that conversation about polyelectrolyte. I also -- and -- yes, I wrote to David and said -- because I wanted to actually get back to something more production-orientated, and explained my experience, and I got a letter by return of post saying: Yes, when are you going to start?

So that's what happened.

Q. You then moved to Speywood. Physically, where were you based when you were working for Speywood?

A. Wrexham.

Q. In Wrexham?

A. Yes.

Q. Did you have anything to do with the office in Nottinghamshire?

A. Not really. We occasionally -- we went over there occasionally. Myself and the production, I guess you mean the production director, Dr Costello, (?) ** and -- he was in charge of the Wrexham site. We occasionally went over there, but just to talk about progress with porcine Factor VIII.

Q. So you're essentially going there for meetings, but never being based there; is that right?

A. No, never been based there.

Q. Your title was chief scientist?

A. Yes.

Q. What did that role entail?

A. Well, I sometimes thought it was because I was the only scientist. At the time.

It involved -- my going there was primarily to develop porcine Factor VIII. There was a problem with the current product, which was not soluble, and couldn't be used. I subsequently sorted that problem out -- actually, quite quickly -- then went over to the States to pick up the polyelectrolyte, which seemed to have been now working for Factor VIII. So that's the way it went. I then came back and scaled the polyelectrolyte method up to produce Hyate:C.

Q. That's the porcine product?

A. The porcine product.

Q. But when you say you went over to the States, should we understand that to be literally --

A. -- (overspeaking) -- Dr Johnson's lab.

Q. Did you stay there for long and conduct research or was it literally to pick up the polyelectrolyte --

A. Well, I stayed there -- I think I stayed there three or four weeks, just to make sure that the method worked, and to -- because I didn't -- because it previously hadn't, for Factor VIII, but it did work. So I then picked up the polyelectrolyte, brought it

back to Wales, which is where we were, to Wrexham.

Q. So that we are clear, this is for polyelectrolyte that was being licensed from Monsanto?

A. Yes, it was.

Q. The accountant's report from 1981 that we looked at earlier -- and I know you were in the room when we were going through the presentation earlier -- it referred to there being 21 staff in Wrexham. I am not going to ask you for what each one of them did, as of 1981, but what kind of roles were those people doing? What were people doing in --

A. Initially, there were not 21 but there was -- initially, there was a technician in the lab who was doing Factor VIII assays, mostly, and there were a collection of three or four or maybe five individuals who were responsible for collecting the blood on the abattoir.

Q. The pig blood?

A. Yeah, collecting and separating it.

Q. Then there was you, as chief/sole scientist?

A. Yes. And then there was Dr Costello (?) ** who, actually, was a botanist but he was obviously a scientist, as well. But he was in overall charge of the site, and the personnel.

Q. Who gave you directions about what it was that you

should be doing?
A. Me.
Q. We heard in the presentation about the importation of Koate and Humanate --
A. Yes.
Q. -- and its sale within the United Kingdom. What role, if any, did you have in the importation and sale of Koate and Humanate?
A. I had no -- very little knowledge of it. I certainly had no input at all.
Q. We saw from the data sheet that it was -- the address given was the Nottingham address.
A. Yeah.
Q. So far as you're aware, was the Koate and Humanate business run from Nottingham --
A. Yes.
Q. -- or from Wrexham?
A. No, from Nottingham.
Q. Were you ever involved in the processes of seeking product licences or dealing with the DHSS, insofar as it related to Koate and Humanate?
A. No.
Q. I'm going to quickly ask you, before we have a break, about porcine Factor VIII and Hyate:C. You said -- you've explained how you went and you picked up

Factor VIII assays are particularly difficult to standardise, and we did have a problem with porcine Factor VIII because the kinetics of the production of porcine Factor VIII are different between human and pigs. And there was a pig standard which was supplied by a commercial company, which turned out to be wrong because of the way it was -- had been assayed. So yes, I had quite a lot of input into that. It's an interesting topic, the kinetics of blood clotting in pigs versus human. Sorry.
Q. I won't go into too much detail about that, and you'll forgive me. But were you involved in any of the applications for product licences for Hyate:C?
A. Somebody else wrote them, because I wasn't there at the time.
Q. But you left the company by that stage?
A. I was either -- I may not have left. I might have been somewhere else, like at Elstree or in Paris, or I also worked on deficient plasmas and various other things. So I was away from, sometimes away from Speywood, and I don't think that licence was applied for until the facility, the manufacturing facility, had been built. And so I was -- I'm not -- I did -- don't think -- I might have done. I don't remember whether I did or not.

a polyelectrolyte and understood that it now worked in respect of Factor VIII, and then you solved the problem that they had been having with it. In your statement, I won't take you to it, but at paragraph 14 you say:
"I developed a production scale process to recover porcine Factor VIII."
A. Yeah.
Q. Then at paragraph 37 you say that you had little involvement in porcine Factor VIII thereafter.
A. I had -- after scaling up, yes, I showed the method to others, the other people, and they were perfectly capable of handling it. It was a very easy process, really. The difficulty with any Factor VIII or Factor IX concentrate, it's not so much making it, it's knowing you've got the right thing at the end of it, in terms of assays, and analytical work, and knowing that there's no potential for clotting when you don't want clotting. So thrombogenicity, as we call it.
Q. Did you have any role in that aspect of the work in terms of Hyate:C?
A. The assay?
Q. The assay and the checking, the quality control and --
A. Yes, to an extent, because I had experience of --

