

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 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 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 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

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

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

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

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.

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

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

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

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 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 haemophilic 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 [anamneasic] response ..."

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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 **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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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 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:RAG)
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 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 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

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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 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 **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

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:

31

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

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

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

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

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

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

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

17 Over to the next page, please.

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

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

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

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

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

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

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

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

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

15 He says:

16 "Eighteen months ago, Hyate:C was priced at 16p
 17 per unit to UK and European hospitals. The previous
 18 management considered that a low price in comparison
 19 with the two competitive products FEIBA and Autoplex
 20 was appropriate. This policy was a disaster. When
 21 distributors are employed, then any price to hospitals
 22 has to be discounted by 30%-50% to arrive at the net
 23 return to Speywood. The company's operating expenses,
 24 with the utmost economy, are unlikely to be less than
 25 £150,000 per month. It follows, therefore, that a 16p

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

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

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

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

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

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

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

41

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 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.

42

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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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)

(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 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 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 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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1 Scientific Products Division and those products, of
 2 course, included Profilate.
 3 In August 1978, Abbott US, the American company,
 4 sold the Scientific Products Division to the newly
 5 formed Alpha Therapeutic Corporation. This is the
 6 American company and I will, at points, refer to it as
 7 "Alpha US". Alpha US was, at that time, owned by the
 8 Green Cross Corporation of Japan. In a letter
 9 explaining the position to customers, regulators and
 10 other interested parties, it was stated that Alpha US
 11 had acquired, and I quote, "all the personnel,
 12 premises, plant and knowhow and expertise of the
 13 former Abbott division". So that's the Scientific
 14 Products Division. That's DHSC002197_172.
 15 The Krever Report described Alpha Therapeutic
 16 Corporation as follows, this is the US company, and
 17 I quote:
 18 "Alpha, owned by the Japanese pharmaceutical
 19 company Green Cross, is one of the major producers of
 20 blood products in the world. In 1981 it sold more
 21 than US\$10 million worth of products in the
 22 United States. By 1988, this figure had increased to
 23 US\$38 million."
 24 That's pages 735 and 736 of the Krever Report.
 25 Initially, the British operations of Alpha US

1 seemed to have been in the hands of a German company
 2 called Alpha Therapeutic GmbH. However, a UK
 3 subsidiary, Alpha Therapeutic Limited, was established
 4 in 1979. And again, the clue is the use of the word
 5 "Limited" indicating the UK company, as opposed to the
 6 US or German company.
 7 1994 company filings, which are available at
 8 Companies House, record that the UK subsidiary was
 9 wholly owned by Alpha US, and that the ultimate
 10 holding company was the Green Cross Corporation. So
 11 Green Cross sits at the top, then Alpha US, then the
 12 UK subsidiary.
 13 A further reference is DHSC0002197_168.
 14 According to records held the Companies House in
 15 1977 a Spanish company, Grupo Grifols SA, purchased
 16 a majority shareholding in the British subsidiary,
 17 Alpha Therapeutic limited and became its holding
 18 company, though Green Cross continued to be listed as
 19 the ultimate holding company. The UK company's name
 20 was changed to Grifols (UK) Limited in 1998.
 21 Now the corporate links between Grifols, Green
 22 Cross and Alpha, on an international level, date back
 23 to the 1980s. They can be explored further if
 24 required, but for today's purposes I don't think
 25 that's going to help us.

1 In December 2002, Alpha US sold various assets
 2 to Baxter Healthcare Corporation. What remained of
 3 Alpha was by then owned by a company called Mitsubishi
 4 Pharma Corporation, rather than Green Cross. That
 5 sold some of those remaining assets to the Spanish
 6 company Grifols in July 2003.
 7 Now, the Inquiry has evidence from two witnesses
 8 about the corporate structure and about the
 9 limitations on disclosure that that has resulted in.
 10 The first is Kevin Gogay, he is the UK and Ireland
 11 finance director of an existing UK company called
 12 Abbott Laboratories Limited; which is an affiliate of
 13 Abbott, which is still headquartered in Chicago. So
 14 Abbott, as you'll recall, was the first company to
 15 produce Profilate.
 16 That statement provides an overview of the
 17 corporate relations between Abbott and Alpha in the
 18 1970s, and he also states that the existing UK
 19 company, Abbott Laboratories Limited, had conducted
 20 searches in response to requests from the Inquiry, and
 21 believes that it doesn't hold or control any relevant
 22 documents relating to Profilate.
 23 Mr Gogay pointed in particular to the sale of
 24 the Scientific Products Division of Abbott to Alpha in
 25 1978. He says the then existing books and records

