

Tuesday, 5 October 2021

(10.00 am)

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

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

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

With thanks to Mr Evans, a document throws

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

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

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

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

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

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

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

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

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

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

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

We know that from its establishment in 1973, Speywood Laboratories had investigated the development of animal Factor VIII for the treatment of haemophilia patients with high inhibitor levels. There was initially work done on bovine and porcine Factor VIII, but increasingly, the porcine Factor VIII became the better route that was being explored. The initial product rights and basic know-how were purchased from a firm called Maws Limited and that seems to have worked in cooperation with the Protein Fractionation Laboratory in Oxford under Dr Biggs. The references there are IPSN0000167\_004, IPSN0000089\_001.

In 1975, Speywood registered the trade name "Hyate"; the reference for that is IPSN0000089\_001.

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

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

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

15 The reference for that, sir, is SHPL0000108\_034.

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

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

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1 IPSN0000324\_011.

2 That's 7 December 1979 saying that it's ready  
 3 for use. The first usage appears to have come in  
 4 June 1980, and if we could have on screen, please,  
 5 Soumik, IPSN0000331\_001.

6 This is a letter to Dr Aronstam at Treloar dated  
 7 30 July 1980. We looked at it I think on Friday in  
 8 another context, but I'm just going to concentrate now  
 9 on the porcine element. The letter is from  
 10 Mr Williams, the marketing director. He wrote, in  
 11 respect of porcine Factor VIII:

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

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

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

6 That article was written before Speywood  
 7 concluded a licence agreement with Monsanto. That  
 8 happened, we think, in 1979, and it was the licence  
 9 agreement for the use of polyelectrolyte technology.  
 10 The reference is IPSN0000134\_001. We heard from  
 11 Ms Middleton what polyelectrolyte technology involved,  
 12 and it was used both for the porcine product and for  
 13 the human product and, indeed, it seems to have been  
 14 more successful in terms of the porcine product, and  
 15 more successful in separating the Factor VIII molecule  
 16 from other molecules within the pig plasma.

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

20 It doesn't appear that a clinical trial  
 21 certificate was obtained at this time, and its use was  
 22 restricted to response to medical emergencies. So it  
 23 would have been on a named-patient basis and only in  
 24 extremis. References are of the -- the reference is  
 25 IPSN0000334\_001 and a further reference at

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

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

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

17 There does appear to have been some additional  
 18 use of the product because, by October, we can see  
 19 that there have been more than 60 uses. Could we have  
 20 IPSN0000338\_001, please, Soumik.

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

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1 actually Koate but he asked him to keep that  
 2 information confidential.  
 3 If we go to the fourth substantive paragraph,  
 4 starting "Incidentally", Mr Williams wrote this:  
 5 "Incidentally, we have now had considerable  
 6 successes with our new porcine factor VIII:C  
 7 preparation, Hyate:C. It appears that we have  
 8 completely removed the thrombocytopenia activity and  
 9 that other clinical side-effects are minimal. In over  
 10 sixty transfusions, we have seen around five minor  
 11 shivering episodes, which can be adequately covered  
 12 with hydrocortisone and Piriton.  
 13 "The thing that we did not expect, is that  
 14 Hyate:C, [I'm afraid I can't quite decipher that] in  
 15 [something] cases so far, has not resulted in  
 16 a rise" --  
 17 **SIR BRIAN LANGSTAFF:** I think it's probably something  
 18 typed over, but it looks like "all the", with the  
 19 something underlying it.  
 20 **MR HILL:** I think that's right, sir. Yes, it's typed  
 21 over, so it's:  
 22 "... the thing we did not expect, is that  
 23 Hyate:C, in all the cases so far, has not resulted in  
 24 a rise in the pig antibody levels, even several weeks  
 25 post treatment. Two of the cases treated have

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1 specifically referring to the use of this product in  
 2 inhibitor patients.  
 3 The start of the letter refers to the  
 4 difficulties in treating such patients. In the last  
 5 sentence of the first paragraph, the authors say:  
 6 "Therefore, we would like to report our  
 7 experience with a new compound, highly purified  
 8 porcine Factor VIII, (Hyate, Speywood).  
 9 "A 16-year-old boy was admitted with  
 10 haemarthrosis in his right elbow and right knee. He  
 11 had been diagnosed as having haemophilia A six months  
 12 after birth with a Factor VIII:C level of less than 1  
 13 ..."  
 14 I'm afraid I can't decipher that.  
 15 **SIR BRIAN LANGSTAFF:** That's 1 per cent.  
 16 **MR HILL:** Is it 1 per cent?  
 17 "Ten years later, an inhibitor to Factor VIII  
 18 was detected. After that, bleeding episodes were  
 19 treated with FEIBA (Immuno Ltd) or Factor IX  
 20 concentrates from Oxford. His new inhibitor varied  
 21 from 2.0 to 78 RB units (New Oxford). On this  
 22 occasion, his haemarthroses was treated with Factor IX  
 23 concentrate and subsided. However, he then had  
 24 a melaena and subsequently passed frank blood per  
 25 rectum. A total of 2,720 units of Factor VIII

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1 received multiple injections at varying intervals for  
 2 different bleeding episodes. In no case has there  
 3 been a problem, even in the most desperate  
 4 life-threatening circumstances.  
 5 "If you have an inhibitor problem, I would be  
 6 very grateful if you can consider using this  
 7 material."  
 8 So we can see there the report from Mr William's  
 9 perspective on over 60 uses by October. I note, sir,  
 10 the prohibition that was in place at the time on  
 11 advertising products which did not have a product  
 12 licence.  
 13 The use of Hyate:C attracted comment in the  
 14 medical literature from 24 January 1981. Could we  
 15 have on screen, please, IPSN0000005\_023.  
 16 This, sir, is the first reference to Hyate:C  
 17 that I have found, at least, in the medical  
 18 literature.  
 19 We can see -- if we could expand the page,  
 20 please, Soumik. This is from the British Medical  
 21 Journal, volume 282, 24 January 1981. The report  
 22 comes from Dr Mayne and Drs Madden, Crothers and  
 23 Ingles from Belfast. It is a letter, and it refers to  
 24 the highly purified porcine Factor VIII in haemophilia  
 25 A with inhibitors to Factor VIII. So it's

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1 concentrate was given, but despite this, he continued  
 2 to bleed. We then decided to change to Hyate. This  
 3 was given as an infusion of 2,200 units over 6 hours.  
 4 This was continued for 36 hours, and a total of 13,200  
 5 units were given. There was a very satisfactory rise  
 6 in Factor VIII levels [there's reference to a table  
 7 that is contained in the article], and his bleeding  
 8 came under rapid control. There was a modest rise in  
 9 human Factor VIII antibody noted, but porcine Factor  
 10 VIII antibodies failed to develop."  
 11 Final paragraph:  
 12 "Previous attempts at treating haemophilia A  
 13 with porcine Factor VIII were abandoned because of  
 14 allergic reactions and because the presence of  
 15 platelet aggregating factor caused thrombocytopenia.  
 16 Neither was a problem in this patient. Therefore, we  
 17 conclude that highly purified porcine Factor VIII  
 18 (Hyate) is of value in treating haemophiliacs who have  
 19 developed antibodies to Factor VIII."  
 20 So an optimistic -- sorry, not optimistic, but  
 21 a positive report on Hyate:C from Dr Mayne in  
 22 January 1981, specifically referring to the importance  
 23 of the fact that the purified product didn't seem to  
 24 do what the old product did, in terms of low platelet  
 25 counts and in terms of creating inhibitors in the

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(3) Pages 9 - 12



1 patient.  
 2 There is some evidence from within Speywood  
 3 that, by January 1981, considerable optimism was being  
 4 shown and considerable ambition about the prospects of  
 5 this product. If we could have, please,  
 6 IPSN0000260\_010.  
 7 This is a handwritten document. We don't know  
 8 who the author is. It's headed "Monsanto". It's  
 9 recovered from the Speywood files. What the author  
 10 wrote is this:  
 11 "I am now reasonably confident that porcine  
 12 Factor VIII can completely replace the need for human  
 13 Factor VIII preparations. The timetable for such an  
 14 operation is complex and difficult to predict.  
 15 However, a product licence in the UK should be  
 16 feasible within 3 years; USA within 5 years.  
 17 Third-world countries could supply an almost immediate  
 18 market, and sales without a licence to inhibitor  
 19 patients could be very substantial.  
 20 "To protect our interests, we must ensure that  
 21 the polyelectrolyte patents are strengthened and  
 22 policed properly. The polymers must not get into the  
 23 hands of our competitors. Monsanto can and must  
 24 provide this protection, including registration of new  
 25 patents.

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1 allergic reactions and thrombocytopenia. Hyate:C is  
 2 a highly purified preparation of porcine factor VIII  
 3 that contains only trace amounts of non-factor VIII  
 4 protein, thus reducing side effects. Unfortunately,  
 5 the severe reaction after its use in our patient  
 6 suggests that, as with other porcine products,  
 7 allergic reactions that might limit its usefulness may  
 8 occur. A small test dose should therefore be  
 9 administered before infusion of therapeutic doses to  
 10 identify more clearly patients who might be at risk of  
 11 developing such problems."  
 12 Then if we could go to page 2, please. This is  
 13 a letter in response to that from Drs Kernoff and  
 14 Tuddenham, from the Royal Free. They say, in the  
 15 second paragraph:  
 16 "There is no doubt that  
 17 polyelectrolyte-fractionated porcine factor VIII  
 18 [Hyate] should be used with caution, but transfusion  
 19 reactions severe enough to necessitate stopping  
 20 therapy are unusual. Over the last year we have given  
 21 34 courses of PE porcine VIII therapy to eight  
 22 patients with circulating antibodies to factor VIII  
 23 ... Of a total 216 infusions, only one was followed by  
 24 a reaction judged sufficiently severe to justify  
 25 stopping treatment. Although reactions of lesser

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1 "In the anticipated agreement with Monsanto, we  
 2 must try and establish the right to sell animal  
 3 Factor VIII:C worldwide in perpetuity at a 5-year lead  
 4 time before Monsanto can manufacture animal  
 5 Factor VIII:C itself."  
 6 So we can tell from that that this is an  
 7 internal Speywood document. The reference to porcine  
 8 Factor VIII completely replacing human Factor VIII is  
 9 made as of January 1981, but with the, you may feel,  
 10 significant caveat that the timetable is complex and  
 11 difficult to predict.  
 12 In the medical literature, there was a little  
 13 more circumspection. Could we have, please,  
 14 IPSN00000005\_024, please, Soumik.  
 15 This is a case report from the British Medical  
 16 Journal, dated 20 June 1981.  
 17 It is from the Department of Haematology in the  
 18 Glasgow Royal Infirmary. It's Drs Erskine and  
 19 Davidson. The case report deals with a severe  
 20 anaphylactic reaction after the use of Hyate:C in  
 21 a patient. The case details are given, I won't go  
 22 through them. I will just turn to the comment, which  
 23 is:  
 24 "Use of porcine factor VIII concentrates has  
 25 previously been severely restricted because of

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1 degrees of severity are relatively common -- 27  
 2 infusions were followed by some significant reaction  
 3 and 21 courses of therapy were complicated by at least  
 4 one -- reactions were generally short lived, well  
 5 tolerated by patients, and did not give rise to  
 6 serious clinical concern."  
 7 If we could go down, please, to the penultimate  
 8 paragraph beginning "Bleeding in patients", thank you:  
 9 "Bleeding in patients with anti-VIII [that's  
 10 anti-Factor VIII] is often severe and difficult to  
 11 control, and risks of therapy must be weighed against  
 12 likely benefits. We have found PE porcine VIII to be  
 13 highly effective in stopping major bleeding which has  
 14 failed to respond to human factor VIII. It has also  
 15 been used successfully to cover elective surgery. The  
 16 material lacks several of the disadvantages of earlier  
 17 or alternative preparations and we believe its  
 18 introduction to be a real therapeutic advance.  
 19 Porcine heparin and insulin given intravenously are  
 20 rarely complicated by transfusion reactions and one is  
 21 optimistic that the problems with [polyelectrolyte]  
 22 porcine VIII can be similarly resolved. Meanwhile, we  
 23 suggest that the material should be used only in major  
 24 haemophilia centres, where adequate facilities and  
 25 expertise are available for stringent monitoring. In

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

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

8 We looked on Friday at Dr Tuddenham's Toronto  
9 lecture from 1981. If we could have that on screen,  
10 please, IPSN0000156\_101.

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

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

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

3 Professor Tuddenham gave evidence to this  
4 Inquiry on 22 October last year. I won't take you to  
5 that, sir, but he does comment on this at pages 54 to  
6 55 of that evidence. He said that he was thinking  
7 primarily of countries in the developing world when he  
8 was saying that but we can see that, again, the  
9 prospect of Hyate:C porcine Factor VIII being used in  
10 non-inhibitor patients is being considered.

11 Can we have on screen, please, IPSN00000005\_024,  
12 please, Soumik. Can we have page 3 of this document.  
13 A further piece of the letter from the medical  
14 journals. This from The Lancet dated 27 March 1982,  
15 so a little later in time, from doctors Hewitt, Mackie  
16 and Machin at the Middlesex Hospital. In the first  
17 paragraph, they say:

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

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

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

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

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

2 **MR HILL:** Anamnestic, sorry.

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

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

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

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

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

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(5) Pages 17 - 20

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

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

7 If we could also go, please, to BPLL0016008\_034,  
8 this is a document that we looked at on Friday in the  
9 context of human Factor VIII. It is Dr Jim Smith's  
10 internal memo for BPL about a Speywood meeting at  
11 Uberlingen on 24 April 1982. As we know, Dr Smith was  
12 no fan of Speywood. He said that the meeting was  
13 intended to present the merits of porcine Factor VIII  
14 to influential German clinicians, and this is what he  
15 records of the meeting, in respect of porcine  
16 Factor VIII and, indeed, Factor IX, and he says:

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

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

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

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

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

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

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

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

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

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

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

9 Can we have on screen, please, but -- actually  
10 I won't put it up -- the Hyate marketing plan for  
11 1983, a document that we looked at on Friday,  
12 IPSN0000025, set out an objective of a sales target of  
13 £1.32 million and capitalisation on probable  
14 regulatory approval in the UK in respect of Hyate:C.

15 It was said that the market segment most  
16 accessible to Hyate:C was "for high responder  
17 haemophilia A inhibitor market", which comprised about  
18 1,688 patients in Western Europe, the USA and Japan.  
19 The value of that market -- sorry, I'm not -- that  
20 figure is incorrect, sir, forgive me. It's -- the  
21 inhibitor market in Western Europe, USA and Japan was  
22 valued at a total of £16.88 million based on various  
23 calculations that were contained in the business plan.

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

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

4 If we could have on screen, please, Soumik,  
5 IPSN0000264. This is a letter from Mr Williams dated  
6 16 February 1983. While the business plan had  
7 stressed the inhibitor market, Mr Williams, as we will  
8 see here, has some wider thoughts about the expansion  
9 of the product to non-inhibitor patients, as well.  
10 But what he wrote is this:

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

20 "There are two prime indications:

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

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

25

1 transmission of hepatitis.