Q. I haven't found many papers with your name on in connection with the Hyate:C --
A. The product. The product licensing or --
Q. And indeed the product licensing.
A. Yes, well, okay, in that case I didn't.
Q. We haven't looked at this in the presentations and we will come back to that at a later date, but we know that the application for the product licence was made on 29 November 1983 --
A. Oh, right. Okay.
Q. -- and the licence was granted on 3 December 1984.
A. Right.
Q. Would you have still been working at Wrexham for Speywood at that time?
A. Um ... well, no, I don't -- now you come to mention it I actually don't know, because I did have a very -- I didn't really work full time at Wrexham, for a long time before -- a long time after -- after I went and worked down at the -- at Elstree.
Q. At BPL?
A. At BPL. And I don't know -- if you ask where I was, I know I was doing work at the Royal Free on depleted plasmas, for example, and I just was working in other people's labs, I think.
Q. Is it fair to say, then that, certainly from your

current recollection, you didn't have a great deal of input into the finalisation of the product Hyate:C?
A. No, I don't think I did.
Well, in the sense that I did formulate it, and I did run -- develop assays, and various other things, and I did have an interaction with NIBSC, N-I-B-S-C, about the assay, because that caused us all a lot of confusion at one stage. So I was doing that.
Q. Were you involved in, for example, directing the thinking about where this product should be used, and which cohort of patients it should be used with?
A. Not really. It was inhibitor patients, as far as I was concerned.
Q. That's where my question is leading to. When the product licence went in, we'll look at this in due course, it is very expressly said to be for inhibitor patients.
A. Yeah.
Q. One question that the Chair may wish to consider, in due course, is why porcine Factor VIII, in the mid-1980s at a time of risk of both hepatitis and AIDS, was directed towards inhibitor patients rather than the wider population of --
A. Of patients without an inhibitor?
Q. Yes, exactly, without inhibitors.

A. Yeah.
Q. Are you able to give any insight into that question from your perspective?
A. Well, from what I knew, first of all, porcine -- original porcine Factor VIII had a shocking reputation. This is before Hyate:C. It was a really toxic product. It produced thrombocytopenia, platelet reduction because of this so-called platelet activating factor, which was thought to cause this problem. They had allergic reactions to the protein, et cetera. When it came to Hyate:C, it was much more highly purified and actually was very well tolerated by patients. But there was the concern that it would, potentially, in non-inhibitor patients, produce a cross-reacting inhibitor to human Factor VIII.
Q. It follows from that, that by taking this product, they would then render themselves incapable of taking a human --
A. Yes.
Q. -- Factor VIII plasma product in the future?
A. Yes, and that was the big unknown concern.
Q. Were there any other reasons, you think, that --
A. Well, I think you were going to be giving pig protein to people and, again, that might be a risk of creating allergic reactions to the pig protein, which had been

seen in the past, with much more -- much less pure products, so I don't think people wanted to use it.
Q. We will come back to that, sir, as I say, in due course, when we look at some further papers. I am going to move on from porcine Factor VIII to human Factor VIII, so I wonder if now might be a convenient moment?
SIR BRIAN LANGSTAFF: Well, how much longer do you think you might be?
MR HILL: Probably, sir, about another half an hour or so.
SIR BRIAN LANGSTAFF: Because I am concerned that we need plenty of time for you to pick up questions from those Core Participants who might want to ask them. Yes, so we'll take 25 minutes, and come back, therefore, at ten to four.
MR HILL: Thank you, sir.
(3.23 pm)
(A short break)
(3.50 pm)
MR HILL: Ms Middleton, I'd like to turn now to the fractionation of human Factor VIII, by the polyelectrolyte method. I won't take you to your statement but you say in it that shortly after, relatively shortly after joining Speywood, you were seconded to BPL, and you subsequently spent some time

in Paris as well at the CNTS lab.
A. Yes.
Q. I think that was in April, from April 1981.
We heard in the presentation about how there was some optimism about the product in 1981, which gave way fairly quickly to a more pessimistic view of the prospects of the product.
A. Mm.
Q. Can I ask, you have said in your statement that yields were variable, and that problems soon became apparent with the product. Could you explain what those problems were, and how quickly they became apparent to you, and to others?
A. Well, as you probably know, blood clotting is a very -- it's quite a complex process. It's a cascade. That's to make the blood clot. There are also a lot of mechanisms in there to stop blood clotting when it's not supposed to. So it's quite a complex system to deal with. And if you are making Factor VIII, purifying it, depending on the starting material, you, have plasma which is in various -- once you collect plasma or blood from the body, it's immediately not as stable as it was when it was in the body, because you've exposed it to surfaces, you've generally exposed it to the air and you've generally

changed the profile of it. And the inhibitors to blood clotting and the procoagulant. So, particularly with the polyelectrolyte, the Factor VIII, it proved to be very difficult to control the clotting, if you like, because the Factor VIII became -- was probably becoming activated during the process. And how activated it became depended on the quality of the starting material, quite often.

But it did result with -- with huge variability, trying to control the process, and it proved, in my hands anyway, very difficult to control it with any of the sort of different parameters that I tried.