1 relating to the business were sold at the same time,
 2 and that was obviously some 42 years ago.
 3 Further details are contained in the statement,
 4 which is at WITN4130001.
 5 The second witness statement, or series of
 6 statements, is from David Bell. Now, Mr Bell gives
 7 statements with different hats on, as it were. He
 8 acted as an external lawyer for Alpha Therapeutic
 9 Corporation, the US company, from 1981, including as
 10 lead counsel in the US HIV litigation, and he joined
 11 the company for around two-and-a-half years from
 12 October 2000. So one of Mr Bell's statements
 13 addresses the activities of Alpha and its predecessors
 14 from the 1970s, based on, as he put it,
 15 "non-confidential information that is in the public
 16 domain". It should be noted and remembered that
 17 Mr Bell, as a lawyer, is bound by rules of
 18 professional privilege, which meant that he can't
 19 disclose privileged information without being given
 20 permission by his client.
 21 Mr Bell also provided a letter as general
 22 counsel and chief innovation officer at Grifols. This
 23 dealt with issues concerning the way in which
 24 different parts of Alpha were divested during the
 25 1980s and the 1990s. I won't go into the details but

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)

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

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

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

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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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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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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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

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."

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.

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."

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

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

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,

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.

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, Profilate 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

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

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

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

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

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

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

1 year.

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

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

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

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

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

24 "The advent of heat-treated concentrates in
 25 1984/5 to combat the threat of hepatitis and AIDS was

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

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

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

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

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

6 Back to another quote from Mr Marshall:

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

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

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

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

1 both PFC and BPL, would have been widely used as well.
 2 As we have heard from previous presentations,
 3 the DHSS, as of November 1984, encouraged other
 4 companies to apply for product licences for
 5 heat-treated products, and Alpha Therapeutics UK did
 6 so on 3 January 1985. We have looked at the
 7 manufacturing process from that application. The
 8 references are MHRA0033388_033, and the same stem
 9 _029. The application was signed by Ian Marshall and
 10 the applicant was Alpha Therapeutics UK. So the UK
 11 company rather than the German company.

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

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

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

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

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

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

1 donor products should be preferentially utilised
 2 whenever feasible."

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

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

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

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

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

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

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

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

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

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

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 Antihæmophilic 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

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

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

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

13 So product information on that study.

14 "Hepatitis:

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

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

22 "A full report with patient data collated up to
23 1 February 1986 is available from clinical trial
24 coordinator Dr Kernoff."

25 Underlined is the following comment, and I

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

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

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

20 And the letter from 28 November 1985 states
21 this:

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

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1 quote:

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

8 Then it says:

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

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

15 I stress, sir, that this letter is
16 18 March 1986, so we have progressed about a year in
17 time where those additional donor screening tests have
18 been taken. But the importance is the claim that the
19 product has been shown to make significant reductions
20 in NANB hepatitis as well as inactivating AIDS.

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

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

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

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

24 "None of the patients [halfway through the
25 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."

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

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

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

1 new:
 2 "The incidence of post-infusion non-A, non-B
 3 hepatitis in patients receiving a first exposure to
 4 unheated and Factor VIII concentrates approaches 100%.
 5 In contrast Profilate Heat Treated has been shown to
 6 be effective in reducing the risk of transmission of
 7 non-A, non-B hepatitis."
 8 Various references are given to literature in
 9 support of that. In bold, and I quote:
 10 "However, testing methods presently available
 11 are not sensitive enough to detect all units of
 12 potentially infectious plasma and treatment methods
 13 have not been shown to be totally effective in
 14 eliminating viral infectivity from this product.
 15 Despite all precautions taken by the manufacturer it
 16 cannot be assumed that this product is totally free of
 17 HIV or hepatitis virus. As with all drugs the risks
 18 associated with use must be weighed against the
 19 benefits of therapy."
 20 So sir, the warning against hepatitis infection
 21 and AIDS infection remains -- or HIV infection
 22 remains.
 23 Among the new information about NANB infection
 24 that was provided with this product application was
 25 a paper by Drs Kernoff, Savidge and others, which is