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

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

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

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

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

18 Back to the letter:

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

26

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

4 That is Mr Williams's letter to Mr Mottram,  
5 copied to Mr Heath, so an internal Speywood document,  
6 16 February 1983 and, as we saw on Friday, sir, this  
7 is just before Speywood entered into a period of some  
8 corporate changes at the top of the company, with  
9 Mr Heath and Mr Williams, in effect, losing out to the  
10 investors' choice of executives and directors.

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

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

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

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

27

1 **MR HILL:** It had never had a clinical trial certificate.

2 It had been used in patients and reports had been  
3 given, but it hadn't -- as far as I'm aware, it was  
4 not subject to a formal clinical --

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

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

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

19 The licence was eventually granted on  
20 3 December 1984. The references for that are  
21 IPSN0000477 and MHRA0033477\_011.

22 But it's helpful, I think, to look at some of  
23 the documentation about the product licence  
24 application. If we could have on screen, please,  
25 IPSN0000007\_001.

28

(7) Pages 25 - 28



1 We can see from the front page that this is the  
 2 Speywood application for a product licence. If we  
 3 could go to page 3, please, Soumik. This is the part  
 4 four of that, which is the studies in humans.  
 5 On page 3, we can see that the name of the  
 6 product is Hyate:C, but the application is being  
 7 sought by Speywood Laboratories Ltd. The Wrexham  
 8 address is given. And if we could go to the bottom of  
 9 the page, please, the date is 29 November 1983, and  
 10 it's signed by Mr Wain who was a director at that  
 11 time.  
 12 If we could then turn to page 5, please.  
 13 Section 4, "Uses", it's said:  
 14 "Hyate:C is intended for the treatment or  
 15 prevention of bleeding in patients with haemophilia A  
 16 who have inhibitors to Factor VIII:C."  
 17 So very expressly stated to be for the use of  
 18 inhibitor patients. That was also stated in the  
 19 covering letter, which I need not take you to, but the  
 20 reference is MHRA0033477\_003.  
 21 If you could go to the bottom of that page,  
 22 please, there is perhaps some explanation as to why.  
 23 "Contraindications, precautions and warnings:  
 24 "There are no known contraindications to  
 25 Hyate:C.

29

1 resuscitation should be immediately available for the  
 2 treatment of acute infusion reactions."  
 3 Page 17, please, Soumik. If we go to the third  
 4 paragraph down there, "Hyate:C has been used". Thank  
 5 you:  
 6 "Hyate:C has been used clinically in the  
 7 United Kingdom, Italy, France, Sweden and the USA for  
 8 the emergency treatment or prevention of bleeding  
 9 episodes in inhibitor patients in whom no other form  
 10 of treatment had proved effective. The product was  
 11 used on a named-patient basis in all countries except  
 12 the USA where an IND is held for Hyate:C."  
 13 That's the equivalent, as I understand it, of  
 14 a clinical trial certificate in the UK, so there was a  
 15 trial being done in the United States:  
 16 "The effectiveness of Hyate:C and its side  
 17 effects were monitored as part of the normal course of  
 18 treatment, and these results are presented in this  
 19 section. Although the advantages of comparative  
 20 clinical trials are well appreciated, it was not  
 21 considered feasible to carry out such a study on  
 22 Hyate:C for the following reasons."  
 23 This is the one that I was raising earlier, sir:  
 24 "Possible comparative forms of treatment."  
 25 And what it says in this paragraph is:

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1 "Infusion reactions.  
 2 "Despite its very low protein content, Hyate:C  
 3 may on occasion give rise to reactions such as fever,  
 4 chills, headache, nausea, vomiting, and skin rashes.  
 5 Such reactions are more common after the first  
 6 infusion of a course of treatment and tend to lessen  
 7 in frequency and severity as further infusions are  
 8 given. Hydrocortisone and/or antihistamine may  
 9 alleviate these effects and may be prescribed as  
 10 a precautionary measure."  
 11 Over the page, please.  
 12 "Immune response to Hyate:C.  
 13 "In some patients, treatment with Hyate:C is  
 14 followed by a rise in levels of inhibitor to both  
 15 human and porcine Factor VIII:C. Inhibitor levels to  
 16 both porcine and human Factor VIII:C should therefore  
 17 be determined at regular intervals after treatment.  
 18 "Effect on the platelet count:  
 19 "A significant fall in the patient's platelet  
 20 count has only very rarely been reported after  
 21 infusion of Hyate:C. However, regular monitoring of  
 22 a platelet count during the treatment period is  
 23 recommended."  
 24 Then "Caution", in capital letters:  
 25 "Adrenaline, hydrocortisone and facilities for

30

1 "The concentrates of clotting factors commonly  
 2 used in the treatment of inhibitor patients are human  
 3 VIII:C, non-activated prothrombin complex concentrates  
 4 and activated prothrombin complex concentrates. The  
 5 rationale for the latter two forms of treatment is not  
 6 clearly understood, and their effectiveness cannot be  
 7 assessed by objective laboratory methods and has thus  
 8 not yet been fully evaluated. In addition, the  
 9 activated prothrombin complex concentrates are not  
 10 licensed in the UK. Human Factor VIII:C would  
 11 therefore seem to be the most suitable choice of  
 12 comparative treatment."  
 13 And we go on:  
 14 "It seems indisputable that human VIII:C should  
 15 be the treatment of choice for those patients who  
 16 respond favourably and do not show significant  
 17 increases in inhibitor titre as a result of treatment.  
 18 However, the patients for whom Hyate:C is most  
 19 beneficial are frequently those for whom human VIII:C  
 20 either is ineffective at practical dose levels or  
 21 produces an undesirably high anamnestic response in  
 22 antibody titre. Thus, if patients are selected for  
 23 treatment with Hyate:C on the basis of their  
 24 unsuitability for treatment with human VIII:C, this  
 25 negates the rationale for a comparative study of the

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(8) Pages 29 - 32

1 two concentrates."  
 2 You can see there, sir, why it is they felt it  
 3 was difficult, or indeed impossible, to establish an  
 4 effective trial with a controlled product.  
 5 I draw your attention, sir, to the first line of  
 6 that sentence, in light of the discussion that there  
 7 had been about the possibility of using Hyate:C for  
 8 non-inhibitor patients. I read it again:  
 9 "It seems indisputable that human VIII:C should  
 10 be the treatment of choice for those patients who  
 11 respond favourably and do not show significant  
 12 increases in inhibitor titre as a result of  
 13 treatment."  
 14 So in the product licence application for  
 15 Hyate:C, there is an acceptance that human Factor VIII  
 16 is the product of choice for non-inhibitor patients.  
 17 And as we have seen in the list of potential side  
 18 effects, you can understand why that view was taken at  
 19 that time.  
 20 At page 19 of this document, there is a list of  
 21 the 144 treatment episodes that had been reported. I  
 22 won't go through that, sir, but we can see there the  
 23 number of reactions; a small number, but listed and  
 24 set out in the application.  
 25 And if we go to page 20, please, the

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1 antibodies to Factor VIII."  
 2 And you will remember, sir, that the Royal Free,  
 3 and particularly Drs Kernoff and Tuddenham, were two  
 4 of the supporters, if I may put it that way, of  
 5 Hyate:C. Two of the more enthusiastic clinicians.  
 6 If we could go to page 2 of the document,  
 7 please, Soumik. Just to pick up in the second  
 8 sentence that:  
 9 "Over an 18-month period, eight patients with  
 10 Factor VIII inhibitors were treated with 45 courses,  
 11 297 infusions, of polyelectrolyte fractionated porcine  
 12 Factor VIII."  
 13 So that's Hyate:C.  
 14 Then the document goes on to record the  
 15 observations on those patients. I won't go through  
 16 all of it.  
 17 If we could turn to page 18, please, the  
 18 "Discussion" section. Again, I will summarise this,  
 19 rather than reading from it. The authors found  
 20 porcine Factor VIII to be an effective treatment.  
 21 They developed a strategy whereby patients with low  
 22 inhibitor levels were usually treated with human  
 23 Factor VIII. Those with intermediate levels were  
 24 generally treated with porcine Factor VIII, by which  
 25 they meant Hyate:C, and generally had an excellent

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1 conclusions, it says this:  
 2 "In the management of haemorrhagic disorders,  
 3 prompt and effective treatment is vital. Any delay  
 4 may lead to irreversible damage to the patient.  
 5 "Most haemophiliacs with inhibitors live with  
 6 the constant fear that a major haemorrhage may prove  
 7 unresponsive to conventional therapy and may lead to  
 8 death or permanent disablement. Even minor  
 9 haemorrhages may lead to hospitalisation, and surgery  
 10 of any kind is hazardous, if not impossible.  
 11 "Hyate:C has indisputably proved life-saving in  
 12 a number of cases and offers certain patients the  
 13 opportunity of resuming a comparatively normal  
 14 lifestyle. Under these circumstances, the small  
 15 degree of risk related to the possible side effects of  
 16 the product is thought to be amply justified."  
 17 That is the case made for Hyate:C, but it is  
 18 made in respect of inhibitor patients only.  
 19 Submitted as part of that application is an  
 20 article by Drs Kernoff, Thomas, Lilley, Matthews,  
 21 Goldman and Tuddenham from the Royal Free. It's  
 22 IPSN0000005\_007.  
 23 The paper is entitled "Clinical experience with  
 24 polyelectrolyte fractionated porcine Factor VIII  
 25 concentrate in the treatment of haemophiliacs with

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1 clinical response to the product. And then over on to  
 2 the next page, please.  
 3 **SIR BRIAN LANGSTAFF:** Well, if we go down just five lines  
 4 there:  
 5 "The relatively high risk ..."  
 6 **MR HILL:** "The relatively high risk of adverse effects is  
 7 acceptable only because of the inherently serious  
 8 nature of the disorder and the lack of reliably  
 9 effective alternatives."  
 10 **SIR BRIAN LANGSTAFF:** Yes.  
 11 **MR HILL:** The final stage of the strategy is that they  
 12 found that porcine Factor VIII was of limited -- or  
 13 their impression was that it was of limited effect in  
 14 patients with high levels of inhibitors, although they  
 15 had very few such patients.  
 16 If we could go over, please, to page 20. I  
 17 think this captures the essence of the report. From  
 18 the paragraph starting "Although", it says:  
 19 "Although porcine VIII is an obviously much  
 20 improved version of the conventionally fractionated  
 21 product, we have encountered all the problems of the  
 22 older material, albeit infrequently and/or in a mild  
 23 form. Of most concern has been the occurrence of  
 24 infusion reactions which, because of their typical  
 25 clinical characteristics, seem most likely to be

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

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

Over to the next page, please.

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

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

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

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

Final two sentences of this report:

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

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

The Committee on Safety of Medicines considered the application on 22 and 23 March 1984. I won't take you to it, but the reference is MHRA0033475\_018. There were also reports from the sub committee on the safety, efficacy and adverse reactions, and on the biologicals sub committee. References are MHRA0033476\_009.

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

An internal document from Speywood. IPSN0000378\_001. This is a memorandum from Mr Mottram to the chairman and managing director of Porton International. It's dated July 1984, so in the period between the application and the granting of the licence. This is at a time when the new management of Speywood is taken over. And if we could have a look at the second page, please, we'll see what Mr Mottram says about price -- the price of the product.

He says:

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

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

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

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

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

IPSN0000036\_012, please, Soumik. This is another Speywood document, which goes through the current approaches to the treatment of inhibitor patients in the UK on a centre-by-centre basis. It notes that, out of the total -- this is based on 1983, the document is dated 2 November 1984, we can see that on the bottom left-hand corner of that page, please, Soumik.

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

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

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

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

16 "Most centres thought that cost was the most  
17 significant factor in deciding which product to use  
18 for a mild bleed, and efficacy and cost when deciding  
19 for a severe bleed. The cost of using porcine  
20 [Factor] VIII relative to using high dose human  
21 [Factor] VIII was frequently mentioned (porcine being  
22 approximately 4 times the price of human) as was the  
23 cost relative to FEIBA, (which is currently 20p/unit).  
24 "Several centres would like to have Hyate:C in  
25 stock on a 'sale or return' basis and feel that in

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

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

6 One further point which goes to the question of  
7 why Hyate:C wasn't used more widely in non-inhibitor  
8 patients is that the 1986 Speywood marketing plan  
9 records that it had to be stored at minus 15 degrees  
10 Celsius, which, obviously contrasted with storage at  
11 4 degrees Celsius in the fridge for a factor  
12 concentrate, minus 15 would obviously require  
13 a freezer. The reference for that is IPSN0000580\_001.

14 The company Speywood, and Porton, which took it  
15 over, had some success in marketing Hyate:C  
16 internationally. Product licences were obtained in  
17 Canada and the United States in 1986, IPSN0000477, and  
18 there was marketing in France and Germany as well,  
19 IPSN0000420, though the marketing efforts involved  
20 an emphasis on viral safety of the product, the  
21 references for that are IPSN0000133\_002, and  
22 IPSN0000148\_012.

23 Just to close this section, sir, with two  
24 further observations. If we could have  
25 IPSN0000073\_001 on screen, please.

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

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

12 What Dr Kasper wrote is this:

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

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

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

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

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

21 The reference to that is IPSN0000057\_093, so we  
22 can see from those articles in 1977 and 1979 that  
23 porcine Factor VIII had a good record on viral safety  
24 but it was -- when we put it this way -- it was not  
25 seen as a magic bullet that could be used in all

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(11) Pages 41 - 44

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

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

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

13 (11.13 am)

14 (A short break)

15 (11.45 am)

16 **SIR BRIAN LANGSTAFF:** Yes?

17 **MR HILL:** Sir, just before I turn to Abbott, Alpha,  
18 Grifols, if I could just correct a reference from this  
19 morning. The Carol Kasper article in Hemophilia  
20 Notes, the reference should be IPSN0000073\_003.

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

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

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1 1980s and on variants of the Factor VIII product,  
2 Profilate.

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

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

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

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

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1 disclosure.

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

10 We will briefly look at the replacement of  
11 Profilate Heat Treatment, HT, with Profilate SD,  
12 a solvent detergent product, in and around 1989 and  
13 1990. For each of these products we'll look at the  
14 licensing position and the communication of risk  
15 associated with the product, and we will do that  
16 chronologically rather than separating those two  
17 elements out in this instance.

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

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

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1 spend much time on it. There is a period in 1984 to  
2 1985 when heat-treated Profilnine was available and  
3 was taken up by UK haemophilia doctors because there  
4 was no equivalent heat-treated NHS product.

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

11 Here, we're going to use some of the information  
12 that we're going to come back to in November to try to  
13 set out what the position was in the 1970s and the  
14 1980s before the changes were made in response to  
15 AIDS.

16 So we begin then with corporate structure and  
17 with Abbott. This is an American company that dates  
18 back to 1888 and Dr Wallace Abbott of Chicago. The  
19 company was incorporated in 1984 and was renamed  
20 Abbott in 1915. An office was first opened in England  
21 in 1907, and a UK subsidiary was incorporated on  
22 24 June 1937. This was renamed as Abbott Laboratories  
23 Limited in August 1949.