So you absorb onto the polyelectrolyte and then you wash off. That's essentially what you have to do. By controlling -- the way you absorb it, or the things you add to it to try to keep it stable, the way you elute it off, can all affect what happens in terms of the stability of the final product, and what it proved to be -- relatively easy, you could elute things off, and you could measure a Factor VIII level that seemingly was high, remembering that the assays themselves could sometimes not discriminate as to whether you'd got an activated system or not, and then, as you stored it, let it stand, the activity dropped off because the Factor VIII was becoming

activated and lost.

So it proved very difficult to control and that in essence was confirmed, because when we made Factor VIII sequencing, that was Professor Tuddenham's project, he had to use a very serious anti-proteolytic agent -- it was actually nerve gas -- to stop the clotting factors prevent activation of the clotting cascade, in order to get pure Factor VIII at the end of it.

Q. If I can just interject there, a couple of things arise from that. The variability of the product.

A. Yes.

Q. Does that make it hard to translate from a laboratory-based product on which you can do your experiments and test the potential, into a mass produced product which could actually be marketed?

A. Yes, the main thing you have to remember when you're producing any product is quality, safety, and efficacy. If you're getting variability yields and you don't know why, then you don't have the quality. And not the safety, either.

Q. The process you were talking about with Dr Tuddenham there -- I'm going to come on to recombinant shortly, but there's an article that he's written that I know that you have seen. I'm not going to bring it up, but

the reference is HSOC0022968. And he is describing how he worked with you and with others in order to try to purify Factor VIII that he can then go on to use in gene sequencing which would then give rise to recombinant products?

And he said that by 1982 he had devised a multi-step procedure, which had -- which led to that -- in cooperation with others, I should emphasise.

A. Mm.

Q. And he said:

"The bulk processing capacity of polyelectrolyte, combined with the exquisite specificity of monoclonal antibodies, overcame all remaining problems, although Frances Rotblat and Don O'Brian (?) ** in my laboratory found that they needed to use large amounts of highly poisonous nerve gas type enzyme inhibitors to keep the Factor VIII stable."

A. Yes.

Q. So that is what you were referring to a moment ago?

A. Yes.

Q. I don't think it needs to be stated why using a nerve agent --

A. Yes.

Q. -- as part of a product --

A. Not suitable for a therapeutic product, no.

Q. Thinking back now, are you able to put a timescale on when you became aware that these problems were going to be insurmountable in terms of bringing a product to market?

A. Well, I think I became aware of it when I was actually at Elstree.

Q. This is 1980 to 1981?

A. Yes. If that's when it was, yes. And I spent a couple of months after that in Orsay, in Paris, and we had the same problems. We couldn't get the thing to be stable. You know, one day, we got something that we thought was 75% yield, then if you left it on the bench, it had gone down to 25 per cent. So it was really not looking very viable at this stage in Elstree.

Q. You were in Paris from April 1981, according to paragraph 17 of your statement, for a few months?

A. Yes, for a few months, yes.

Q. By that stage do you think you were aware that this wasn't really going to be --

A. Well, it did just never seemed to -- no, I ...

Q. I am just going to ask from a document to be brought up on the screen. It's BPLL00016007_018, please,

Soumik. BPLL0016007_018. This a letter which is written to Mr Heath from Dr Allain in Paris.

A. Mm.

Q. I know you have seen this in the files we provided you with. He says:

"Dear David.

"I enclose a summary of the results of PE5 phase 1 which has worked out very well.

"We are presently doing some additional experiments on filtration and freeze drying that looks very promising. The loss in yield seems quite reasonable.

"I have done all the background work for the next step and the raw material is now being prepared. I am confident that step 2 will be as successful as step 1."

So that's Dr Allain's view in this letter on 27 May 1981.

A. Yes.

Q. I'm cautious about reading too much into one letter in a snapshot in time, but around that time, had you already doubts developing in your mind?

A. I did. And obviously Jean-Pierre Allain and I worked together on the preparation in stage -- I think it was step 2, in Paris, and, we had the same problems as I'd

had at BPL. So I think his letter was optimistic.

Q. This letter, of course, is referring to him at the end of step 1.

A. Yes.

Q. You subsequently worked with step 2 --

A. Yes.

Q. -- and it was disappointing?

A. Yes. And we never really went to step 3, I don't think.

Q. We heard earlier, I believe you were in the room for it, about Dr Tuddenham's lecture from some point in 1981 in which he expressed some optimism.

A. Mm.

Q. There is also a paper -- I won't bring it up, but BPLL0016007_026 -- the authors are Tuddenham, Lane, Rotblatt, Johnson, Snape, you and Kernoff, "Response to infusions of polyelectrolyte fractionated human factor VIII concentrate ..."

A. Yes.

Q. "... in human haemophilia A and von Willebrand's disease.

A. Yes.

Q. Both of those -- both the lecture and the paper -- express some hope for the method?

A. Yes. We made a batch at BPL with carefully

collected -- in fact I think it was almost fresh -- cryoprecipitate, from very good quality -- specifically for those clinical trials, because it was done on four patients, I think, three haemophiliacs and one von Willebrand.