1 levels. A resulting high level of viral contamination
 2 in this batch may have been sufficient to overwrite
 3 the effects of the sterilisation process. All
 4 patients remained anti-HIV seronegative at 17-28
 5 months of follow-up."
 6 So, sir, I note there is one additional patient
 7 from The Lancet letter in September 1985 who has now
 8 been identified as having been infected by NANB, but
 9 it is still 5 of 18 patients, as opposed to the usual
 10 100% of patients.
 11 If we could just go down on that page to the
 12 "Patients and Methods" section. It states that:
 13 "The patients were admitted to the study between
 14 September 1984 and August 1985, and followed for at
 15 least 40 weeks ..."
 16 If we could go over to the next page, please.
 17 The second paragraph down, this refers to the product
 18 used. It says, and I quote:
 19 "Factor VIII concentrate was bought from Alpha
 20 Therapeutics UK Limited and had been manufactured from
 21 US-derived commercial plasma pools obtained from
 22 approximately 5000-32 000 donations, none of which had
 23 been screened for ALT or anti-HIV. Nine different
 24 batches of concentrate were used."
 25 I pause there, sir, to note, again, that figure

1 worth looking at for a number of reasons, and it's
 2 NHBT0042403, tab 76. You well recall, sir, that the
 3 letter to The Lancet gave evidence in September 1985
 4 of a study of 18 patients, and this paper, in the
 5 British Journal of Haematology, 1987, volume 67,
 6 pages 207-211 takes that study forward.
 7 I'll try again NHBT0042403, thank you. The
 8 study is entitled "Reduced risk of non-A, non-B
 9 hepatitis after a first exposure to 'wet heated'
 10 factor VIII concentrate".
 11 The summary states this, and I quote:
 12 "The risk of post-infusion non-A, non-B
 13 hepatitis ... in patients receiving a first exposure
 14 to unheated or conventionally 'dry heated' factor VIII
 15 concentrates approaches 100%, implying invariable
 16 contamination of these products. Amongst 18 patients
 17 who received a first treatment with a 'wet heated'
 18 concentrate, five (28%) developed asymptomatic NANBH,
 19 suggesting a more sufficient inactivation of NANBH
 20 agent(s) by this process. 2/9 (22%) of the batches of
 21 concentrate used in the study were implicated in NANBH
 22 transmission. One of these two batches, responsible
 23 for NANBH in four patients, had been prepared from
 24 a plasma pool containing an unusually large proportion
 25 of donations with high alanine aminotransferase (ALT)

1 of 5,000 to 32,000 donors is given.
 2 Because the patients were selected between
 3 September 1984 and August 1985, that pre-dates the
 4 screening of the donor pools with ALT testing and HIV
 5 testing, which, as we've seen from the documents we've
 6 been looking at, came in a little later.
 7 If you can turn to the "Results" column. It
 8 talks about the five patients (28 per cent) who
 9 developed acute NANB, and then it goes on to say that:
 10 "In three of the five patients who developed
 11 hepatitis, transaminase abnormalities were resolved
 12 within the 40-week follow-up period. In the other
 13 two, abnormalities persisted beyond 40 weeks,
 14 indicating the development of chronic hepatitis. Two
 15 additional patients (3 and 5) developed mild,
 16 transient, ALT abnormalities which did not fulfil the
 17 criteria for diagnosis of hepatitis."
 18 If we go over, we just see at the bottom of that
 19 page it says:
 20 "Two of the nine batches of concentrate (22%)
 21 were implicated" --
 22 If we go over to the next page underneath the
 23 diagrams:
 24 "Two of the nine batches of concentrates
 25 were" --

1 If we go to the text just beneath these
 2 diagrams:
 3 "Two of the nine batches of concentrates ...
 4 were implicated in transmission of NANBH. One of
 5 these batches [batch D] caused hepatitis in all four
 6 recipients, suggesting a batch-related rather than
 7 process-related problem."
 8 We will pick up what happened with batch D
 9 shortly.
 10 If we could go over, please, to the final -- the
 11 penultimate page, page 4, in the "Discussions"
 12 section. If we pick it up about halfway down the
 13 left-hand column, commercial Factor VIII concentrates.
 14 The authors write:
 15 "Commercial factor VIII concentrates subjected
 16 to 'dry heating' at 60°C for 30-72 [hours] have been
 17 found to transmit [non-A, non-B] to 84-100% of
 18 recipients [papers are cited] attack rates which are
 19 similar to those associated with unheated
 20 concentrates, whether derived from commercial or
 21 volunteer plasma ... The lower transmission rate found
 22 in this study suggests that the method used to prepare
 23 the concentrate, which included heating at 60°C for
 24 20 [hours] while the material was in a slurry with
 25 n-heptane, was more effective than conventional 'dry