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

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(12) Pages 45 - 48

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

In August 1978, Abbott US, the American company, sold the Scientific Products Division to the newly formed Alpha Therapeutic Corporation. This is the American company and I will, at points, refer to it as "Alpha US". Alpha US was, at that time, owned by the Green Cross Corporation of Japan. In a letter explaining the position to customers, regulators and other interested parties, it was stated that Alpha US had acquired, and I quote, "all the personnel, premises, plant and knowhow and expertise of the former Abbott division". So that's the Scientific Products Division. That's DHSC002197\_172.

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

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

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

Initially, the British operations of Alpha US

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

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

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

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

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

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

A further reference is DHSC0002197\_168.

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

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

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

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

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

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

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1 the key point for present purposes is that when  
 2 Grifols acquired some of Alpha's assets in July 2003,  
 3 these did not include the product licences for  
 4 Profilate or Profilnine and, as a result, there isn't  
 5 disclosure for that company to give to the Inquiry.  
 6 The references are WITN4514001 and WITN4514002.  
 7 I don't intend to say anything more about  
 8 corporate structure, sir. It's a matter that we can  
 9 return to if needs be.  
 10 Profilate. We know from the documents that we  
 11 have that Profilate received a product licence in  
 12 1975. It's not clear from the material that we have  
 13 seen whether and to what extent it was used in the UK  
 14 before then. We know that some UK clinicians were at  
 15 least aware of the product, which is perhaps  
 16 unsurprising. Archives from the Oxford Haemophilia  
 17 Centre show that promotional materials from 1973 were  
 18 obtained by the Oxford Haemophilia Centre but it's not  
 19 clear whether or not those were circulated more widely  
 20 in the UK. The reference is BPLL0008067.  
 21 Perhaps we could just have that on screen as it  
 22 shows the way in which the product was being licensed  
 23 at that time. What we can see on the first page is  
 24 a compliments slip dated March 1973 saying:  
 25 "Some of the Abbott literature (selected by me)

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1 a diluent and administered without the side effects  
 2 occasionally associated with plasma. Every bottle is  
 3 labelled with the number of Factor VIII units it  
 4 contains. So when the individual patient factors  
 5 affecting dosage have been established, the patient's  
 6 average dosage can be accurately calculated and  
 7 administered; even allowing the hemophiliac to be  
 8 treated on an out-patient basis. It can reduce the  
 9 incidence and severity of bleeding episodes, and the  
 10 pack contains all the components needed -- AHF,  
 11 diluent, and administration set -- for immediate use."  
 12 If we look at the next column, under the heading  
 13 "Caution", it says:  
 14 "This product is prepared from units of human  
 15 plasma which have been tested and found non-reactive  
 16 for Hepatitis Associated Antigen. However, it is  
 17 recognized that presently available methods are not  
 18 sensitive enough to detect all units of potential  
 19 infectious plasma and the risk of transmitting  
 20 hepatitis is still present."  
 21 We can see there, sir, the way the product is  
 22 being marketed as of 1973 and the advantages of  
 23 concentrate that are being stressed at that time. If  
 24 we could go over to the next page, please, Soumik.  
 25 This is a data sheet that was provided with the

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1 ..."  
 2 If we could then go to the next page, please,  
 3 I suspect this is from -- the initials which were  
 4 underneath the redaction were EB, so probably Ethel  
 5 Bidwell.  
 6 Then the next page says, "From Dr Rizza",  
 7 7 March 1973. If we expand the page out, please,  
 8 Soumik, we can see, bottom right-hand corner that this  
 9 is literature provided by Abbott Scientific Products  
 10 Division. I stress we don't know whether or not this  
 11 was circulated within the UK or whether or not it just  
 12 came into the possession of Drs Bidwell and Rizza. If  
 13 we could have a look at page 3, please. We can see  
 14 there is a picture of two young boys playing, climbing  
 15 a log or a tree, and the literature says:  
 16 "Boys will be boys ...  
 17 "Even if one is a Hemophiliac."  
 18 It goes on to say:  
 19 "Hemophilia. The constant threat of  
 20 haemorrhage. Now ABBOTT Scientific Products Division  
 21 Antihemophilic Factor (Human) AHF offers the  
 22 hemophiliac the opportunity to lead a more normal  
 23 life.  
 24 "Antihemophilic Factor (Human) Lyophilized is  
 25 a stable, dried concentrate, easily reconstituted in

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1 literature. I won't take you through it, at the  
 2 bottom right-hand column we can see that there is  
 3 a caution. That is in the same terms as the one that  
 4 I have just read to you from the main literature.  
 5 **SIR BRIAN LANGSTAFF:** Where?  
 6 **MR HILL:** If we could expand, please, "This product is  
 7 prepared".  
 8 **SIR BRIAN LANGSTAFF:** That's the very bottom?  
 9 **MR HILL:** The very bottom of the right-hand column.  
 10 **SIR BRIAN LANGSTAFF:** No, we got the wrong expansion  
 11 a moment ago.  
 12 **MR HILL:** This product is prepared from units of human  
 13 plasma which have been tested and found non-reactive  
 14 for Hepatitis Associated Antigen. However, it is  
 15 recognized that presently available methods are not  
 16 sensitive enough to detect all unite of potential  
 17 infectious plasma and the risk of transmitting  
 18 hepatitis is still present."  
 19 **SIR BRIAN LANGSTAFF:** Could we just have the very bottom  
 20 right-hand corner of the page where the date is of  
 21 this? October 1971. Thank you. So in October '71,  
 22 they were warning about the risk of hepatitis.  
 23 **MR HILL:** Yes.  
 24 **SIR BRIAN LANGSTAFF:** Thank you.  
 25 **MR HILL:** The trademark Profilate was registered in the

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1 United Kingdom on 31 July 1974. That is taken from  
2 paragraph 7 of Mr Gogay's witness statement. Shortly  
3 thereafter in August 1974, Abbott Laboratories  
4 Limited, so the UK company, applied for a product  
5 licence. This was considered at the meeting of the  
6 Committee on Safety of Medicines Biologics  
7 Subcommittee in November 1974. If we could have that  
8 on screen, please, Soumik. MHRA0000091\_005. Top  
9 right-hand corner, we can see that this another report  
10 by Dr Duncan Thomas. It is for a meeting to be held  
11 in November 1974. The date received is  
12 23 August 1974. I take that to be the date in which  
13 the product licence application was received.

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

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

25 If we could go to the second page, please,

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

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

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

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

16 So RIA testing was being used.

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

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

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

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

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

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

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

21 "Single dose container for intravenous  
22 administration'

23 "Discard unused contents'

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

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

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

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

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

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

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

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

25 "Recommendation". [This is Dr Thomas's

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(15) Pages 57 - 60

1 recommendation]:  
 2 "That a product licence be granted."  
 3 We don't, sir, as I've said, have the full set  
 4 of records of this licensing process. But we do know,  
 5 from a letter dated 10 December 1974, that Dr Duncan  
 6 of the DHSS -- that's Dr Mary Duncan -- informed the  
 7 company that the CSM -- that's the Committee on Safety  
 8 of Medicines -- had advised that a licence should be  
 9 granted, subject to two conditions concerning batch  
 10 release and using international units as the method of  
 11 describing the product. Abbott agreed to both of  
 12 those conditions. The reference is MHRA0000091\_012,  
 13 pages 14 to 16.  
 14 An indication, therefore, that the licence is  
 15 going to be granted, but the licence wasn't actually  
 16 granted at that stage. There was some further  
 17 correspondence -- Abbott applying for a variation to  
 18 the licence to cover, as they put it, "new stages in  
 19 the manufacturing process and consequent other  
 20 changes". These were changes which had been accepted  
 21 by the FDA. The reference is MHRA0000091\_012. And at  
 22 the same time, Abbott identified additional donor  
 23 centres.  
 24 If we could have, please, that document,  
 25 MHRA0000091\_012, on the screen, please, Soumik.

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1 "We do feel this matter has dragged on for too  
 2 long."  
 3 So it seems to be something of a chaser from  
 4 Abbott Laboratories Limited to the DHSS. That  
 5 reference is MHRA0000091\_008.  
 6 It seems to have done the trick because the  
 7 product licence was granted on 22 May 1975. It was  
 8 granted to Abbott Laboratories Limited, and the formal  
 9 document was dated 30 January 1976. The reference is  
 10 CBLA0000006\_009. So the product was licensed from  
 11 22 May 1975.  
 12 A data sheet for Profilate appeared in the 1976  
 13 edition of the Association of the British  
 14 Pharmaceutical Industry compendium, a publication that  
 15 we have looked at before. Could we have on screen,  
 16 please, Soumik, ABPI0000008. We can see this is the  
 17 entry for Abbott in the 1976 compendium. As we have  
 18 seen, these compendiums are prospective, and so it is  
 19 likely that the data sheet was inspected in the final  
 20 quarter of 1975 before its entry into this document.  
 21 If we could have the second page, please, we can  
 22 see in the left-hand corner towards the bottom that  
 23 this is the entry for Profilate, and it contains the  
 24 usual information about presentation, uses, the dosage  
 25 and administration. Then if we go on to the next

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

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

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(16) Pages 61 - 64



1 terms. The reference for that is ABPI0000014.  
 2 Turning to market share of the unheated  
 3 Profilate. Two DHSS documents from 1976 provide some  
 4 insight into this. The first was prepared by  
 5 Dr Sheila Waiter for a meeting in March 1976, and it  
 6 is a memo entitled "Survey of commercially produced  
 7 and NHS produced Factor VIII concentrates". It's at  
 8 DHSC0100007\_004. If we could have had on screen,  
 9 please.  
 10 We know that Dr Waiter was the author because of  
 11 the way that the document was discussed at a meeting  
 12 on 11 March 1976. The reference of that is  
 13 DHSC0100007\_003. I needn't take you to that document.  
 14 If we could go down to the second paragraph,  
 15 please, Soumik. It says this, and I quote:  
 16 "This paper is concerned with the available  
 17 forms of freeze-dried Factor VIII concentrate, the  
 18 advantages and disadvantages of these, and the  
 19 resulting clinical preferences. As the declared  
 20 intention is to make the NHS independent of commercial  
 21 producers of the therapeutic agent, it is essential to  
 22 produce within the NHS concentrates which are as  
 23 acceptable and as effective as those made  
 24 commercially."  
 25 That, sir, provides the context of this

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1 but the product is expensive.  
 2 "At present, three products are available:  
 3 Hemofil, Kryobulin, and Profilate.  
 4 A fourth firm will shortly be given a product  
 5 licence, and a fifth is likely to apply for one."  
 6 Likely to be references to Armour and to Cutter.  
 7 If we could go over on to the next page, there's  
 8 a discussion of the NHS sources of product. And  
 9 I just note, sir, for future reference, the  
 10 paragraph -- the first substantive paragraph of this  
 11 page where Dr Waiter says, and I quote:  
 12 "The three NHS production units make  
 13 freeze-dried Factor VIII concentrate by the same  
 14 process, which is that described by Newman et al,  
 15 based on cryoprecipitation and purification of the  
 16 cryoprecipitate by washing."  
 17 So that's describing the NHS methods which we  
 18 will come back to in due course.  
 19 Then on to the next heading which is "Clinical  
 20 preferences for the available Factor VIII  
 21 concentrates". And as we have seen from the context,  
 22 Dr Waiter is seeking to understand what the clinicians  
 23 want, in part to inform the NHS about their own  
 24 products so that they can meet the clinician's demand.  
 25 What Dr Waiter says is this, and I quote:

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1 document.  
 2 Under the next heading "Preparations of  
 3 Factor VIII", this refers back to the pool method of  
 4 preparing cryoprecipitate, and it states this, and  
 5 I quote:  
 6 "In 1964, Judith Pool prepared a method of  
 7 preparing cryoprecipitate which is still the most  
 8 widely used preparation of Factor VIII. It is made in  
 9 the Regional Transfusion Centres from fresh frozen  
 10 plasma and distributed on demand to clinicians. Its  
 11 main disadvantage is that the activity can vary  
 12 considerably from Centre to Centre and from batch to  
 13 batch. Unless held at suitably low temperatures and  
 14 infused shortly after thawing, activity may be  
 15 diminished."  
 16 If we could go over to the next page, please,  
 17 and underneath the heading "Commercial services of  
 18 freeze-dried Factor VIII concentrate". This is the  
 19 position as described by Dr Waiter in March 1976, and  
 20 I quote:  
 21 "Product licences have been granted to three  
 22 overseas commercial firms, enabling each to sell its  
 23 product in the UK but restricting the market available  
 24 to the firms to designated Haemophilia Centres.  
 25 Supplies are more than adequate to meet UK demands,

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1 "A limited survey among users of Factor VIII  
 2 concentrates (14 clinicians in 9 centres) has revealed  
 3 clear preferences, usually for one product.  
 4 "Factors mentioned as being significant are:  
 5 "1. Availability;  
 6 "2. Cost;  
 7 "3. Presentation, including availability of  
 8 a selection of dose sizes ...  
 9 "4. Volume of diluent required;  
 10 "5. Solubility;  
 11 "6. Activity of reconstituted product;  
 12 "7. Risk of transmission of viral hepatitis;  
 13 "8. Presence of blood iso-agglutinins;  
 14 "9. Levels of fibrinogen and other proteins."  
 15 Sir, I say now that, having read the document as  
 16 a whole, I do not read that as being listed in order  
 17 of importance; they are just the nine factors that  
 18 have been raised by the clinicians.  
 19 If we turn to the next page, please,  
 20 "Availability of the product". Dr Waiter wrote, and  
 21 I quote:  
 22 "There is a more than adequate supply of  
 23 commercially produced Factor VIII concentrate.  
 24 Hemofil is the product most commonly bought; more  
 25 Kryobulin is now being bought; there has been little

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(17) Pages 65 - 68

1 uptake of Profilate."  
 2 If we could go to the next heading, "Cost of  
 3 Factor VIII concentrates", we can see the current  
 4 prices are listed. Hemofil at 12p per unit, the same  
 5 as Kryobulin; Profilate slightly cheaper at 10p per  
 6 unit.  
 7 If we could then turn to page 6 of the document,  
 8 please, Soumik.  
 9 Entry 7, "Hepatitis", and I will read an  
 10 extended quotation from what Dr Waiter wrote.  
 11 "The risk of acquiring hepatitis, and in  
 12 particular hepatitis B, following infusion of  
 13 Factor VIII concentrates has recently been  
 14 highlighted. The commercial products are prepared  
 15 from large pools of fresh human plasma which may  
 16 contain the causative agents of viral hepatitis.  
 17 "This is especially likely if the sources of the  
 18 raw material are paid donors or donors from  
 19 geographical areas where the diseases are more  
 20 prevalent. It is not possible to subject the  
 21 concentrate to any treatment known to diminish the  
 22 risk of hepatitis ..."  
 23 I pause there. We can see that originally typed  
 24 were the words:  
 25 "... since such treatments greatly increase the

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1 If I could continue the quotation:  
 2 "Some clinicians accept the risk of using  
 3 Hemofil, claiming that the benefits of using a high  
 4 purity product outweigh the risk of transmitting  
 5 hepatitis, particularly for the severely affected  
 6 patient who is less susceptible following repeated and  
 7 frequent treatment. Others prefer to use an NHS  
 8 product, regardless of the relative inconvenience of  
 9 using these products to avoid the risk."  
 10 If we could turn to the next page, please,  
 11 Soumik, page 8. The summary of the users' views.  
 12 Dr Waiter, after reminding the reader that only  
 13 a small group of users was approached, says that there  
 14 was a fairly consistent preference, which is  
 15 summarised in the following way:  
 16 "1. Users like the ease of reconstitution of  
 17 the commercial products and the resulting small volume  
 18 of a haemostatic dose of factor VIII, even for adult  
 19 patients."  
 20 Then added in handwriting:  
 21 "This is particularly true of Hemofil."  
 22 "2. For home therapy, a small volume dose is  
 23 essential. Some patients on home therapy use  
 24 cryoprecipitate, but the majority are on high or  
 25 intermediate purity concentrates."