Q. Yes.

A. Yes. And specifically for that. It was made in the clean room at BPL, and -- specifically for that experiment. And that showed that the Factor VIII that we got was good recovery, which suggests it was quite good Factor VIII, and that it didn't work in von Willebrand's disease, which is what we might have expected because of the nature of the protein at that point.

Q. So an example of how, when it is done in very closely controlled circumstances, it could work, but that --

A. Yes, and that was probably due to the fact that the cryoprecipitate was very good quality. The stuff -- the product I was working with at BPL was mostly freeze-dried product that had failed quality control for some reason. Mostly due to pyrogenal bacteria, or pyrogen really, or something of that order. So I worked on that, which had been freeze-dried and was not terribly good quality.

The stuff that probably -- the cryo that I

worked with on this -- on that product, was possibly fresh and probably never been even frozen. It was probably made straight from that. So if you had perfectly good quality cryo, then maybe it would work.

Q. You also wrote a short paper on viral inactivation which is dated October 1983.

A. Yes.

Q. I won't bring it up, but it's ISPN0000409_009.

A. Viral separation.

Q. Sorry, viral separation, my error.

If I may summarise the paper, it's that the in vitro experiment that you did showed viral separation.

A. Yeah.

Q. But as per Dr Tuddenham's lecture, there was a need to look at that in clinical trials if that were to be proved to be safe and efficacious?

A. Yes, we showed that in Professor Thomas's lab. We added hepatitis to the concentrate and then worked it over the polyelectrolyte, and that showed that there was no absorption of the virus to the ion-exchange resin.

Q. Meaning that the ultimate product would be free --

A. Yes.

Q. -- of hep B?

A. Would be separated from it, yes.
Q. Was there any expectation that it would also clear NANB hepatitis?
A. Possibly for the same reason.
Q. You say "possibly" but that, of course, couldn't be tested for at the time?
A. No, no.
Q. Hence the need for clinical trials. We will come back to the clinical trial in a second. Before I do, we know that you developed your concerns about how viable this was going to be as a product. Did you share those concerns with Mr Heath?
A. Yes.
Q. We've seen some of the things that he was saying in 1981. To give you just one example from July 1981, the human protein plan. He said:

"Recent production yields, clinical trials and hepatitis tests have adequately demonstrated that the major protein, Factor VIII:C, can be produced economically, is very efficacious and is most probably free from hepatitis activity."

That is from July 1981. In your view, was that a claim that was justified?
A. Err ... I think it was optimistic at that point.
Q. This was at a point in time when Mr Heath and Speywood

was seeking a £4 to 5 million investment, half of which was coming from public funds. In that context, do you think that that claim was one that could reasonably have been made?
A. Um ... with hindsight, it was perhaps a bit economical with the truth.
Q. Were you involved in any way in the --
A. No, no.
Q. If you had been involved, what would you have said to Mr Heath about it at the time?
A. Well, I would have said -- I would have suggested that he moderated his language.
Q. Sorry --
A. Well, I think I should say something about David, because he was very entrepreneurial, and he was entrepreneurial from very early -- he took on a porcine Factor VIII; why on earth would he do that? He was a pharmacist. It was a very strange thing to do. But he saw the potential in it. He took on the polyelectrolyte fractionation to improve that porcine Factor VIII, which, again, was very entrepreneurial. And obviously the recombinant Factor VIII came from him and he worked on it.

But the trouble was that he was very -- not very good at man management, and people let him down in

some of the things they did and that was a shame. And he also ended up -- he could very easily, because he was the way he was, put people's backs up, and that was certainly the case with the bio products laboratory, because of the different cultures. Bio products was there to make blood products, and get as much as possible out for the population.

David was constantly looking into the future, and trying to raise money, in those days, was difficult, and therefore you tend to overpromise, or he was over-promising.

The porcine Factor VIII was working very well, mainly because I think a lot of the clotting that happened and the problems with clotting happened before the plasma ever got from the abattoir to what we were working with, and we were left and the yields were probably pretty dreadful from porcine blood, but it was easier, in that sense, because we had -- but with Factor VIII you were so totally dependent on fresh frozen good quality human plasma, human blood that you had to be so careful about the yield.

So he had -- he was optimistic because the porcine was going well. He maybe thought that the human should be going well because the porcine was, and that was his -- probably his reasons for doing it.

Q. But by July 1981 he was aware, was he, of your reservations?
A. He knew but he probably thought I was just being, you know, slightly negative on the subject, quite likely.
Q. You were the chief scientist of Speywood, and he was a pharmacist by trade, as I understand it?
A. Yes, he was.
Q. The clinical trial of Mono C, *(sic)* the Factor VIII product. Were you involved in putting the application for the clinical trial together?
A. Well, I must have been but I don't remember doing it. But we must have done it.
Q. We know that it went in at some point in 1982, and we also know that progress on the product had slowed by that stage. What was the purpose of having a clinical trial in those circumstances?
A. I think it was to -- well, basically to check to see whether it was safe and whether the concept of Factor VIII:C, which is what it was, the clotting activity, as opposed to the complex, which circulates in plasma with the von Willebrand factor sort of attached to it, or that's what was thought, whether it would survive like that in the circulation.
Q. Was there any feasible prospect, as of 1982, of bringing this to a product that could be placed on the

market?
A. At the time of clinical trial?
Q. Yes.
A. Um ... maybe in some -- I don't -- I don't know how to answer that question.
Q. Let me --
SIR BRIAN LANGSTAFF: As best you can.
A. As best I can. Um ... because the question is: why did you do a clinical trial?
MR HILL: No smoke and mirrors here, that's the --
A. That's the question.
Q. If you're in the circumstances where it is unlikely that this will ever be made into a --
A. Well, it was made at the bio products laboratory, that product. So they must have thought something positive about it at that stage, in spite of the difficulties that we had with it. So maybe they thought that they should check that it would work, because it was a different entity. So, maybe, you know, things might -- things might work out. Maybe I was being too negative about it. Maybe it was possible to make it work.