1 source material for US-derived commercial clotting
 2 factor concentrates is now invariably derived from ALT
 3 screened donors. This was not the case in 1984/85,
 4 when the concentrate used in the present study was
 5 manufactured, and examination of the product history
 6 of one of our two implicated batches [batch D]
 7 suggested that its propensity to cause [non-A, non-B
 8 hepatitis] might have been at least partially related
 9 to an unusually high level of NANB viral contamination
 10 in the plasma pool from which it was derived.
 11 "The plasma used to prepare batch D was
 12 collected in the USA in early 1985, and some was
 13 provided by independent contract plasma suppliers. In
 14 1985 the West German Health Authorities ruled that all
 15 plasma products destined for use in that country
 16 should be derived from donor plasmas which have been
 17 individually screened for elevated ALT levels. This
 18 was not, and still is not, a requirement in the UK.
 19 Without the knowledge of the manufacturers, one of
 20 their contract suppliers diverted plasma which had
 21 failed to meet the German requirements, and this was
 22 used to prepare batch D. The source plasma pool is
 23 now known to have contained a much higher than usual
 24 proportion of high ALT plasma, and it seems possible
 25 that this resulted in a high level of viral

1 heating' and resulted in a lesser degree of viral
 2 contamination of the final product. This conclusion
 3 is reinforced by the course of patient 2, whose lack
 4 of evidence of NANBH during the first 11 months of
 5 follow-up is clearly unlikely to be attributable to
 6 host resistance factors. Reduced transmission rates
 7 have been found by other investigators using both the
 8 same and another 'wet heated' concentrate ..."
 9 References are given to other texts. If you
 10 could go over to the next column, please, in the first
 11 full paragraph in, starting "The risk". This, sir,
 12 goes back to batch D, the batch that gave rise to four
 13 of the infections:
 14 "The risk of ... [non-A, non-B hepatitis] by
 15 factor VIII concentrates depends not only on the
 16 efficiency of any sterilization process, but also on
 17 characteristics of the source plasma. In the absence
 18 of any reliable serological markers for [NANB
 19 hepatitis], interest in donor screening as a means of
 20 reducing viral contamination of concentrates has
 21 centered on the possibility of using 'surrogate'
 22 tests, including [anti-hepatitis B core antigen] and
 23 ALT. There is good evidence that ALT screening, in
 24 particular, is likely to result in a reduced risk of
 25 NANBH in non-pooled products ... and plasma used as

1 contamination which was sufficient to override the
 2 effects of the sterilization process. The
 3 asymptomatic course of the patients who developed
 4 NANBH may be indicative of a partial neutralization of
 5 NANB agent(s), since hepatitis associated with
 6 unheated commercial concentrates is usually
 7 symptomatic ... All concentrates now manufactured by
 8 the company are derived from plasma donations which
 9 have ALT levels less than twice the upper limit of
 10 normal, and have been screened for anti-HIV. Whether
 11 or not such screening will eliminate or reduce the
 12 risk of post-infusion NANBH can only be assessed by
 13 a second clinical study, which is currently in
 14 process."
 15 A couple of things to pick up from that, sir.
 16 First is the general point made that there has been
 17 some success in inactivating NANB hepatitis by use of
 18 Profilate HT methods, although there have been some
 19 instances where it has still been transmitted.
 20 The second point relating specifically to batch
 21 D is the fact that the plasma was supplied under
 22 contract to Alpha, rather than from one of Alpha's own
 23 plasmapheresis centres and, in this instance, it seems
 24 that the plasma for batch D had failed the test put in
 25 place by the West German authority relating to ALT

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

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

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

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

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

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

15 "The Group agreed:

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

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

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

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

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

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

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1 within the DHSS] at all stages."