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1 loss of Factor VIII activity during preparation."  
 2 That has been struck through, that final clause,  
 3 and it's not clear whether or not that was -- or why  
 4 that was done.  
 5 **SIR BRIAN LANGSTAFF:** Well, the result, as it says, is you  
 6 can't do it at all, whereas previously it says you can  
 7 do it but you lose an awful lot of Factor VIII in  
 8 doing so.  
 9 **MR HILL:** Yes.  
 10 The next paragraph states, and I quote:  
 11 "The commercial products available in the UK  
 12 carry a warning that a risk of acquiring hepatitis,  
 13 although small, accompanies the infusion of these  
 14 products. It is now obligatory for commercial firms  
 15 to test individual donations of blood or plasma for  
 16 HBsAg and to batch test the final product by  
 17 radioimmunoassay."  
 18 It then goes on to discuss the NHS products. It  
 19 says they too carry a risk of transmitting  
 20 hepatitis B. Dr Waiter says, and I quote:  
 21 "However, this risk is considerably less than  
 22 that accompanying the use of commercial products."  
 23 And, of course, that reflects the understanding  
 24 at the time. You have seen other evidence about what  
 25 was known later.

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1 Added in handwriting:  
 2 "A small dose, approximately 250 millilitres of  
 3 Hemofil given early often produces haemostasis."  
 4 "3. The risk of transmission of viral  
 5 hepatitis, particularly following the use of Hemofil  
 6 and particularly to the less severely affected  
 7 haemophiliac, is recognised. All the clinicians  
 8 interviewed would, for this reason, prefer an NHS  
 9 product. A few consider the risk of infection  
 10 acceptable as the product is effective. Some patients  
 11 are reported to have refused commercial concentrates  
 12 following recent publicity.  
 13 "4. The presentation is important."  
 14 I won't go through the detail there, sir.  
 15 "5. Ease of reconstitution."  
 16 And it is noted that Hemofil is, on average, the  
 17 quickest and the easiest, and that the NHS products  
 18 take the longest time to reconstitute.  
 19 "Conclusions", and I quote:  
 20 "Clinical preference is for the commercial  
 21 product, based on ease of reconstitution and delivery,  
 22 but there is every indication that NHS products of  
 23 comparable solubility and ease of reconstitution and  
 24 of consistently high potency would be used to the  
 25 exclusion of commercial products."

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1 If we go down a couple of paragraphs, Dr Waiter  
 2 also writes:  
 3 "Costs will be an incentive, also the safety of  
 4 the product, but attention must be paid to  
 5 presentation."  
 6 I stress that "presentation" here is used to  
 7 mean what is provided with the product so that it can  
 8 be used, not just the mere external appearance or  
 9 anything like that.  
 10 So that's Dr Waiter's paper of March 1976. An  
 11 interesting paper more generally, but for Profilate it  
 12 shows a limited market penetration at that time.  
 13 If we could now go to DHSC0003719\_118, this  
 14 a document that we have seen on several occasions  
 15 before. It is Mr Drew's minute from a supply  
 16 department, dated 21 December 1976, sent to Dr Waiter,  
 17 listing the different products that are used in the  
 18 12 months to 31 October 1976 and their value.  
 19 Factor VIII is listed first. I have now, in my own  
 20 time, done the maths, and Factor VIII is -- the  
 21 average cost of it is 8p, if one takes the value and  
 22 divides it by the number of units. As you said, sir,  
 23 that is a crude way of doing it because you would  
 24 expect a sliding scale with discount for bulk. But  
 25 just doing it in that crude way, Armour's Factor VIII

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1 years, dating from 22 May 1980. The reference is  
 2 MHRA0000091\_006.  
 3 If we could have on screen, please, PRSE0003437,  
 4 this is a table showing the position of the different  
 5 products in 1980 and 1981. We can see the first  
 6 manufacturer listed is Abbott for Profilate, even  
 7 though by this time it's actually Alpha who was  
 8 providing the product. International units provided  
 9 in 1980 is about 1.65 million, and in 1989 (*sic*) it's  
 10 1.9 million. We can see that is the lowest other than  
 11 Speywood's Humanate in 1980, which is 615,000 and in  
 12 1981 is 1.5 million. It compares with the market  
 13 leader, Factorate, which is 16.5 million units in 1980  
 14 and 14.6 million units in 1981. So considerably more  
 15 than Profilate.  
 16 We can also see from the same table that Koate  
 17 and Hemofil and Kryobulin were also more popular than  
 18 Profilate. There is a reference to Interhem from  
 19 Hyland, which I think may be a reference to the  
 20 higher-purity product which Hyland have been -- sorry,  
 21 the intermediate purity product that Hyland had been  
 22 producing at that time.  
 23 So, overall, Profilate making up 1.6 million  
 24 units of a 34.7 million unit market in 1980, and  
 25 1.9 million units of a 34.8 million market in 1981,

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

9 The following year, November 1977, the annual  
 10 DHSS purchasing guide lists a price of 12p per unit  
 11 for Profilate. That's DHSC0002187\_085.

12 That brings us to 1978, when the Scientific  
 13 Products Division of Abbott was sold to Alpha US.  
 14 I don't need to take you to the documents, but it  
 15 appears that an agreement was struck so that Abbott  
 16 continued to provide the product to the UK market for  
 17 a transitional period in 1978 before Alpha took over.  
 18 The reference is DHSC0002197\_171.

19 On 10 September 1979, so the following year, the  
 20 DHSS cancelled Abbott's licence and transferred it to  
 21 Alpha Therapeutic GmbH, that is the German company.  
 22 The reference is MHRA0000091\_006, and the same stem  
 23 \_007. A new product licence number was issued, so  
 24 same product but being sold by a different company.

25 That product licence was then renewed for five

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

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

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

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

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1 Mr Bell's reference to receiving a licence in 1981,  
 2 I would take to be a reference to receiving an FDA  
 3 licence. The application in the UK came on  
 4 30 August 1982. It was considered by the Committee on  
 5 Safety of Medicines Biologicals Subcommittee in  
 6 March 1983, and Dr Fowler's medical assessment was  
 7 that the variation should be granted, subject to  
 8 a satisfactory pharmaceutical assessment. That  
 9 assessment was carried out by Mr Betts and the  
 10 assessment was that a number of points required  
 11 answering before the variation could be granted.  
 12 If we could have on screen, please,  
 13 MHRA0000091\_004. If we could have page 23 of that  
 14 document, please. So this is the pharmacist Mr Betts  
 15 commenting on the document. The areas requiring  
 16 further information include, at 1.1, "Source  
 17 Material":  
 18 "Details of the collection and testing  
 19 procedures actually used should be stated clearly.  
 20 "1.2 Information should be supplied on the  
 21 control exercised by Alpha Therapeutic Corporation  
 22 over the listed plasmapheresis centres and affiliated  
 23 centres."  
 24 If we go to section 2, "Manufacture of the  
 25 Product", 2.1:

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1 assess this variation."  
 2 Underneath that, we can see an extract from  
 3 another set of minutes has been pasted on to this  
 4 document, saying that:  
 5 "This application was considered by the  
 6 Sub-Committee at their March meeting. The application  
 7 was not subsequently considered by CSM as it was  
 8 decided that insufficient information had been  
 9 supplied in support of this variation."  
 10 The only other point I would note about this  
 11 application, sir, is that a data sheet was provided --  
 12 the reference is page 6 of this same document -- and  
 13 that contained a hepatitis warning in the same terms  
 14 as that contained in the 1976 Compendium, which we  
 15 have looked at.  
 16 So far as the Inquiry is aware, no product  
 17 licence variation was granted to allow the  
 18 polyethylene glycol step.  
 19 That application was made in August 1982. In  
 20 October 1982, Alpha was involved in an application --  
 21 another application, this time for a clinical trial  
 22 certificate, for the product Mono VIII, which was made  
 23 by Speywood. We referred to this, sir, on Friday, and  
 24 I would just like to show one or two documents  
 25 relating to it. If we could have on screen, please,

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1 "The size of the production batches should be  
 2 stated."  
 3 There are a number of other points here, I won't  
 4 go through them all. If we go down to 4, please,  
 5 "Development Pharmaceuticals":  
 6 "Evidence should be supplied to demonstrate the  
 7 improved purity and the physical characteristics of  
 8 the PEG material over the currently licensed product.  
 9 "Evidence should be provided that the upper  
 10 limit of PEG is non-hazardous in man."  
 11 If we could turn over the page, please, to  
 12 a "Pharmaceutical Recommendation", and I quote:  
 13 "A variation to the Product Licence should be  
 14 refused until full information is received on the  
 15 above points."  
 16 The Committee on Safety of Medicines  
 17 Subcommittee on Biologicals followed that advice and  
 18 advised in the same terms. If we could have page 1,  
 19 please, on the screen -- the same document, first  
 20 page -- and we can see that it's recorded that:  
 21 "On the evidence before them the Sub-Committee  
 22 were unable to recommend that the product licence  
 23 should be varied as indicated in the application.  
 24 "The Sub-Committee considered that inadequate  
 25 information had been presented by the Company to

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1 DHSC0003949\_102.  
 2 It is important to stress, sir, that this not  
 3 the product that was the subject of the study by  
 4 Professor Tuddenham and Ms Middleton. That was  
 5 produced by BPL, and was only used on four patients,  
 6 and it was using BPL cryoprecipitate. This is  
 7 an application for a further clinical trial  
 8 certificate, for a wider clinical trial; it would  
 9 again use the polyelectrolyte fractionation technique  
 10 that Speywood had developed but the source material  
 11 was going to be, and I quote:  
 12 "Bulk cryoprecipitate manufactured by: Alpha  
 13 Therapeutic Corporation ..."  
 14 So instead of using the cryoprecipitate taken  
 15 from BPL, which would have come from UK voluntary  
 16 donors, it is instead using commercially sourced  
 17 cryoprecipitate from America.  
 18 If we look at this document, we can see that it  
 19 is an application for a clinical trial certificate.  
 20 It is received on 20 October 1982, and is to be  
 21 considered at the Subcommittee on Biologicals meeting  
 22 of March 1983. There is also a reference to another  
 23 meeting, PSM, on 4 November 1982. I am afraid I can't  
 24 assist with what that is.  
 25 It was assessed by Dr Fowler and Mr Betts, the

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1 same team that assessed the previous application that  
 2 we were looking at. The proposed certificate licence  
 3 holder is Speywood. But if we expand the document,  
 4 this part of the application concerns the "Bulk  
 5 Cryoprecipitate manufactured by [Alpha]", and that is  
 6 at 1.2, the "Product Summary".  
 7 Then if we look at the final section, 1.5.1,  
 8 dealing with the "Proposed Uses", it says:  
 9 "Mono-VIII-C is to be studied for efficacy and  
 10 clinical tolerance in the treatment of haemarthrose  
 11 involving the knees, elbows and ankles of severe  
 12 haemophiliacs."  
 13 If we could now have on screen DHSC0003949\_104.  
 14 We have a little more information provided about the  
 15 particulars of the trial. If we could go down to  
 16 item 6, please, "Patient selection", it's stated that  
 17 the trial will involve:  
 18 "Up to 50 males aged 7 years to 18 years ... All  
 19 will be severe haemophiliacs with hemarthroses of the  
 20 knee, ankle or elbow."  
 21 If we could now have DHSC0003949\_105, please.  
 22 This explains a little of the structure of the  
 23 application. Under the heading -- it explains  
 24 a little more of the proposed trial -- "Indications":  
 25 "[Mono C] is to be studied for efficacy and

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1 **SIR BRIAN LANGSTAFF:** Yes.  
 2 **MR HILL:** As was mentioned on Friday, Dr Aronstam of  
 3 Treloar was the person who was listed as participating  
 4 in this trial, there had also been some indication  
 5 that the Royal Free may have been involved as well.  
 6 I needn't take you to the document, but at  
 7 DHSC0003949, there is an explanation that a separate  
 8 application has been filed for the cryoprecipitate  
 9 stage of the trial, and a separate application for the  
 10 Mono C side of the trial, and the application of that  
 11 to the patients, obviously to be considered together.  
 12 It is stated that:  
 13 "Full details on donor selection, collection  
 14 procedures, quality control and manufacturing methods  
 15 are given in the product licence application."  
 16 If we could now have, please, DHSC0003949\_106,  
 17 this the medical report, so Dr Fowler. If we could  
 18 have -- thank you, the second page under the heading  
 19 "Bulk Cryoprecipitate", Dr Fowler explains the way in  
 20 which the application has been structured, with  
 21 separate application for the cryoprecipitate, which is  
 22 one that's being considered here. Under the heading  
 23 "Manufacture", Dr Fowler states, and I quote:  
 24 "There is nothing in the process which would  
 25 render the product incapable of transmitting hepatitis

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1 clinical tolerance", as we have seen.  
 2 "Patient election", it says:  
 3 "A total of 200 bleeds will be required for the  
 4 study, of which 100 will be treated with Mono-VIII:C  
 5 and 100 with intermediate purity commercial  
 6 concentrate ..."  
 7 If we could turn over to the next page, page 2,  
 8 and it's section 5, "Duration":  
 9 "The duration of this study is anticipated to be  
 10 approximately 8 months."  
 11 Then on to the next page, page 3, section 9, the  
 12 investigator is Dr Aronstam of Treloar.  
 13 **SIR BRIAN LANGSTAFF:** Could you just go back a page. Yes,  
 14 the trial is -- the "Trial design", it's a random  
 15 double-blind study which compares Mono VIII:C with  
 16 unspecified, intermediate purity commercial  
 17 concentrate.  
 18 **MR HILL:** The following page has the control products  
 19 listed.  
 20 **SIR BRIAN LANGSTAFF:** Let's have a look at that.  
 21 **MR HILL:** Under section 8, it says most control products  
 22 are Hemofil, Factorate, Koate, Proflate and  
 23 Kryobulin. I should have stressed at the outset, sir,  
 24 this is about the human Factor VIII product that  
 25 Speywood was producing, not the porcine product.