But the other question that needed to be answered is would it actually work in the circulation? Never mind whether the -- you know, because if you can

get the production process to work, which I couldn't, but other people might have got it to work, would Factor VIII:C on its own last in the circulation? And yes, it did.
Q. Do I take it from your answer that you were trying now to help us by looking back and thinking what the thinking might have been, but you weren't actually -- you're not able to say what you yourself thought at the time?
A. Yes.
Q. I should say, out of fairness, that we looked at the 1983-1985 business plan and, as we discussed during the presentation, the door was not being closed absolutely on Factor VIII through polyelectrolyte fractionation, although there were concerns about how feasible it was going to be.
A. Mm.
Q. We know that the initial application was turned down, and I referred to a meeting that you attended on 2 June 1983. If we could have that on screen, please, Soumik. It's IPS --
A. That wasn't the same product.
Q. Ah. If we bring it up on screen, perhaps you can assist us with it. IPSN0000165_109, please.
A. Yeah.

Q. So this is a meeting on 2 June 1983.
A. Yeah.
Q. The subject "Clinical trials certificate for Mono VIII:C".
A. Yes.
Q. Then "source of cryoprecipitate"?
A. Which was this Alpha cryoprecipitate, which was being bought in 100-kilo lots -- was it 100-kilo lots -- in large lots, as a frozen cryoprecipitate, to make -- to try to make Mono Factor VIII:C out of. It wasn't that material that went into the patients. The product that went into patients came from Elstree.
Q. Yes, I think we're at slightly cross purposes.
A. Oh right, okay.
Q. So the paper I referred you to earlier, which you co-wrote with Dr Lane, et cetera, et cetera, and Dr Tuddenham, that was a product that was made in Elstree --
A. In Elstree, yes.
Q. -- and that was used, as you said, on three patients --
A. And one von Willebrand's.
Q. -- with haemophilia A and one von Willebrand's patient.
A. Yes.

Q. This is different. This is the application for the clinical trial --
A. Yes.
Q. -- which was made at some point in 1982?
A. Yes.
Q. That was what I was discussing with you a moment ago?
A. Yes, yes.
Q. Why it was that there was an attempt to have a clinical trial at that stage.
A. Oh, from this -- yes.
Q. Does that alter your assessment, any of your answers, now that we're clear about what we're talking about?
SIR BRIAN LANGSTAFF: I don't see why it should alter your answers, but just that we now know you're talking about -- we're quite clear which trial you're now talking about.
A. Yes. I can't ... I recall this and, as you know in the plans, there was the idea of building a facility to make human Factor VIII from this frozen cryoprecipitate. I wasn't certain about it at all. But I'm not sure why we applied for a clinical trial certificate using this material.
MR HILL: The idea was that the material -- the cryoprecipitate would come up in from Alpha, and then you would fractionate it --

A. It was a frozen paste that you re-suspended. We did -- I did do some work with it. It was a frozen paste that was re-suspended and then put over the polyelectrolyte.
Q. I'd like to just look at what was to said at this meeting. There was you and Anne Walton from Speywood?
A. Yes.
Q. The note is by -- the initials are EAW. Is that Anne Walton?
A. Yes.
Q. Who was Anne Walton?
A. She was -- she did some marketing but she also focused in on regulatory affairs.
Q. Was she a scientist?
A. Yes.
Q. The participants from the DHSS, a Dr Fowler and Dr Purves.
A. Yes.
Q. And if we could just look at the note and I'll read it through to you.

"1. Dr Fowler was of the opinion that, despite the controversy surrounding US imports as a result of AIDS, our application will not be judged prejudicially by the CSM if we pursue it with Alpha cryo cited as source material. There have been suggestions in

certain quarters about the banning of importation of all US blood products but the impracticality of this is recognised by those who were well informed in this area and a ban does not, therefore seem likely. An application based on Alpha cryo would (or should) be judged solely on its scientific merit.

"2. The possibility of leaving an application open-ended with respect to source material was discussed and dismissed as unacceptable.

"3. We were advised that if a change in source material is desired, the application might proceed more easily if the licensing of the import or the cryo were included in the CTC application. The responsibility wore the quality of the raw material would then be entirely Speywood's and in addition, the cryo would then be licensed for importation only for the purpose covered by the CTC."

If we go over to the next page, the possible courses of action are discussed. I won't go thorough that, but it says:

"In conclusion it appears that the use of US cryo will not prejudice our case with the licensing authorities and therefore our choice of source material can be based on commercial and scientific grounds."