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

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

13 On 14 November 1989, Mr Wilson of the Medicines
14 Control Agency circulated a memo identifying his
15 concerns about the group's reasoning and the proposed
16 actions that came out of that meeting. If I could
17 take you to that, please, it's DHSC0001351. We can
18 see that the minute is from Mr Wilson, nominally sent
19 to Mr Franks but also a number of people copied in,
20 including a number of those who were present at the
21 meeting, such as Dr Fowler, and other individuals
22 within the DHSS who had an interest. I pick out the
23 name in particular of Dr Rotblat there, who will be
24 referred to. Dr Rotblat being one of the scientists
25 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

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

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

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

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

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

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

25 He then goes on to propose a further meeting and

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

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

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

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

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

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

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

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

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

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

20 What it says is this:

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

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

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

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

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

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

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

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

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

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

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

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

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

25 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

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

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

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

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 haemophilic
 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 haemophilic 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

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 haemophilic patients
 25 to heptane treated Profilate. It is likely that BPL

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 Haemophilic 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

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 haemophilic
 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

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 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 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 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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1 could take several months.
 2 "The Annex refers to the consequences of taking
 3 either course, for the company, for patients and for
 4 the Licensing Authority.
 5 "Immediate Suspension
 6 "Professional advice is that, on balance, we do
 7 not have sufficient evidence to support immediate
 8 suspension. This position was reached taking into
 9 account the theoretical risk posed by the deficiencies
 10 noted by the inspectors, the lack of problems in the
 11 batch release of the product from NIBSC and the fact
 12 that there is no clinical evidence about the use of
 13 a product which gives rise to concern. On the basis
 14 of that advice, immediate suspension would cause
 15 unwarranted concern to the many patients who are or
 16 have used PROFILATE. Such action has to be seen also
 17 in the context that (having studied the company's
 18 dossier) we now think it most likely that the
 19 Licensing Authority will be able to agree their
 20 application for a variation to their existing licence
 21 before the end of January. (The Committee on Safety of
 22 Medicines will consider it on 25 January). Once that
 23 variation is agreed it will no longer be possible for
 24 the company to market further supplies of the heptane
 25 treatment PROFILATE in the UK. The company has, we

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1 the production process. It would seem fully
 2 warrantable. Such action by the Licensing Authority
 3 would not be made public. The company could then
 4 choose to exercise its 'appeal' rights but we think
 5 this is unlikely. The company must indicate whether
 6 or not it wishes to do so within 28 days. Any such
 7 action would in practice be likely to be overtaken by
 8 the grant of the variation before [the] end [of]
 9 January and the company will no doubt take that into
 10 account in deciding how to respond.
 11 "We should seek in discussion with the company
 12 to press them to exchange existing heptane treatment
 13 PROFILATE held by health authorities in the UK for the
 14 new product. We believe that the company may be
 15 receptive to this approach and will be anxious to
 16 co-operate.
 17 "Conclusion
 18 "If the Minister wishes regulatory action to be
 19 taken we would accordingly advise that this should not
 20 be with immediate effect.
 21 "Is the Minister content? If so we will proceed
 22 urgently with action as at [paragraphs] 5 and 6 above.
 23 We would be happy to discuss if she wishes."
 24 That is signed by Mr Wilson and I remind you,
 25 sir, that is 15 December 1989.

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1 understand, ample stocks of the new (solvent detergent
 2 treated) PROFILATE and will wish to supply it to the
 3 UK market without delay.
 4 "So immediate suspension is now likely only to
 5 cut short cessation of supply of the product by
 6 a matter of a few weeks. With that in mind and given
 7 the lack of clinical evidence of any abnormal safety
 8 hazard, the concern immediate suspension would cause
 9 to the haemophiliacs and the serious public questions
 10 to which it would give rise, our advice to Minister
 11 must remain strongly against such action. It is true
 12 that we cannot say that there is not a potentially
 13 greater risk of infection from Profilate because of
 14 manufacturing deficiencies. But that risk has to be
 15 assessed as very remote given the usage of Profilate
 16 in recent years.
 17 "Proposal to Suspend
 18 "As an alternative, we could however inform the
 19 company that we propose to suspend the licence (but
 20 not with immediate effect) unless they are willing
 21 voluntarily to cease to market the heptane treatment
 22 product. A proposal to suspend would leave the
 23 company in no doubt that we were dissatisfied both
 24 with their lack of progress in putting right the
 25 deficiencies and with the present situation regarding