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1 but some claims have been made that PE fractionation  
 2 removes [hepatitis surface antigen]. As the source  
 3 cryo has been screened for this, one is more concerned  
 4 with [non-A, non-B] hepatitis. This is not  
 5 mentioned."  
 6 If we could turn, please, to page 4, and the  
 7 final paragraph. There is a reference to the fact  
 8 that the company has provided a published paper by  
 9 Tuddenham et al about the efficacy of the treatment.  
 10 That is the paper we looked at on Friday, in which  
 11 Dr Tuddenham referred to the four patients that were  
 12 treated with the BPL product.  
 13 If we could turn to page 5 now, please, "Medical  
 14 Comments". Dr Fowler wrote this:  
 15 "This [clinical trial] application by Speywood  
 16 is dependent upon the parallel [product licence]  
 17 application by Alpha Therapeutics for the importation  
 18 of bulk cryo paste to be used as raw material for the  
 19 manufacture of Mono-VIII:C. If the Alpha licence is  
 20 not granted, this Speywood application is seriously  
 21 deficient in that respect.  
 22 "The Speywood application gives no indication of  
 23 the precautions taken to ensure that the Alpha bulk  
 24 cryo remains frozen throughout its journey from  
 25 Los Angeles to Wrexham via an un-named UK airport,

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1 beyond replenishment of the dry ice at the UK airport.  
 2 Who, in fact, is responsible for this replenishment  
 3 and, possibly, recording whether the cryo is still  
 4 frozen on arrival?  
 5 "PE fractionation has never before been used for  
 6 any blood product licensed in the UK. It might  
 7 therefore be thought essential for the company to  
 8 demonstrate conclusively that their product prepared  
 9 in this way was no more toxic than [Factor] VIII  
 10 prepared in the conventional way."  
 11 I pause there, sir. I erroneously stated  
 12 earlier that this is Dr Fowler considering the cryo  
 13 aspect. It's not, it's Dr Fowler considering the  
 14 Speywood application but obviously with reference to  
 15 his concerns about the way in which the  
 16 cryoprecipitate is going to be shipped to Speywood.  
 17 **SIR BRIAN LANGSTAFF:** Well, he's asking whose job is it to  
 18 make sure it remains frozen.  
 19 **MR HILL:** That question hasn't been answered, so far as he  
 20 can tell, from the application.  
 21 If we could turn to page 6, please.  
 22 **SIR BRIAN LANGSTAFF:** Just pause for a moment.  
 23 **(Pause)** Yes.  
 24 **MR HILL:** The point made in the final paragraph, sir,  
 25 about the single paper. What I understand Dr Fowler

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1 reflect the recommendations made in the preceding  
 2 paragraph. The company should be advised now about  
 3 the amount and nature of safety and efficacy data  
 4 which will be required to support any future  
 5 application for a product licence."  
 6 That is the medical report from Dr Fowler about  
 7 the Speywood element, obviously referring to the  
 8 cryoprecipitate but not primarily focused on the  
 9 cryoprecipitate. The CSM Main Committee, if we could  
 10 have DHSC0003946\_060, this is the Main Committee's  
 11 conclusion about the cryoprecipitate element.  
 12 What the main committee, at their meeting on  
 13 24 March 1983, say is, and I quote:  
 14 "On the evidence before them the Committee had  
 15 reason to think that on grounds relating to safety and  
 16 quality they would be unable to advise the grant of  
 17 a product licence for this preparation and directed  
 18 the Secretary to notify the applicant ...  
 19 "The Committee provisionally concluded that:  
 20 "1. The bulk cryoprecipitate should be prepared  
 21 by Alpha Therapeutic only from Source Plasma ...  
 22 derived from their own licensed plasmapheresis  
 23 centres,  
 24 "2. Evidence should be provided to show that  
 25 the cryoprecipitate is at least equivalent in quality

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1 to be saying there is that, although Dr Tuddenham's  
 2 paper has been presented, that product, of course, was  
 3 made using UK cryo from BPL, which is different from  
 4 the application which is being pursued now, which  
 5 using American cryo.  
 6 If we could turn over to the top of page 6,  
 7 please, Dr Fowler says:  
 8 "The proposed study poses no fundamental  
 9 problems but two matters deserve consideration. Some  
 10 indication of the way in which clinical tolerance is  
 11 going to be monitored should be given and some  
 12 restriction should be put on the number of treatments  
 13 an individual patient may receive during the trial.  
 14 In view of the fact that the product is effectively  
 15 coming straight from bench to clinic, it might be  
 16 thought that 200 bleeds in a possible 200 patients,  
 17 was excessive at this stage of a product's  
 18 development. A smaller number or, perhaps, an interim  
 19 report to the Committee on, say, the first 50 might be  
 20 desirable."  
 21 The "Medical Opinion" is:  
 22 "Subject to the grant of a product licence to  
 23 Alpha Therapeutics for the imported bulk  
 24 cryoprecipitate used as a raw material, a Clinical  
 25 Trial Certificate should be issued. This should

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1 to that used for the manufacture of Alpha  
 2 Therapeutic's US licensed Factor VIII,  
 3 "3. Inadequate information was presented on the  
 4 control of the material during transportation to the  
 5 UK,  
 6 "4. An undertaking should be given that donor  
 7 lists should be available to the manufacturer of the  
 8 finished dosage form,  
 9 "5. In the event of a licence being granted for  
 10 this product, the batch release procedure should  
 11 apply, to include the provision of protocols and  
 12 samples of bulks as required,  
 13 "6. There were inadequate details on the  
 14 manufacturing process."  
 15 "Remarks" are given are, including at 2, and  
 16 I quote:  
 17 "The Committee advised that special attention be  
 18 given to the inspection of the Company's premises in  
 19 the [United States]."  
 20 Sir, we can see that the importation of  
 21 cryoprecipitate for the Speywood trial was refused  
 22 with those comments made. That relates directly to  
 23 the Alpha side of the application.  
 24 We looked at some documents about this on Friday  
 25 and we asked Ms Middleton about it and, as far as she

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1 was aware, the trial did not, in fact, go ahead and we  
 2 have seen no documentation to suggest that it did go  
 3 ahead. A further point to note, sir, is that by the  
 4 time of this decision, March 1983, information  
 5 knowledge had grown about the risk of AIDS. So, even  
 6 if the application had been successful, Dr Aronstam  
 7 and others would have had to consider the position in  
 8 1983, in light of the knowledge of AIDS, as to whether  
 9 or not to continue with that trial. The fact that  
 10 they made the application in 1982 does not necessarily  
 11 mean they would have gone through with it in 1983.

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

17 **MR HILL:** Yes, sir.

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

19 **MR HILL:** We will be looking at that in due course.  
 20 I note the time, sir, but there are just couple  
 21 of documents which we may have time for before lunch  
 22 about the unheated product, before turning to the  
 23 heat-treated product.

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

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

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

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

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

8 **SIR BRIAN LANGSTAFF:** Thank you.

9 **MR HILL:** The final document, which I won't take you to,  
 10 but we'll just refer to, BAYP0000026\_008. This is  
 11 a marketing plan from Cutter dated October 1983, so  
 12 commenting on its rivals. In respect of Profilate, it  
 13 says that was making some gains due to its low price,  
 14 which tallies with the table we have just seen.

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

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

19 (1.02 pm)

20 (Luncheon adjournment)

21 (2.00 pm)

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

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1 penetration that Profilate had as of 1983.

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

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

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

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

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

14 **MR HILL:** Haha. DHSC0002229\_055. I'm afraid I don't  
 15 have -- that's the one document I don't have in paper  
 16 copy in front of me. If we could have the second page  
 17 of that, please, Soumik.

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

25 Another point to note from that table is that

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1 n-heptane. It may be helpful to just bring up  
 2 MHRA0033388\_029, please, Soumik. Page 16.

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

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

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

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

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1 not less than 20 hours. It was then filtrated out of  
 2 the suspension, dried again, freeze-dried, and that  
 3 creates the final product.  
 4 **SIR BRIAN LANGSTAFF:** So this isn't dry heating. It isn't  
 5 pasteurisation as it is conventionally understood.  
 6 It's a sort of in-between in which a solvent other  
 7 than -- a solvent is used and heat applied.  
 8 **MR HILL:** Yes. It's usually referred to as heating in  
 9 suspension in some of the documents.  
 10 **SIR BRIAN LANGSTAFF:** Yes.  
 11 **MR HILL:** It's unflatteringly referred to as slurry  
 12 heating, to give the idea that the solid is still  
 13 there. But it's, as you say, sir, between dry heat  
 14 and between what is conventionally called  
 15 pasteurisation, which is fully heated within  
 16 a solution.  
 17 **SIR BRIAN LANGSTAFF:** Yes.  
 18 **MR HILL:** The only product that I am aware of that  
 19 underwent true pasteurisation of this form was for the  
 20 Behringwerke product, but that was not, as of 1983,  
 21 1984 and 1985, available in the UK. It became  
 22 available later.  
 23 **SIR BRIAN LANGSTAFF:** Yes. I mean, it had been available  
 24 earlier, but it obviously wasn't actually distributed.  
 25 **MR HILL:** I'm afraid, sir, I --

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1 procedure reduced the final yield of Factor VIII and  
 2 was costlier to implement, it provided, in Alpha's  
 3 opinion, a more robust inactivation of viruses.  
 4 (A simple analogy is: dry heat is similar to placing  
 5 your hand in an oven; wet heat is like placing your  
 6 hand in a hot water bath -- the transmission of heat  
 7 in the bath is much greater.) Alpha's protocol for  
 8 this additional processing step was established in the  
 9 fall of 1982 and submitted to the FDA.  
 10 "Studies conducted pursuant to FDA licensure  
 11 demonstrated that Alpha's heat treatment process  
 12 inactivated significant quantities of marker virus,  
 13 hepatitis B and non-A, non-B hepatitis. However, both  
 14 the Bureau of Biologics of the FDA and the haemophilia  
 15 treatment community raised concerns about the  
 16 possibility of neoantigenicity related to the heat  
 17 treatment. This concern centred around researchers'  
 18 and physicians' belief that heating the concentrate  
 19 altered the molecular structure of the Factor VIII  
 20 molecule, which could have a deleterious effect on  
 21 persons using heat-treated concentrates, essentially  
 22 making a treatable patient untreatable.  
 23 "Studies conducted by Alpha failed to show any  
 24 evidence of neoantigenicity. However, the treatment  
 25 community did not fully accept these results until the

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1 **SIR BRIAN LANGSTAFF:** That's a detail we can deal with  
 2 later.  
 3 **MR HILL:** Yes. Yes. But it is a significantly different  
 4 process to the pure dry heat that we have seen with  
 5 other products.  
 6 David Bell, in his statement dated  
 7 2 February 2021, gives some evidence about the  
 8 background to this. If we could have on screen,  
 9 please, Soumik, WITN4514001, page 6, please.  
 10 If we could highlight the last two paragraphs of  
 11 that page, starting in early 1982. Mr Bell said this:  
 12 "In early 1982, Alpha began an additional  
 13 programme to inactivate any residual hepatitis virus  
 14 through heat, which culminated in a licensed product  
 15 in February 1984."  
 16 I pause there, sir, to note that that reference  
 17 is to an FDA licence in February 1984.  
 18 "After evaluating various inactivation  
 19 processes, researchers at Alpha concluded that heating  
 20 the concentrate in a liquid solvent without added  
 21 stabilisers might not have the undesirable effect of  
 22 stabilising any residual virus in addition to the  
 23 Factor VIII protein. Unlike other entities who  
 24 utilised 'dry heat', Alpha developed a procedure using  
 25 'wet heat' (a suspension in n-heptane). While this

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1 end of 1985. Until haemophilia treaters' concerns  
 2 about neoantigenicity were allayed, non-heat treated  
 3 concentrates continued to be prescribed and  
 4 recommended by physicians as the principal treatment  
 5 of choice."  
 6 That concerns primarily the American position  
 7 and we will come on to see the UK position. If I may  
 8 take you to page 3 of the same document, in response  
 9 to some questions by the Inquiry, and in a statement  
 10 dated 6 July 2021, Mr Bell provided a little more  
 11 detail. He said, and I quote:  
 12 "Alpha began its research program for factor  
 13 concentrates prior to the initial reports of HIV. The  
 14 program was in response to the potential risks of  
 15 hepatitis and was undertaken by senior Alpha  
 16 scientists including Martha Heinski and Charles  
 17 Heldebrant. Prior to the work initiated by Alpha and  
 18 others in the 1970s/early 1980s in response to the  
 19 risk of Hepatitis, the scientific and clinical  
 20 understanding was that, while heat  
 21 treatment/pasteurization was utilised for viral  
 22 inactivation in Albumin, it required the addition of  
 23 specific stabilizers. As it related to heat treating  
 24 factor concentrates, it was believed that the factor  
 25 concentrates were very heat labile and, even in the

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

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

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

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year.

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

An indication of the move toward heat-treated products and in particular Profilate, in 1984, is available in an article from The Haemophilia Society Update from 1989. Could we have HCDO0000276\_047, please.

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

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

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

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

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

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

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

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

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

Back to another quote from Mr Marshall:

"We had to introduce rationing' ..."

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

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

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

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

As we have heard from previous presentations, the DHSS, as of November 1984, encouraged other companies to apply for product licences for heat-treated products, and Alpha Therapeutics UK did so on 3 January 1985. We have looked at the manufacturing process from that application. The references are MHRA0033388\_033, and the same stem \_029. The application was signed by Ian Marshall and the applicant was Alpha Therapeutics UK. So the UK company rather than the German company.

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

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

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

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donor products should be preferentially utilised whenever feasible."

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

Following the provision of the application, there was a process of correspondence between the DHSS and Alpha Therapeutics UK. I don't think I need to take you to the detail of that. I would note that at one point the DHSS requested or required Alpha to include in its literature the fact that the product had been heated at 60 degrees centigrade for 20 hours, and it also said that it should be specified that that step had been taken, and I quote, "in order to reduce the risk of transmission of infectious agents". So, as we have seen with other products, not referring to hepatitis or AIDS, but "infectious agents" generally. The reference is MHRA0033388\_018.