A couple of points about that. Paragraph 1, the discussion of the potential ban on US blood products, and the recognition that that was impractical. Are you able to help us with who was saying that it would be impractical to ban US blood products?
A. No.
Q. Would you or Anne Walton have been in a position to make that observation? Do you think it's more likely to have come from the DHSS officials?
A. I think it's more likely to have come from the DHSS officials.
Q. But the references to the source material choice being "based on commercial and scientific grounds", as opposed to what other grounds?
A. Um ... as opposed, presumably, to citing the source of the raw material. So in other words, it's coming from the US. I don't know what else.
Q. Are you able to assist us any further now about the contents of that meeting and what was discussed at it? Can you remember it at all?
A. I can't remember it. I can't remember it very well at all, no.
Q. Do you know why it was that you were asked to go from Speywood?
A. Well, Anne would have set it up, and I would have gone

along because of being -- whenever that meeting was, still being chief scientist of Speywood. The most experienced for the human Factor VIII.
Q. Can you help us with whether or not a further application was made for a clinical trial certificate on that product?
A. I don't think it was.
Q. Do you know why it wasn't pursued?
A. No -- well, yes, I probably do, because I don't think there was anywhere to make it.
Q. The facility that had been planned wasn't built?
A. No. And I think at one stage it might even have been thought you could share the facility with porcine, but that became a no-goer when -- because of virus concerns, and it had to be separate.
Q. That is something we saw with the business plan about the DHSS no longer allowing a multi-purpose site.
A. Yes.
Q. Looking back on human Factor VIII and polyelectrolyte fractionation, was this always a project that was ultimately bound to fail, given the knowledge and equipment and availability of material in the early 1980s, or were there any missed opportunities to have developed it further?
A. Sorry, do you mean with respect to human Factor VIII?

Q. Yes.
A. I don't think it was going to fly. It worked very nicely for porcine Factor VIII.
Q. But not for human?
A. But not for human.
Q. On recombinants -- I'm going to take this very briefly, if I may -- your role was important but limited in helping to provide the purified -- the first step of the purification process?
A. Yes.
Q. And then passing that on to Dr Tuddenham and his team to work on thereafter?
A. Yes.
Q. Mr Heath's view that we heard earlier was that this was something of a tragic failure by the UK to capitalise upon the work that was done, because the -- ultimately the work was taken forward by Genentech, an American company, and subsequently by other American pharmaceutical companies as well?
A. Yes.
Q. Could I ask for your opinion on that view from Mr Heath, and in particular upon the question of whether, if other steps had been taken, it would have led to a quicker development of recombinant products or just a development by a British firm as opposed to

an American firm?
A. I think what happened with the recombinant Factor VIII was that, as I understood it, the -- there was a certain amount of money brought forward by Prutec and BTG, and that was sort of -- that money was dispersed around various Oxford facilities to try to clone the gene, to sequence it -- sequence it first, purify it, et cetera -- and none of that programme really worked out. The only bit of that programme that worked out was Ted Tuddenham's purification.

The UK didn't really have the technology at the time. In a paper that Ted wrote, Ted Tuddenham wrote, he said that they had, and I recall that they did, they interviewed Genentech, Genetics Institute, with -- another American company, and Celltech in this country, after Ted had presented his work on purification. And Celltech in this country was at the stage of making protein -- I think it was rennet -- in bacteria. Factor VIII was a big protein. Nobody knew what the structure was. It needed to be done in mammalian cells.

David had actually written into the original agreement that if it was mammalian cells then the UK manufacturing rights would stay here. So he was astute enough to realise that, and they realised that

it was never going to be a bacteria. And the Oxford people, who were working on the project, were working in yeast, which was not terribly much better for a big protein like Factor VIII. There was not much known about the structure either.

I do recall that after some had been purified, it was sent to ICRF, but Mike Waterfield, who was going to do some sequencing, couldn't get time on the sequencer.

So when it went over to Genentech, they had a whole department with several people, sequences dedicated to the project. It was just completely different.

So going back to your original question, which I've probably not answered, I don't know, but it came down to the fact that I think the funding from Prutec and BTG was not used in a very constructive way, and that goes back to what I said originally about David, that he gave responsibility to people for doing things, and the person that stood out was Ted Tuddenham. The rest of them didn't really have the technology to do it. And Prutec and BTG got a bit upset about that, and that's when the trouble came, and David was removed and put to one side.

He wasn't terribly popular with a lot of people

because of his, sort of, rather -- what shall we say -- his sort of -- his energetic sort of -- I can't think of the right word, but he wanted -- he was passionate about what he wanted, but that passion tended to make him promise too much and achieve -- not achieve it, and I don't think that made him a very good source for somebody to invest in. I don't think they were very happy with it.

MR HILL: Thank you. Those are the questions I have for you.

Sir, may I suggest a few minutes break while we allow the Core Participants -- I don't anticipate there will be many questions from them -- I received a great deal of assistance in advance, Ms Middleton's --

SIR BRIAN LANGSTAFF: Well, we will see, because the question may have prompted some questions. What we'd always do, I don't know if you've watched any of the Inquiry at all before you came, but what we always do is we take a break when a witness has finished the evidence which the Inquiry counsel has to ask to allow the Core Participants -- they come from all different perspectives -- to ask questions through counsel of the witness and, that way, we make sure that we try to collect as many different questions, answering

different viewpoints, as there may be.