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1 The annexes to the document are at pages 4 to 6.
 2 I'm not going to take you all of the way through
 3 those. I would point out -- sir, if we could go to
 4 page 4, please, Soumik. We have the consequences for
 5 the company set out, and that discusses some of the
 6 possibilities that have been raised in the main
 7 minute. Then the consequences for people with
 8 haemophilia, including the need to switch to a
 9 different product. At the top of page 5, underlined:
 10 "We cannot say that patients switching from
 11 PROFILATE to other commercial products would
 12 necessarily be transferring to a potentially less
 13 risky product. Indeed we suspect that in some cases
 14 the reverse might be the case;
 15 "there may be in the order of 2,000 patients
 16 currently using PROFILATE."
 17 The consequences for the Department. If you
 18 look at paragraph 4, we can see that it's noted that:
 19 "Any announcement of immediate suspension would
 20 give rise to public/Parliamentary questions about the
 21 basis for the action ... which could receive
 22 considerable media attention ..."
 23 I quote from the document:
 24 "It would not be easy to explain why action was
 25 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 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 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 can 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 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)**

I N D E X

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3	Presentation from Counsel to the	1
4	Inquiry on the Pharmaceutical	
5	Companies (continued)	
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<p>MR HILL: [51] 1/5 3/25 4/5 9/20 11/16 20/2 26/12 28/1 28/7 36/6 36/11 45/17 56/6 56/9 56/12 56/23 56/25 70/9 82/18 82/21 83/2 85/19 85/24 89/17 89/19 89/25 90/3 90/11 90/14 91/7 91/9 91/22 93/8 93/11 93/18 93/25 94/3 108/11 108/15 132/8 142/15 148/4 148/7 148/10 148/13 148/19 149/13 149/15 157/18 157/22 157/24</p> <p>SIR BRIAN LANGSTAFF: [52] 3/5 4/1 9/17 11/15 20/1 26/11 27/24 28/5 36/3 36/10 45/11 45/16 56/5 56/8 56/10 56/19 56/24 70/5 82/13 82/20 83/1 85/17 85/22 89/12 89/18 89/24 90/2 90/9 90/13 91/3 91/8 91/17 93/4 93/10 93/17 93/23 94/1 108/9 108/12 132/2 142/14 148/3 148/6 148/8 148/12 148/17 149/12 149/14 157/15 157/21 157/23 169/16</p> <p>'71 [1] 56/21 'appeal [1] 163/4 'at [1] 153/24 'Discard [1] 58/23 'dry [4] 94/24 122/14 125/16 125/25 'hospital [1] 139/6 'manageable [1] 22/18 'me [1] 22/3 'me-too [1] 22/3 'new [1] 166/4 'other [1] 144/14 'person [2] 143/21 157/6 'Profilate [1] 133/13 'regulatory [1] 160/13 'sale [1] 41/25 'Single [1] 58/21 'surrogate [1] 126/21 'The [1] 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97/25</p>	<p>1,688 [1] 24/18 1.02 [1] 91/19 1.1 [1] 77/16 1.2 [2] 77/20 81/6 1.3 [1] 57/14 1.32 million [1] 24/13 1.5 [1] 57/16 1.5 million [2] 40/2 75/12 1.5.1 [1] 81/7 1.6 million [1] 75/23 1.65 million [1] 75/9 1.9 million [2] 75/10 75/25 10 [4] 91/4 105/2 137/19 139/20 10 December 1974 [1] 61/5 10 o'clock [1] 169/23 10 September 1979 [1] 74/19 10-fold [1] 22/13 10.00 [2] 1/2 169/25 100 [6] 82/4 82/5 121/4 122/15 123/10 125/17 101 [1] 17/10 102 [1] 80/1 104 [1] 81/13 105 [1] 81/21 106 [1] 83/16 10p [3] 40/1 69/5 74/3 11 [4] 59/18 126/4 137/19 139/20 11 January 1990 [1] 168/25 11 March 1976 [1] 65/12 11.13 [1] 45/13 11.45 [1] 45/15 113 [1] 116/3 118 [1] 73/13 12 [3] 45/12 45/12 114/16 12 March [1] 108/23 12 months [1] 73/18 12p [4] 69/4 74/1 74/2 74/10 13 [2] 2/11 137/21 13 March 1985 [1] 105/21 13 November [1] 141/5 13 November 1989 [1] 132/16 13,200 [1] 12/4 14 [4] 61/13 68/2 105/1 156/6 14 November 1989 [1] 140/13 14.6 million [1] 75/14 144 [1] 33/21</p>	<p>14p [1] 113/24 15 [4] 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