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

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

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have this on screen, please, is MHRA0033388\_026. You will recall, sir, that Dr Thomas's letter about Kryobulin, Koate and Hemofil, dated 8 January 1985 formed part of our presentation on Kryobulin. This is a letter from nine days later, specifically about Profilate. What Dr Thomas said was this:

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

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

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

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

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

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

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1 MHRA0033388\_14 and 15.  
 2 In a letter dated 10 April 1985, Alpha UK  
 3 explained that it would continue to supply the product  
 4 on a named-patient basis until the labelling and  
 5 packaging had been approved and was available. That  
 6 reference is the same stem \_008.  
 7 If we could have on screen, please,  
 8 MHRA0033388\_006. If we could have page 4 of that  
 9 document, please. This is the proposed label for the  
 10 heat-treated product, as part of the discussions that  
 11 went on between the DHSS and the company. We can see,  
 12 under the "Caution", it says:  
 13 "This product is prepared from human plasma of  
 14 donors who have been individually tested at each  
 15 donation and found nonreactive to hepatitis B surface  
 16 antigen by approved test. However, it is recognized  
 17 that presently available methods are not sensitive  
 18 enough to detect all units of potentially infectious  
 19 plasma."  
 20 That's the draft label. A draft data sheet, as  
 21 of 13 March 1985, is at MHRA0033388\_007.  
 22 I'll try that again MHRA0033388\_007. Thank you.  
 23 This is the -- I said data sheet, sorry,  
 24 actually this is a package insert. Underneath the  
 25 "Description", we can see that the same warning is

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1 terms to the one that we have looked at before and, on  
 2 AIDS, the warning section says, and I quote:  
 3 "The causal factors of Acquired Immune  
 4 Deficiency Syndrome ... have not been fully defined.  
 5 However HTLV-III/LAV virus has been implicated as  
 6 a possible agent of the disease. It is not presently  
 7 known if other transmissible agents are involved.  
 8 Alpha uses screening procedures to eliminate high risk  
 9 plasma donors and a heat-treatment step of the  
 10 manufacturing to reduce the risk of transmitting AIDS.  
 11 However, despite the careful selection of donors, it  
 12 may be possible that the AIDS causative agents may  
 13 still be present in and be transmitted through this  
 14 product."  
 15 In November, we will come back to the steps that  
 16 are taken.  
 17 Thank you. If we could take that down, please,  
 18 Soumik.  
 19 So those are some of the documents that were  
 20 provided with the application to the UK authorities  
 21 for the product licence and the correspondence that  
 22 followed it.  
 23 An internal Alpha document, which is a UK  
 24 inventory dated 31 August 1985, records that the  
 25 company had 2.5 million units of heat treated

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1 given about hepatitis. Then the third paragraph down,  
 2 we can see that it says:  
 3 "The process used in the manufacture of  
 4 Profilate Heat-Treated includes a step designed reduce  
 5 the risk of transmission of hepatitis, Acquired Immune  
 6 Deficiency Syndrome ... and infection by other  
 7 viruses. However, no method has been shown to be  
 8 totally effective in removing hepatitis, AIDS, or  
 9 other viral infectivity from Antihaemophilic Factor  
 10 (Human)."  
 11 Sir, I note that the reference to the step being  
 12 taken to reduce hepatitis and AIDS is one that the  
 13 DHSS picked up upon and asked to be changed and, in  
 14 later versions of this document, it is changed.  
 15 There follows a section on clinical  
 16 pharmacology. I'm not going to take you through it,  
 17 sir. I think it can be fairly summarised as saying  
 18 that it describes the newly recognised retrovirus that  
 19 had been implicated as a possible causative agent of  
 20 AIDS, and it goes through how that has been tested in  
 21 Profilate, and the -- the chimpanzee studies and the  
 22 viral load studies that have been conducted. If we  
 23 could go over onto the next page, please.  
 24 In the warning section, a bit further down,  
 25 again, we have a warning about hepatitis in similar

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1 Profilate at the time. The same inventory notes that  
 2 the company had about 735,000 units of what was termed  
 3 standard concentrate, which was presumably non-heat  
 4 treated. But the fact that those units were present  
 5 doesn't mean that they were actually being sold at  
 6 that time, nor indeed that any customers would have  
 7 been willing to buy them. And that is August 1985,  
 8 the reference being CGRA0000565.  
 9 **SIR BRIAN LANGSTAFF:** It also means that neither had they  
 10 been junked nor returned.  
 11 **MR HILL:** No. They were within the --  
 12 **SIR BRIAN LANGSTAFF:** And it amounted to roughly 20 to 25%  
 13 of the -- from the figures you've given me -- of the  
 14 available stock.  
 15 **MR HILL:** Yes. But what that stock was available for  
 16 is -- isn't expressed in the document.  
 17 Turning to market share. A letter dated  
 18 18 March 1986 shows the approach that Alpha was taking  
 19 to marketing heat treated Profilate at that time.  
 20 NHBT0096602\_005, please.  
 21 This is sent to Mr Rhodes of the north western  
 22 Regional Health Authority, and it's thanking him for  
 23 an enquiry of 12 March.  
 24 It refers to two alternative preparations that  
 25 are available, the first being Profilate heat treated

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

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

So product information on that study.

"Hepatitis:

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

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

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

Underlined is the following comment, and I

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quote:

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

Then it says:

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

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

I stress, sir, that this letter is

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

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

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

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

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

And the letter from 28 November 1985 states this:

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

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

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

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

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

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

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

18 While the publication came in September 1985,  
19 there is considerable evidence that the results were  
20 being discussed among haemophilia clinicians before  
21 that date, and that, as a result, Profilate had  
22 quickly established a strong market position among the  
23 heat-treated products, despite selling at a price,  
24 14p, that may have been higher than some of its  
25 competitors.

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

6 I note here, sir, that by October 1985, this  
7 preference was reflected in the treatment guidelines  
8 at the Cardiff centre, which can be found at  
9 WITN000029003. Profilate HT was seen as the second  
10 safest product after 8Y, the BPL product.

11 A Cutter memorandum of 20 May 1985 recorded that  
12 Dr Savidge had presented his own Profilate HT trial  
13 results and that they supported what was described as  
14 Alpha's claim that Profilate HT was free from non-A,  
15 non-B hepatitis. His results were said to support  
16 those of Dr Kernoff and Dr Wensley. And according to  
17 the Cutter memo, some haemophilia directors were now  
18 saying, and I quote, that it was "unethical to use  
19 anything but Profilate HT, especially on virgin  
20 haemophiliacs and children." Reference is  
21 BAYP0000024\_230.

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

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1 A Cutter report from January 1985 noted that  
2 Dr Wensley in Manchester had switched to Profilate  
3 heat treated and appeared, and I quote, "To believe in  
4 the wet heat treatment process," though he was  
5 reserving judgment until liver function studies were  
6 known. Reference to that is BAYP0000024\_070.

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

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

15 That reference is TYWE0000014.

16 On 12 April 1985, Professor Bloom in Cardiff  
17 wrote to his chief pharmacist, and if we could perhaps  
18 have this on screen. It's CVHB0000002\_028. Dr Bloom  
19 wrote that he was -- and this letter concerns ordering  
20 Factor VIII -- he says -- he complains about the Koate  
21 product, and then says, and I quote:

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

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1 patients seemed to develop non-A, non-B hepatitis,  
2 having used Profilate. That reference is  
3 BAYP0000007\_113.

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

7 If we could have on screen, please,  
8 BAYP0000008\_059. This is another Cutter memorandum in  
9 which it's recorded -- this is 16 January 1986:

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

12 His reasons were explained as follows:

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

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1 also only use Alpha material -- Sheffield, the  
 2 Royal Free, and Cardiff."  
 3 The author of the memo goes on to describe the  
 4 major blow of losing Newcastle.  
 5 So we can see, sir, a march is being stolen by  
 6 Profilate HT in the heat treated product market.  
 7 An application was made to vary the licence and  
 8 change the labelling in November 1986, and it was  
 9 seemingly approved on 15 January 1987. The references  
 10 are MHRA0033387\_010, and same stem \_011, and the same  
 11 stem \_012.  
 12 We can see some of the labelling that was being  
 13 used at the time. If we could have on screen, please,  
 14 MHRA0033387\_014. As part of the application, the  
 15 company provided the copies of the vials that were  
 16 being -- copies of the packaging that were -- was  
 17 being used at the time. And we can see that this is  
 18 used on the small vial. The warning says:  
 19 "This product is prepared from large pools of  
 20 human plasma which may contain the causative agents of  
 21 non-A, non-B hepatitis, hepatitis B and other viral  
 22 diseases. See package insert.  
 23 "Each unit of plasma has been tested and found  
 24 non-reactive for HB surface antigen and HTLV-III  
 25 antibody by FDA-approved tests."

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1 text and the proposed text, and if we could have that  
 2 on screen, please, at MHRA0033389\_050. If we could go  
 3 to page 2, please.  
 4 We can see on the left-hand side, in the  
 5 left-hand column, is the present text as of July 1987,  
 6 and the proposed text is on the right-hand side. If  
 7 we could go, please, to page 3 and the section on  
 8 warnings. I should say sir, that the comparison is  
 9 slightly confused by the fact that some of the text in  
 10 the proposed warnings is placed elsewhere on the -- in  
 11 the package inserts so it's not -- the fact that it's  
 12 not present next door to the existing wording doesn't  
 13 mean that it has somehow been cut.  
 14 If we look at the present text, it states this,  
 15 and I quote from left-hand column:  
 16 "This product is prepared from pooled units of  
 17 human plasma which have been individually tested and  
 18 found nonreactive for hepatitis B surface antigen and  
 19 antibody to human T-lymphotropic virus type III  
 20 (HTLV-III). Other screening procedures are used to  
 21 eliminate high risk plasma donors and the  
 22 heat-treatment step of the manufacturing process is  
 23 designed to reduce the risk of transmitting viral  
 24 infection."  
 25 I note, sir, that that is the request that the

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1 So that's the small vial. If we look now at  
 2 MHRA0033387\_016, this is the large vial concentrate.  
 3 The warning is different. It says:  
 4 "This product is prepared from human plasma of  
 5 donors that have been individually tested at each  
 6 donation and found non-reactive for hepatitis B  
 7 surface antigen by FDA required test. However, it is  
 8 recognised that methods presently available are not  
 9 sensitive enough to detect all units of potentially  
 10 infectious plasma, and the risk of transmitting  
 11 hepatitis is still present."  
 12 Different warning, depending on the size of the  
 13 product that you were providing.  
 14 These are the packets that are to be replaced,  
 15 and we can see the proposed text for labels and  
 16 cartons at MHRA0033387\_017. And that text, sir,  
 17 contains no warning on it, although it does refer the  
 18 reader to the package insert, and we will come on to  
 19 that in a second.  
 20 The application -- sorry, there was a further  
 21 application on 30 July 1987, which was for  
 22 a rationalisation and update of the text, including  
 23 incorporation of new information about non-A, non-B  
 24 hepatitis, that's at MHRA0033389\_049.  
 25 The data sheet helpfully sets out the present

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1 DHSS have made and that has been followed. The  
 2 proposed text says, again, that:  
 3 "[The] product is prepared from pooled units of  
 4 human plasma which have been individually tested and  
 5 found nonreactive for hepatitis B surface antigen and  
 6 antibody to Human Immunodeficiency Virus (HIV). The  
 7 plasma used in the preparation of this product has  
 8 been screened for Alanine Aminotransferase (ALT)  
 9 levels in an effort to reduce the transmission of  
 10 non A, non B hepatitis. Each unit used in the  
 11 manufacture of this product has been found to have  
 12 an ALT level less than 2 times the upper limit of  
 13 normal for the test. Other screening procedures are  
 14 used to eliminate high risk plasma donors and a  
 15 heat-treatment step in the manufacturing process is  
 16 designed to reduce the risk of transmitting viral  
 17 infection."  
 18 If we could go over to the next page, please.  
 19 Some detail is given about the testing of the product  
 20 with spiked HIV and the reduction of 3.25 logs of HIV,  
 21 and about the chimpanzee studies. Although we can see  
 22 there is no equivalent text in the left-hand column,  
 23 that material was actually contained a little earlier  
 24 in the old version of the document, so it's not new.  
 25 If we go down to the third paragraph, this is

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new:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The summary states this, and I quote:

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

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

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

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

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

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

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

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

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

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If we go to the text just beneath these diagrams:  
 "Two of the nine batches of concentrates ... were implicated in transmission of NANBH. One of these batches [batch D] caused hepatitis in all four recipients, suggesting a batch-related rather than process-related problem."

We will pick up what happened with batch D shortly.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 product behind BPL's 8Y and the Behringwerke product  
2 Haemate P, which was, by that stage, available in the  
3 UK. The reference is NHBT0000037\_014.

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

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

14 The reference is CVHB0000002\_071. I won't bring  
15 it up, but what Professor Bloom wrote there was that,  
16 and I quote:

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

25 Sir, we can see from those documents that

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

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

11 That variation was approved in March 1990. The  
12 references are MHRA0033386\_023, same stem \_021, and  
13 the CSM(B) report from Dr Rotblat and Mrs Sylvester is  
14 at MHRA0034913\_003. I don't think, sir, that I need  
15 to take you to any of those documents, or indeed to  
16 the data sheet, save to know that this application is  
17 being considered from October 1989 until March 1990.

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

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1 we return.

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

5 (3.09 pm)

(A short break)

7 (3.40 pm)

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

15 This is a note of a meeting held on  
16 13 November 1989. The meeting is of a body called the  
17 Inspection Action Group, which is within the DHSS. We  
18 can see a list of those who were present, Dr Fowler is  
19 one of those, Mr Sloggem, some other names that are  
20 familiar as well. If we go over to page 4 of this  
21 document, this is item 5 of that meeting, and what  
22 I propose to do, sir, is read this document through  
23 because it provides the background to this issue as  
24 well as the proposals for what should be done next.

25 This item is headed "Alpha Therapeutics

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

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

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1 new product had not been submitted. (Received since  
 2 the inspection report).  
 3 "The company's response to the 1989 inspection  
 4 remained unsatisfactory; the changes to procedures,  
 5 while an improvement, were mainly cosmetic and did not  
 6 address the main problems of a shared air-supply,  
 7 absence of air pressure barrier and the open handling  
 8 of treated and untreated Factor VIII powder in the  
 9 same room. The company acknowledged that the UK  
 10 product was inferior to that marketed in the US. The  
 11 Inspectorate recommended withdrawal of the [product  
 12 licence] for Profilate as the method used to produce  
 13 it did not ensure a virus-free product.

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

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

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

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

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

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

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

13 "Mr Sloggem (Principal Pharmaceutical Officer)  
 14 confirmed that there would be alternative supplies in  
 15 the near future. Two [product licence] applications  
 16 for Blood Products using the solvent detergent system,  
 17 Monoclate P were to be considered by the Committee for  
 18 the Safety of Medicines ... in November 1989, and were  
 19 expected to be approved. A Koate HS product licence  
 20 application was to be submitted to the Biological  
 21 Sub-Committee and CSM in January 1990. A clinical  
 22 trial exemption was in being for the new detergent  
 23 system. The variation application from Alpha for  
 24 Profilate which had been received in early November  
 25 1989, was to be submitted to the CSM, possibly in

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

I pause there to note, sir, that in a subsequent memorandum dated 23 November 1989, Mr Sloggem corrected some of the information contained in this paragraph, which he said didn't accurately reflect what he had said at the meeting. The reference for that is MHRA0033386\_019. I don't think I need to take you to that document.

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

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

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

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

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

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

"The Group agreed:

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

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

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

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

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within the DHSS] at all stages."

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

I won't take you to the inspection report from October 1989 but the reference for it is DHSC0002412\_093. That contains the detail of the point of concern that has been raised at this meeting. There was also some correspondence between Alpha and the DHSS in relation to that report, which can be found at DHSC0003567\_086 and \_087. Again, I won't take you to that now.

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

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

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

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

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

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

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

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

24 "Implementation.