It does mean you've got to wait a little bit longer. I can't promise you how long but we'll say 15 minutes and come back at quarter to five, and we will see then what questions there are, if there are any.

A. Okay.

SIR BRIAN LANGSTAFF: So quarter to five.

THE WITNESS: Right.

(4.27 pm)

(A short break)

(4.45 pm)

Questions from CORE PARTICIPANTS

MR HILL: Ms Middleton, a few questions from some of the Core Participants that I've been invited to ask you. This means we're going to jump rather from one topic to another.

A. Yes, okay.

Q. Starting with your time still in Scotland, and the reference that you made to a colleague sadly dying of hepatitis B, were any changes made to the way you operated in response to that death?

A. Um ... immediately, yes, we did become much more aware, I think, of the potential problems with the plasma we were dealing with. The person that had the accident, it was a known infected patient that caused

the problem there. And that was in a lab, which was a separate lab, where they were doing studies with the hepatitis virus.

But as far as PFC was concerned, obviously we -- I suppose we did become much more aware of the potential.

Q. Do I understand from that answer that the colleague was somebody who worked within the Edinburgh Royal Infirmary rather than within the PFC?

A. Yes, she wasn't in the PFC, she was in the Royal Infirmary. But in the same sort of department, blood transfusion.

Q. Do you know if the accident and the death was notified to any public health body?

A. I'm sure it was. It was a prick. It was an accidental prick with a needle, which was, you know, tiny, but yeah, that's what happened.

Q. Staying with your time in Scotland, and moving to Glasgow, do you recall if the blood that you were dealing with, which was taken from patients with haemophilia, was marked as being high risk?

A. I don't think it was.

Q. Do you remember if any particular procedures were in place for how you dealt with and handled that blood?

A. No, I don't think so.

Q. I am going to -- this is a document that you haven't seen and I don't think is on our system, so I'm just going to read a short passage to you. It comes from a meeting in May 1985, a meeting in Scotland of the Scottish National Blood Transfusion Service. And it refers to a request that has come from you to the SNBTS -- and forgive me, I've just lost my place temporarily.

What is recorded in the minutes is this you have asked:

"... to obtain from the SNBTS about 50 litres per annum of fresh frozen plasma from which to developed a range of reagent biodepleted plasmas."

You had approached SNBTS because of "concern that the haemophiliac plasma substates in use at present might be contaminated with HTLV-III or hepatitis".

A. Yes.

Q. First of all, do you have any recollection of making such a request?

A. I don't, but I do remember the project, so ...

Q. Could you explain what that project was?

A. The project was to use monoclonal antibodies, the ones developed at the Royal Free, to make a Factor VIII-deficient plasma. Factor VIII-deficient

plasmas from haemophiliacs were used as reagents to test for the potency of a Factor VIII concentrate. So rather than use -- these obviously became much more potentially risky -- that was thought to be the case, as reagents. And therefore, we decided to use normal plasma, and deplete it of Factor VIII using monoclonal antibody column to deplete it.

Q. In order to create assays?

A. To use for assays.

Q. So everybody has the reference, it's PRSE0004075, and the minutes record that it was considered not appropriate to provide the material because there was no surplus at the time.

A. Right.

Q. Do you know if you were able to obtain an equivalent material from elsewhere?

A. I did get some from somewhere. I bought some from somewhere. But it wasn't the United States. I'm not quite sure. It can't have been English, British -- I don't know where it -- (overspeaking) --

Q. Because it was commercial?

A. It must have been commercial.

Q. And your desire was to avoid the material coming from the United States because of perceived risk of HTLV-III?

A. Well, it was to come from -- there was no point in doing it unless it came from a clean source. And I can't recall now where it did come from, but we did use that technology, and subsequently it was -- the assay was developed and was sold commercially by an organisation called Diagnostic Reagents who were based in Oxford and who supplied -- probably still do -- reagents for coagulation factors.
Q. Moving on to a different topic, was there any discussion about proposed research concerning AIDS, HIV, HTLV-III, at Speywood during your time there?
A. Not AIDS, no. I think AIDS and HIV were only really identified -- started to be identified in '82, '83.
Q. But Speywood wasn't involved in any --
A. No.
Q. Specific projects that tried to address the risk of --
A. No.
Q. -- HIV, HTLV-III, et cetera?
A. No.
Q. Further question. How much of your work, either at the PFC or at Speywood, informed by a knowledge of the different severities of haemophilia in patients, mild, moderate and severe haemophilia?
A. Um, I'm not sure I understand the question. We were making concentrates to treat haemophilia, whatever the

level, however severe or mild it was.
Q. But were you aware of the distinctions between --
A. Yes.
Q. -- mild, moderate and severe?
A. Yes.
Q. Does it come back to the fact that your role as a scientist was to seek to make the product --
A. Yes.
Q. -- and not to decide how it should be used by the clinician --
A. Yes.
Q. -- and the patient?
A. Yes, yes. Although in discussions with the clinicians -- because we were very close to the clinical use, particularly in the UK -- we did get to learn about what people were doing, what clinicians were doing for treatment, et cetera.
MR HILL: Those are, sir, the questions that we have had from the CPs. I turn to you now, sir, if you have anything further.

Questions from SIR BRIAN LANGSTAFF

SIR BRIAN LANGSTAFF: I just have a couple of questions. You've described life in the basement in the old Royal Infirmary in Lauriston Place, which I can imagine was like working in a basement.