25 "I note that it is said that supply branch and

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1 2 November that a number of steps have been instituted  
2 which appear at least partially to address the alleged  
3 critical deficiencies. Nothing is said in Mr Booth's  
4 minute about whether these steps are regarded as  
5 materially meeting the critical deficiencies, and if  
6 not, why not. Can we have further written comments  
7 from the Inspectorate and medical advice on this  
8 aspect urgently?"

9 Paragraph 4:

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

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

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

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

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

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

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

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

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

He then goes on to propose a further meeting and

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

Two memoranda were prepared in response to this, which I need not take you to, sir. They dealt with the ability of BPL and commercial providers to make up any shortfall. They can be summarised as showing that -- as saying there was an expectation that any shortfall could be met. Though it should be noted that Dr Rotblat, in a minute of 15 November 1989, cast some doubt on the availability of commercial product. The references are DHSC0001357, DHSC001350, and DHSC0002412\_074.

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

What it says is this:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

13 **MR HILL:** Yes, sir.

14 **SIR BRIAN LANGSTAFF:** Right.

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

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1 minister.

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

4 "Summary:

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

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

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

23 "Background. The product.

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

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

9 Go over to the next page, please:

10 "Inspections.

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

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

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

13 "Alternative process:

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

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

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

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

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

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1 could, at least for some months, meet the shortfall in  
 2 supply, though it is also likely that there will be  
 3 increased use of other commercial products, some not  
 4 yet licensed, and some may have a less good clinical  
 5 safety record than Profilate.  
 6 "14."  
 7 And the first sentence is emphasised and  
 8 underlined:  
 9 "However, the clinical record of heptane  
 10 treatment Profilate does not suggest that, on safety  
 11 grounds, the evidence is there to warrant immediate  
 12 suspension. Such action would give rise to  
 13 [underlined] great anxieties amongst the haemophiliac  
 14 community, a very high percentage of whom will have  
 15 used Profilate at some stage. It would not be  
 16 possible to assure them that the problem related only  
 17 to the recent production. Many would also currently  
 18 be using Profilate. There would be much attendant  
 19 publicity. Questions would be asked as to why, if  
 20 suspension is necessary now, the action was not taken  
 21 when our inspectors first became concerned in  
 22 February 1988, insofar as the deficiencies then found  
 23 have not fundamentally changed."  
 24 "No immediate suspension would provide the  
 25 company with time to exercise their right of appeal

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1 before the decision becomes public and took effect."  
 2 There is a footnote which explains that the  
 3 company would have a right under the Medicines Act --  
 4 go down to the bottom, please, Soumik, thank you:  
 5 "The company would have a right under the  
 6 Medicines Act to make representations to a 'person  
 7 appointed' by the Licensing Authority. These are  
 8 formal hearings in private, followed by a report of  
 9 the proceedings to the Licensing Authority. The  
 10 hearing would be in private unless the company wished  
 11 otherwise. The report is private."  
 12 Going back to the main body of the text.  
 13 "This appeal would probably be in private but  
 14 knowledge of it could become public."  
 15 **SIR BRIAN LANGSTAFF:** Just stop there for a moment. We've  
 16 got a highlighted box, which shouldn't be highlighted,  
 17 I think, should it?  
 18 **MR HILL:** It is, sir. If we see the footnote, that is the  
 19 footnote to which I just took you, which explained  
 20 that about the right of appeal.  
 21 **SIR BRIAN LANGSTAFF:** I see, right.  
 22 **MR HILL:** Then back to paragraph 15, and "This appeal" --  
 23 **SIR BRIAN LANGSTAFF:** Very well.  
 24 **MR HILL:** -- picking it up from there:  
 25 "This appeal would probably be in private but

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1 colleagues and the Procurement Directorate, have  
 2 considered the issues.  
 3 "As noted above, they have concluded that,  
 4 whilst the process deficiencies revealed by the  
 5 Inspectorate are a cause of concern, the clinical  
 6 record of heptane treatment Profilate does not suggest  
 7 that these apparently long-standing deficiencies are  
 8 such as to warrant immediate regulatory action against  
 9 the product.  
 10 "They concluded that a better alternative would  
 11 be to open discussions with the company with a view to  
 12 securing early withdrawal of heptane treatment  
 13 Profilate, plus action to speed up consideration of  
 14 the company's application to vary its Profilate  
 15 licence so as to market the newer version of the  
 16 product now sold in the US.  
 17 "MS(H) is invited to note these conclusions and  
 18 to say whether she endorses them."  
 19 That is from Mr Wilson, the date of that  
 20 document is not -- sorry, 24 November 1989. The  
 21 response from the Minister is at DHSC0001366. It is  
 22 dated 6 December 1989, and sent to Mr Wilson from the  
 23 Minister's Private Office. It says:  
 24 "Thank you for your submission of 24 November.  
 25 Mrs Bottomley has considered this and is not happy

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1 knowledge of it could become public. The final  
 2 decision whether or not to confirm the suspension  
 3 would be for Ministers as the Licensing Authority. If  
 4 the product were suspended following an appeal, the  
 5 attendant publicity might be less than with immediate  
 6 suspension but the difficulties could be of the same  
 7 order with questions also as to why, if there were  
 8 safety concerns, action had not been taken earlier.  
 9 "Alternatives to regulatory action  
 10 "The company is known to want to switch  
 11 production for the UK market to its new process. It  
 12 cannot market Profilate made by this process in the UK  
 13 until its product licence has been varied. However,  
 14 it is possible that the company could be persuaded to  
 15 begin withdrawal of the heptane treatment Profilate  
 16 ahead of marketing of the new process product here,  
 17 for commercial reasons. Whilst not making any deal  
 18 with the company we could also expedite processing the  
 19 application to vary the UK licence (though it may take  
 20 some months even so). The company might be helped in  
 21 reaching its decision if they believe that regulatory  
 22 action might be taken against their licence if they do  
 23 not act voluntarily."  
 24 "Conclusions  
 25 "MCA and HS1, with their medical and legal

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1 with the line proposed. She would prefer regulatory  
 2 action to be taken and would welcome advice on the  
 3 consequences of this."  
 4 The response from Mr Wilson comes in a document  
 5 of 15 December 1989, which is at DHSC0001375. We can  
 6 see again copied to a large number of individuals  
 7 including Dr Metters, the Deputy Chief Medical  
 8 Officer, and the Minister of State for Health's  
 9 private office.  
 10 What Mr Wilson says is this:  
 11 "[The Minister of State] has indicated, via your  
 12 minute of 6 December, that she would prefer  
 13 'regulatory action' to be taken against the  
 14 Factor VIII product PROFILATE. This was in response  
 15 to my submission dated 24 November. She asked for  
 16 a note on the consequence of such action. Advice to  
 17 that end is set out in the Annex.  
 18 "Briefly, regulatory action could involve  
 19 "a. Immediate suspension of the product  
 20 licensing for which we have to be satisfied that this  
 21 is necessary in the interests of safety;  
 22 "[or] b. A proposal to suspend, giving the  
 23 company appeal rights provided they give notice within  
 24 28 days. Any suspension would not then take effect  
 25 until the appeal rights had been exhausted, which

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could take several months.

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

"Immediate Suspension

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

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

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

"Proposal to Suspend

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

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

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

"Conclusion

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

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

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

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

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

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

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

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

I quote from the document:

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

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1 problem was a new one. Attention might rapidly switch  
2 to that issue with accusations of negligence by the  
3 Licensing Authority. It would be possible partially  
4 to answer this by reference to the fact that when our  
5 Inspectors first identified the deficiencies  
6 (February 1988) the BPL could not have made up the  
7 then considerably bigger share of the UK market held  
8 by PROFILATE and that we could not be confident that  
9 more acceptable products would have been available.  
10 Clinicians could have chosen, on a named-patient  
11 basis, to prescribe products without a UK licence,  
12 with a possibly greater risk than PROFILATE. But that  
13 response would in turn raise concerns about other  
14 products and would be an admission that we had  
15 regarded the product as potentially unsafe for nearly  
16 2 years.

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

20 It goes on to discuss the consequences for the  
21 company.

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

25 "if the company, facing suspension, decided to

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1 publicise the matter.

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

5 Those are the annexes to the submission of  
6 15 December.

7 The supply to that submission came on  
8 19 January 1990. Could we have on screen, please,  
9 DHSC0001374, sent to Mr Wilson. Again, sent to a  
10 number of others as well, from the Minister of State's  
11 Private Office. The decision is this:

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

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

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

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

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

15 The consequences for the Licensing Authority of  
16 not suspending immediately:

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

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

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1 respect of Profilate Heat-Treated:

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

4 Sir, it's MHRA0033386\_009. Apologies, Soumik.  
5 I should have said that. Sir, this is the letter that  
6 the company sends to the Committee on Safety of  
7 Medicines:

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

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

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

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

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1 that the new facility for the manufacture of Profilate  
 2 Solvent Detergent method, Profilate SD, had been  
 3 inspected and found to be acceptable. The reference  
 4 to that is MHRA0033382\_007.  
 5 That, sir, concludes the section on the  
 6 consideration of the suspension of the Profilate HT  
 7 licence. The outcome appears to be that the company  
 8 was warned that there was a proposal to suspend and,  
 9 in response to that warning, the company voluntarily  
 10 agreed not to import any further products into the UK.  
 11 I note the time, sir. We have left a very short  
 12 section on Factor IX and then a slightly longer  
 13 section on the donors used by Abbott and Alpha.  
 14 I suspect that you may wish to return to that  
 15 tomorrow.  
 16 **SIR BRIAN LANGSTAFF:** Well, you certainly don't have time  
 17 to present that tonight. Not least because it's now  
 18 4.35.  
 19 So we'll take a break until ten o'clock tomorrow  
 20 when you can continue and deal with the -- those two  
 21 remaining matters, at least those matters that remain  
 22 for the moment, in respect of Abbott Alpha. So  
 23 10 o'clock tomorrow.  
 24 **(4.35 pm)**  
 25 **(The hearing adjourned until 10.00 am the following day)**

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[1]</b> 103/1 <b>028 [1]</b> 114/18 <b>029 [2]</b> 92/2 101/9 <b>033 [1]</b> 101/8 <b>034 [2]</b> 5/15 21/7 <b>047 [1]</b> 98/12 <b>049 [1]</b> 118/24 <b>050 [1]</b> 119/2 <b>055 [1]</b> 90/14 <b>059 [1]</b> 116/8 <b>060 [1]</b> 87/10 <b>070 [1]</b> 114/6 <b>071 [1]</b> 130/14 <b>074 [1]</b> 146/13 <b>085 [1]</b> 74/11 <b>086 [1]</b> 140/11 <b>087 [1]</b> 140/11 <b>093 [2]</b> 44/21 140/7  <b>1</b> <b>1 February [1]</b> 109/23 <b>1 October [1]</b> 97/25	<b>1,688 [1]</b> 24/18 <b>1.02 [1]</b> 91/19 <b>1.1 [1]</b> 77/16 <b>1.2 [2]</b> 77/20 81/6 <b>1.3 [1]</b> 57/14 <b>1.32 million [1]</b> 24/13 <b>1.5 [1]</b> 57/16 <b>1.5 million [2]</b> 40/2 75/12 <b>1.5.1 [1]</b> 81/7 <b>1.6 million [1]</b> 75/23 <b>1.65 million [1]</b> 75/9 <b>1.9 million [2]</b> 75/10 75/25 <b>10 [4]</b> 91/4 105/2 137/19 139/20 <b>10 December 1974 [1]</b> 61/5 <b>10 o'clock [1]</b> 169/23 <b>10 September 1979</b> <b>[1]</b> 74/19 <b>10-fold [1]</b> 22/13 <b>10.00 [2]</b> 1/2 169/25 <b>100 [6]</b> 82/4 82/5 121/4 122/15 123/10 125/17 <b>101 [1]</b> 17/10 <b>102 [1]</b> 80/1 <b>104 [1]</b> 81/13 <b>105 [1]</b> 81/21 <b>106 [1]</b> 83/16 <b>10p [3]</b> 40/1 69/5 74/3 <b>11 [4]</b> 59/18 126/4 137/19 139/20 <b>11 January 1990 [1]</b> 168/25 <b>11 March 1976 [1]</b> 65/12 <b>11.13 [1]</b> 45/13 <b>11.45 [1]</b> 45/15 <b>113 [1]</b> 116/3 <b>118 [1]</b> 73/13 <b>12 [3]</b> 45/12 45/12 114/16 <b>12 March [1]</b> 108/23 <b>12 months [1]</b> 73/18 <b>12p [4]</b> 69/4 74/1 74/2 74/10 <b>13 [2]</b> 2/11 137/21 <b>13 March 1985 [1]</b> 105/21 <b>13 November [1]</b> 141/5 <b>13 November 1989 [1]</b> 132/16 <b>13,200 [1]</b> 12/4 <b>14 [4]</b> 61/13 68/2 105/1 156/6 <b>14 November 1989 [1]</b> 140/13 <b>14.6 million [1]</b> 75/14 <b>144 [1]</b> 33/21	<b>14p [1]</b> 113/24 <b>15 [4]</b> 42/12 90/19 105/1 157/22 <b>15 December [2]</b> 167/6 167/12 <b>15 December 1989 [2]</b> 160/5 163/25 <b>15 January 1987 [1]</b> 117/9 <b>15 November [1]</b> 149/12 <b>15 November 1989 [1]</b> 146/10 <b>150,000 [1]</b> 39/25 <b>16 [3]</b> 61/13 92/2 116/9 <b>16 February 1983 [2]</b> 25/6 27/6 <b>16.5 million [1]</b> 75/13 <b>16.88 million [1]</b> 24/22 <b>168 [1]</b> 50/13 <b>16p [3]</b> 39/16 39/25 110/13 <b>16th [1]</b> 103/7 <b>17 [1]</b> 31/3 <b>17 January 1985 [1]</b> 102/25 <b>17-28 [1]</b> 123/4 <b>171 [1]</b> 74/18 <b>172 [1]</b> 49/14 <b>18 [7]</b> 35/17 104/4 112/19 113/6 122/4 122/16 123/9 <b>18 March 1986 [2]</b> 108/18 110/16 <b>18 years [1]</b> 81/18 <b>18-month [1]</b> 35/9 <b>1888 [1]</b> 48/18 <b>19 [1]</b> 33/20 <b>19 February 1985 [1]</b> 104/23 <b>19 January 1990 [1]</b> 167/8 <b>1907 [1]</b> 48/21 <b>1915 [1]</b> 48/20 <b>1937 [1]</b> 48/22 <b>1949 [1]</b> 48/23 <b>1964 [1]</b> 66/6 <b>1970s [7]</b> 5/4 45/25 48/13 51/18 52/14 76/13 97/9 <b>1970s/early [1]</b> 96/18 <b>1971 [1]</b> 56/21 <b>1973 [6]</b> 4/12 53/17 53/24 54/7 55/22 58/6 <b>1974 [7]</b> 57/1 57/3 57/7 57/11 57/12 61/5 62/24 <b>1975 [6]</b> 4/24 53/12 62/19 63/7 63/11 63/20	<b>1976 [11]</b> 63/9 63/12 63/17 65/3 65/5 65/12 66/19 73/10 73/16 73/18 79/14 <b>1977 [3]</b> 44/22 50/15 74/9 <b>1978 [9]</b> 5/6 5/21 46/5 46/7 49/3 51/25 64/25 74/12 74/17 <b>1979 [7]</b> 6/8 6/17 7/2 44/22 50/4 74/19 98/20 <b>1980 [14]</b> 2/7 2/11 2/20 2/21 7/4 7/7 8/22 23/17 75/1 75/5 75/9 75/11 75/13 75/24 <b>1980s [8]</b> 46/1 47/21 48/14 50/23 52/25 96/18 98/22 131/2 <b>1981 [22]</b> 1/16 1/23 2/13 2/16 2/22 3/2 3/3 10/14 10/21 12/22 13/3 14/9 14/16 17/9 49/20 52/9 75/5 75/12 75/14 75/25 76/17 77/1 <b>1982 [19]</b> 18/14 20/14 21/11 23/12 23/14 23/19 24/4 43/3 76/3 77/4 79/19 79/20 80/20 80/23 89/10 89/13 94/11 94/12 95/9 <b>1983 [18]</b> 24/11 25/6 27/6 27/12 27/20 29/9 40/18 40/22 77/6 80/22 87/13 89/4 89/8 89/11 90/1 90/6 91/11 93/20 <b>1984 [19]</b> 28/20 38/20 39/5 39/9 40/19 47/6 48/1 48/19 93/21 94/15 94/17 97/22 98/5 98/10 99/6 99/11 101/3 123/14 124/3 <b>1984/5 [1]</b> 98/25 <b>1984/85 [1]</b> 127/3 <b>1985 [29]</b> 48/2 93/21 96/1 99/3 101/6 102/25 103/3 104/23 105/2 105/21 107/24 108/7 111/20 113/16 113/18 114/1 114/7 114/16 115/6 115/11 115/22 122/3 123/7 123/14 124/3 127/12 127/14 151/2 152/2 <b>1986 [8]</b> 42/8 42/17 108/18 109/23 110/16 116/6 116/9 117/8 <b>1987 [5]</b> 43/11 117/9 118/21 119/5 122/5	<b>1988 [15]</b> 49/22 99/23 100/21 129/22 133/11 134/14 138/5 141/14 141/23 145/20 145/21 145/24 151/11 156/22 165/6 <b>1989 [26]</b> 44/12 47/12 75/9 98/12 98/18 130/5 131/6 131/17 132/11 132/16 133/5 134/21 135/3 136/18 136/25 137/6 140/6 140/13 146/10 149/18 152/7 159/20 159/22 160/5 163/25 168/11 <b>1990 [9]</b> 47/13 130/11 131/11 131/17 136/21 137/1 167/8 167/21 168/25 <b>1990s [1]</b> 52/25 <b>1994 [1]</b> 50/7 <b>1998 [1]</b> 50/20  <b>2</b> <b>2 February 2021 [2]</b> 76/7 94/7 <b>2 November [2]</b> 142/1 147/10 <b>2 November 1984 [1]</b> 40/19 <b>2 times [1]</b> 120/12 <b>2 years [1]</b> 165/16 <b>2,000 [1]</b> 164/15 <b>2,200 [1]</b> 12/3 <b>2,720 [1]</b> 11/25 <b>2-8 degrees [1]</b> 60/12 <b>2.0 [1]</b> 11/21 <b>2.00 [1]</b> 91/21 <b>2.1 [1]</b> 77/25 <b>2.5 million [1]</b> 107/25 <b>2/9 [1]</b> 122/20 <b>20 [7]</b> 33/25 36/16 108/12 115/11 125/24 151/4 155/8 <b>20 hours [3]</b> 91/24 93/1 102/12 <b>20 June 1981 [1]</b> 14/16 <b>20 March 1981 [1]</b> 2/16 <b>20 million [1]</b> 90/19 <b>20 October 1982 [1]</b> 80/20 <b>200 [3]</b> 82/3 86/16 86/16 <b>2000 [1]</b> 52/12 <b>2002 [1]</b> 51/1 <b>2003 [2]</b> 51/6 53/2 <b>2021 [4]</b> 1/1 76/7 94/7 96/10 <b>20p/unit [1]</b> 41/23 <b>20th [1]</b> 58/6
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(44) MR HILL: - 20th