A. (Witness nodded)
SIR BRIAN LANGSTAFF: But you moved to Liberton --
A. Yes.
SIR BRIAN LANGSTAFF: -- did you? That would be about 1973, I think.
A. Possibly, yes.
SIR BRIAN LANGSTAFF: What was life like there?
A. Oh, well, that was very different, because it was purpose-built facility.
SIR BRIAN LANGSTAFF: So you had a purpose-built facility there.
A. Yes.
SIR BRIAN LANGSTAFF: Then when you moved down south to Wrexham, you found yourself in a Portakabin in --
A. And a garage.
SIR BRIAN LANGSTAFF: A garage?
A. Yes. I only did the research work in the garage, I should say.
SIR BRIAN LANGSTAFF: [Laughs]. So I -- would I be right in thinking that David Heath, whose enthusiasm had recruited you to post --
A. Yes.
SIR BRIAN LANGSTAFF: -- he would have had some schemes and dreams for improving those facilities.
A. Well, he did, ultimately. They did improve that

facility and they had a purpose-built production facility for Hyate:C, on the Wrexham estate.
SIR BRIAN LANGSTAFF: So you did eventually get the facilities you wanted, for research as well?
A. Well, it didn't happen until -- um, I'm not even sure of the timing of it, but it was '82/'83. I mean, it was later than I was -- my -- all my work was done in the garage, and the -- and the Portakabin, under laminar flow, I should say. We did clean up the Portakabin.
SIR BRIAN LANGSTAFF: Did you know -- this is a second topic -- anything about the Speywood's continuing to market Koate without, it may be thought, telling Koate they were doing it by buying it and sourcing it --
A. No, I didn't.
SIR BRIAN LANGSTAFF: -- from an intermediary.
A. No, I didn't.
SIR BRIAN LANGSTAFF: Is that the sort of thing that David Heath might do, as you would see him?
A. Well, I suppose -- I guess, I guess he might have done. I'm sorry to say.
SIR BRIAN LANGSTAFF: Well, you have a slightly, I suspect, a slightly ambivalent attitude towards him.
A. Well, he was a-- he was the sort of person -- I had two mentors. One was Jim Smith and one was David

Heath, really, on the business side. But I didn't -- but only in the sense that -- it was all his ideas and everything else that I admired. But when it came to doing -- he did do certain things that I thought were a little bit, a bit near the edge, and I didn't really -- it wasn't my style at all and I didn't really like it, and it was very unfortunate, because it caused problems with BPL, which I could see why. And my two mentors didn't get on at all. Jim Smith and -- because they were opposite ends of the spectrum.

So it caused difficulties.

SIR BRIAN LANGSTAFF: Yes. And --

A. Sir, I'm afraid it was the downside, the upside being he had these amazing ideas, and some of the ideas like putting polyelectrolyte into a donor centre to collect plasma straight from the donor on to the polyelectrolyte and then fractionating it on site, as it were, I mean that's a very interesting idea. But obviously fractionation, plasma fractionation was not going to carry on in the same way it, you know, it was never going to happen in the future, but had plasma fractionation gone on for, you know -- had recombinant technology not started to take over, then it would have -- it was a really good idea.

So he did have very good ideas. But sometimes bringing them to fruition was not quite so good.

SIR BRIAN LANGSTAFF: Yes, it was a case of the next big thing, as it were.

A. A little bit. Yes, I'm afraid so.

SIR BRIAN LANGSTAFF: Yes, well, thank you. That's all that I have to ask.

A. Okay.

MR HILL: Ms Middleton, with all of our witnesses, we ask at the end if there is anything else that you wish to say in your evidence.

A. Um, no, I don't think so. Thank you.

MR HILL: Thank you, sir.

SIR BRIAN LANGSTAFF: Well, we have asked you a number of difficult questions this afternoon, and detained you I think for an hour longer than you might have hoped this afternoon. I'm sorry about that.

THE WITNESS: That's all right.

SIR BRIAN LANGSTAFF: But I'm very grateful. And you've done two, in particular, difficult things it seems to me. You've explained to us how the polyelectrolyte system works in terms which I think I can understand, and those around me will, and you've answered questions which you didn't really want to have to answer, but have done so, and done so in order to help

us. And can I just tell you, that's very much appreciated. And thank you for coming the way you have down here, and I hope you have a good trip back tonight.

THE WITNESS: Thank you.

SIR BRIAN LANGSTAFF: Mr Hill, what does next week hold in store for us?

MR HILL: On Tuesday, sir, we will return to the presentations. We will complete the presentation on Speywood, and then we will move on to the last of the current set of presentations on pharmaceutical companies, which is on Alpha and associated companies. Then later in the week we will move on to some presentations about Haemophilia Centres.

SIR BRIAN LANGSTAFF: Very well. So ten o'clock on Monday. Ten o'clock.

MR HILL: Sir, Tuesday.

SIR BRIAN LANGSTAFF: I've done it again, sorry! I do apologise. It will be ten o'clock for me, or before ten o'clock for me on Monday, but for you, ten o'clock on Tuesday -- for us, ten o'clock on Tuesday.

(5.00 pm)

(The hearing adjourned until 10.00 am on Tuesday, 5th October 2021)

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