F:



<b>2</b>	<b>2p</b> [1] 114/24	<b>5,000</b> [1] 124/1	45/17 45/22 46/4	167/15	138/6
<b>21</b> [2] 5/7 16/3	<b>3</b>	<b>5,000-32,000</b> [1] 112/15	46/12 46/17 48/17	<b>acceptable</b> [7] 36/7	<b>activity</b> [6] 9/8 66/11
<b>21 December 1976</b> [1] 73/16	<b>3 December 1984</b> [1] 28/20	<b>5.2 million</b> [1] 74/1	48/18 48/20 48/22	65/23 72/10 115/5	66/14 68/11 70/1
<b>21 January 1981</b> [1] 2/13	<b>3 January 1985</b> [1] 101/6	<b>50</b> [3] 39/22 81/18	49/3 49/13 51/12	137/4 165/9 169/3	<b>76/14</b>
<b>21 October 1982</b> [1] 23/19	<b>3 June 1989</b> [1] 98/18	<b>5000-32</b> [1] 123/22	51/13 51/14 51/17	<b>acceptance</b> [1] 33/15	<b>actually</b> [11] 9/1 24/9
<b>211</b> [1] 122/6	<b>3 years</b> [1] 13/16	<b>520</b> [1] 2/14	51/19 51/24 53/25	<b>accepted</b> [3] 61/20	27/25 61/15 75/7
<b>216</b> [1] 15/23	<b>3.09</b> [1] 132/5	<b>54</b> [1] 18/5	54/9 54/20 57/3 57/15	62/23 138/9	77/19 93/24 105/24
<b>22</b> [4] 38/20 63/7	<b>3.25</b> [1] 120/20	<b>55</b> [1] 18/6	57/17 58/5 58/15	<b>accepting</b> [1] 62/20	108/5 120/23 142/25
122/20 124/20	<b>3.40</b> [2] 132/4 132/7	<b>6</b>	61/11 61/17 61/22	<b>accessible</b> [1] 24/16	<b>acute</b> [5] 31/2 111/24
<b>22 May 1975</b> [1] 63/11	<b>30</b> [2] 135/24 136/1	<b>6 December</b> [1] 160/12	62/2 62/10 62/14	<b>accompanies</b> [1] 70/13	113/1 113/4 124/9
<b>22 May 1980</b> [1] 75/1	<b>30 August 1982</b> [1] 77/4	<b>6 December 1989</b> [1] 159/22	62/15 62/23 63/4 63/8	<b>accompanying</b> [2] 70/22 103/8	<b>added</b> [5] 62/5 71/20
<b>22 October</b> [1] 18/4	<b>30 January</b> [1] 130/11	<b>6 hours</b> [1] 12/3	63/17 74/13 74/15	<b>accomplished</b> [1] 76/15	72/1 94/20 138/3
<b>23</b> [1] 77/13	<b>30 January 1976</b> [1] 63/9	<b>6 July 2021</b> [1] 96/10	75/6 169/13 169/22	<b>accordance</b> [1] 147/1	<b>addition</b> [8] 32/8
<b>23 August 1974</b> [1] 57/12	<b>30 July 1980</b> [1] 7/7	<b>6-10 October 1989</b> [1] 133/5	<b>Abbott's</b> [2] 48/24	<b>according</b> [3] 61/7	76/10 76/11 94/22
<b>23 December</b> [1] 3/10	<b>30 July 1987</b> [1] 118/21	<b>60</b> [6] 8/19 10/9 40/8	74/20	50/14 115/16	96/22 114/22 134/25
<b>23 December 1980</b> [1] 2/11	<b>30%-50</b> [1] 39/22	92/25 125/16 125/23	<b>ability</b> [1] 146/6	<b>accordingly</b> [2] 153/18 163/19	139/11
<b>23 March 1984</b> [1] 38/20	<b>30-72</b> [1] 125/16	<b>60 degrees</b> [2] 91/24	<b>able</b> [2] 99/7 161/19	<b>account</b> [2] 161/9	<b>address</b> [3] 29/8
<b>23 November 1989</b> [1] 137/6	<b>31 August 1985</b> [1] 107/24	<b>615,000</b> [1] 75/11	<b>abnormal</b> [2] 155/13	163/10	135/6 142/2
<b>230</b> [1] 115/21	<b>31 July 1974</b> [1] 57/1	<b>67</b> [1] 122/5	162/7	<b>accountant's</b> [1] 1/21	<b>addressed</b> [1] 138/12
<b>238</b> [1] 20/13	<b>31 October 1976</b> [1] 73/18	<b>7</b>	124/11 124/13 124/16	<b>accurately</b> [2] 55/6	<b>addresses</b> [1] 52/13
<b>24</b> [1] 21/11	<b>31 October 1980</b> [2] 2/7 8/22	<b>7 December 1979</b> [2] 6/17 7/2	12/11 1/11 1/18	137/8	<b>adequate</b> [6] 16/24
<b>24 January 1981</b> [2] 10/14 10/21	<b>32</b> [1] 123/22	<b>7 March 1973</b> [1] 54/7	4/7 4/8 4/11 8/4 8/24	<b>accusations</b> [1] 165/2	37/14 66/25 68/22
<b>24 June 1937</b> [1] 48/22	<b>32,000</b> [2] 112/15	<b>7 years</b> [1] 81/18	13/4 17/13 20/7 21/10	<b>achieve</b> [1] 40/3	130/13 137/23
<b>24 March 1983</b> [1] 87/13	<b>34</b> [1] 15/21	<b>7.1</b> [1] 58/17	22/9 22/23 23/12	<b>achieved</b> [2] 47/5	<b>adequately</b> [1] 9/11
<b>24 November</b> [3] 149/15 159/24 160/15	<b>36 hours</b> [1] 12/4	<b>70</b> [2] 135/23 151/3	23/20 24/17 25/8	133/22	<b>adhere</b> [1] 104/24
<b>24 November 1989</b> [2] 149/18 159/20	<b>37</b> [1] 60/3	<b>72</b> [1] 125/16	27/13 28/7 28/14	<b>acknowledged</b> [1] 135/9	<b>adjoined</b> [1] 169/25
<b>25</b> [1] 108/12	<b>383,000</b> [1] 74/3	<b>735</b> [1] 49/24	28/23 33/7 39/14	<b>acquired</b> [5] 19/6	<b>adjournment</b> [1] 91/20
<b>25 January</b> [1] 161/22	<b>4</b>	<b>735,000</b> [1] 108/2	40/12 41/11 43/8 45/5	49/11 53/2 106/5	<b>administer</b> [1] 64/21
<b>250 millilitres</b> [1] 72/2	<b>4 degrees</b> [1] 42/11	<b>736</b> [1] 49/24	45/6 45/8 45/22 46/16	107/3	<b>administered</b> [3] 15/9
<b>26 January 1990</b> [1] 167/21	<b>4 million</b> [1] 74/2	<b>76</b> [1] 122/2	46/17 46/25 51/8 51/8	<b>acquiring</b> [2] 69/11	55/1 55/7
<b>26 November 1982</b> [1] 24/4	<b>4 November 1982</b> [1] 80/23	<b>78</b> [1] 11/21	53/7 56/22 60/6 63/24	70/12	<b>administration</b> [5]
<b>27</b> [2] 5/8 16/1	<b>4 times</b> [1] 41/22	<b>8</b>	67/23 70/24 74/1 74/2	<b>act</b> [6] 137/19 139/21	55/11 58/11 63/25
<b>27 March 1982</b> [1] 18/14	<b>4.35</b> [2] 169/18 169/24	<b>8 January 1985</b> [1] 103/3	74/3 75/9 76/24 79/10	157/3 157/6 158/23	64/14 113/12
<b>270</b> [1] 2/8	<b>40</b> [4] 5/7 97/24	<b>8 million</b> [1] 90/21	81/14 82/24 84/9	167/15	<b>administration'</b> [1] 58/22
<b>273</b> [1] 40/22	<b>40-week</b> [1] 124/12	<b>80</b> [2] 135/17 136/1	85/15 85/25 87/2 87/6	<b>acted</b> [2] 52/8 167/20	<b>admission</b> [1] 165/14
<b>28</b> [8] 122/18 123/4	<b>40p</b> [1] 40/9	<b>84-100</b> [1] 125/17	87/11 88/24 88/25	<b>action</b> [47] 115/5	<b>admitted</b> [4] 11/9
124/8 137/20 142/11	<b>42</b> [1] 112/21	<b>85</b> [1] 127/3	89/5 89/14 89/22 94/7	132/17 137/13 137/20	112/20 123/13 138/3
142/12 143/22 160/24	<b>42 years</b> [1] 52/2	<b>86</b> [1] 44/14	95/15 96/2 97/18 98/7	138/5 138/16 138/24	<b>adopted</b> [2] 76/12
<b>28 days</b> [1] 163/6	<b>45</b> [1] 35/10	<b>8p</b> [2] 73/21 74/1	102/20 103/2 103/5	139/14 141/6 141/8	100/15
<b>28 November 1985</b> [1] 111/20	<b>48</b> [1] 20/13	<b>8Y</b> [4] 115/10 130/1	103/21 104/17 106/1	141/9 141/12 141/17	<b>adrenalin</b> [1] 22/18
<b>2805</b> [2] 2/12 3/13	<b>4802</b> [2] 2/6 3/8	<b>9</b>	106/25 108/2 109/2	142/11 143/19 144/19	<b>Adrenaline</b> [1] 30/25
<b>282</b> [1] 10/21	<b>5</b>	<b>9 million</b> [1] 90/21	109/2 110/16 110/24	145/7 145/12 145/14	<b>adult</b> [1] 71/18
<b>29 November 1983</b> [2] 27/20 29/9	<b>5 million</b> [2] 90/5	<b>9.1</b> [1] 59/9	111/9 114/20 118/23	145/19 145/20 149/1	<b>advance</b> [2] 3/6 16/18
<b>297</b> [1] 35/11	<b>5 October 2021</b> [1] 1/1	<b>A</b>	120/19 120/21 121/23	155/15 155/23 156/12	<b>advanced</b> [1] 144/25
	<b>5 years</b> [1] 13/16	<b>A, [4]</b> 109/18 125/17	124/8 125/12 131/19	156/20 158/8 158/9	<b>advantage</b> [2] 37/25
		131/3 154/6	131/21 131/22 135/23	158/22 159/8 159/13	43/21
		<b>abandoned</b> [1] 12/13	139/1 140/15 142/4	160/2 160/16 160/18	<b>advantages</b> [5] 31/19
		<b>Abbott</b> [43] 1/9 45/9	145/6 149/5 151/3	161/16 162/11 163/2	38/8 38/14 55/22
			151/4 153/12 157/20	163/7 163/18 163/22	65/18
			161/12 164/20 165/13	164/21 164/24 167/3	<b>advent</b> [1] 98/24
			<b>above</b> [6] 78/15	167/19	<b>adverse</b> [8] 17/18
			111/16 159/3 163/22	<b>action'</b> [1] 160/13	20/24 36/6 38/18
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