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Wednesday, 2 November 2011

(9.30 am)

DR JAMES SMITH (continued)

Questions by MS DUNLOP (continued)

THE CHAIRMAN: Good morning. Ms Dunlop?

MS DUNLOP: Thank you, sir.

Good morning, Dr Smith.

A. Good morning.

Q. Just to conclude your B3 statement, if we may, that is [\[PEN0121551\]](#) We are actually now at 1572, which is your note 5. Much of this has been mentioned already, Dr Smith. I think if we just read for ourselves the first part.

This is really taking us into the topic of green plasma again, isn't it, Dr Smith?

A. Yes.

Q. Yes. The 1983 development is said to have built on the plasmapheresis of a panel of donors in Leeds under the enthusiastic leadership of Dr Angela Robinson.

Then the next paragraph tells us that by early 1984 PFL had investigated dry heating of several batches of its current product, and just to link back to the supplementary statement we looked at yesterday, that product would be 8CRV/HL. Is that right?

A. Yes.

1 Q. Right. Then there is the discussion of the small trial.  
2 We looked at this trial with Dr Colvin, or more  
3 particularly we looked at the report of the trial. That  
4 reference that you make in the middle of the paragraph  
5 is to a paper of which you were a co-author, along with  
6 Dr Colvin and some others, and we don't need to go to it  
7 but the reference is [\[PEN0171782\]](#). We discussed it with  
8 Dr Colvin when he was here on 14 October and that  
9 discussion is around about page 138 of the transcript  
10 for that day.

11 Dr Colvin made essentially the same point as you are  
12 making here, when you say:

13 "I do not believe today that the 60 degrees/72 hours  
14 applied to those batches necessarily inactivated NANBH.  
15 It is at least as likely that there was no infective  
16 donation in the starting pool of plasma."

17 A. Yes.

18 Q. I don't know if you had a look at what Dr Colvin had  
19 said but I'm inferring that the two of you are saying  
20 much the same thing?

21 A. Indeed. Can I just clarify one thing?

22 Q. Yes.

23 A. At the end of that paragraph it does point out that the  
24 northern centres trial, which was going on in the latter  
25 part of 1983 and 1984, was on the material which

1 Dr Colvin had and Dr Machin had, except that these  
2 batches were not heated. In time we would have learned  
3 whether it was the restriction in number of donors,  
4 whether that was making a difference, and as I say, we  
5 lost interest in that trial somewhat but I believe there  
6 was at least one transmission of non-A non-B Hepatitis  
7 by this limited pool of green four material. That sort  
8 of answers the question retrospectively, I think.

9 Q. Yes. Of course, it may have been both, I suppose. Is  
10 this not scientifically conceivable?

11 A. That is not likely. If there is one donation positive  
12 in a pool of 20 donors of 500 donations, that is quite  
13 likely too -- almost certain to be infective in the  
14 recipients of the product.

15 Q. I suppose I was just thinking aloud, which I shouldn't  
16 be doing, but whether the fact that there might be an  
17 extremely low concentration of the virus might make  
18 a lower heating protocol successful?

19 A. A lower protocol, yes. Absence of heating, no.

20 Q. Oh, I see, yes. I was trying to extrapolate back to  
21 saying if there was one transmission of NANBH by an  
22 unheated batch, it still might mean that there was  
23 a little bit of NANBH in the heated batches but the  
24 heating protocol was enough to deal with it?

25 A. It is possible, yes.

1 Q. So that would be one possible explanation, I think.

2 Then you go on to say that:

3 "PFL started a crash programme ..."

4 This is at the end of 1984 and we have really been  
5 over that already.

6 You gave us the dates in your supplementary  
7 statement and we have some of the same dates here, that  
8 no unheated product was issued from BPL after  
9 2 May 1985. And that's what you say also in your  
10 supplementary statement.

11 You then go on to talk about 8Y, the scaling up of  
12 8Y. And you take us through the introduction of it as  
13 Factor VIII product.

14 You say in the middle of the last paragraph on this  
15 page that:

16 "The criteria for patient selection and  
17 interpretation of any lacunae in testing were not as  
18 rigorous as those promulgated in 1986 by ICTH. This is  
19 perhaps not the place for my views on the merits of  
20 these protocols."

21 From which comment one might deduce that you are not  
22 a wholehearted supporter.

23 A. No -- I was not at the time, largely having listened to  
24 Charles Rizza so long and often and having looked  
25 careful at the protocols used in the project leading to

1 his 1983 paper on transmission of non-A non-B Hepatitis  
2 by NHS and commercial concentrates, in the first  
3 publication by Colvin -- study group paper, our first  
4 proper publication of non-A non-B trials is a full  
5 discussion of how Oxford's view differed from that of  
6 the ICTH protocol, and I think even in Colvin's paper,  
7 on the 84 trial, he pointed out that all the soft  
8 patients who had in fact received a small amount of cryo  
9 before and who would be -- well, would not be eligible  
10 for an ICTH-type trial, all of those did prove to be  
11 susceptible to non-A non-B Hepatitis in the trials in  
12 which they had received these concentrates.

13 This is the reason why Dr Rizza believed that it was  
14 acceptable to include patients who had had a few doses  
15 of cryo, rather than sticking to ones who had had no  
16 treatment whatever, which more or less meant infants.  
17 But I agree -- I think we deal with all these -- the  
18 objections to the Oxford protocol but they were not  
19 persuasive at the time, apparently.

20 Q. Right. I think we can perhaps understand where the  
21 battle lines might be drawn, Dr Smith, and I don't know  
22 that we need to go sufficiently far into it to try to  
23 form a view as an Inquiry.

24 You then go on to say that for various reasons  
25 uptake of 8Y for trial was slow but the handful of brave

1 haemophilia centre directors who agreed to offer  
2 suitable patients were very enthusiastic and then uptake  
3 started to snowball.

4 You had, you say, a handful of data for oral  
5 presentation in Melbourne and London in 1986, where the  
6 trial design was heavily criticised, which must have  
7 been a little disheartening. Or did you --

8 A. The criticism was fair.

9 Q. Right. And then you say:

10 "On first publication in January ..."

11 I think that's actually January 1988?

12 A. Yes, it is.

13 Q. Yes. And we have mentioned this article already too,  
14 just to give the reference for it without going to it,  
15 it's [\[LIT0010330\]](#):

16 "32 patients had been studied without satisfying  
17 these criticisms, which were answered effectively only  
18 in 1990 when the same and later patients were tested for  
19 anti-HCV with no evidence of transmission."

20 So conclusive or close to conclusive evidence for  
21 several understandable reasons was rather slow in coming  
22 through?

23 A. Yes, 1990.

24 Q. Yes. And you say that at that point, by which you mean  
25 the end of 1985, there was only the slightest

1 encouragement:

2 "... six patients not all fully compliant with  
3 protocol who had completed their follow-up. There was  
4 no justification for BPL to jump up and down and  
5 proselytise for 8Y."

6 Then you go on to say that:

7 "BPL's Calvary was not in bringing 8Y to fruition  
8 but in proving that NANBH was not being transmitted.  
9 Fortunately, by September 1985, 8Y was standard issue  
10 for England and Wales and a gratifying number of HCs  
11 adopted it in preference to commercial concentrates.  
12 The safeguarding of our haemophilia population was not  
13 unduly delayed. This would not have happened without  
14 the generous trust and sterling efforts of our HCDs."

15 So possibly a bit of a leap of faith by some at some  
16 point, but in the right direction?

17 A. Yes.

18 Q. Yes. Dr Smith, the final section of your statement, if  
19 we can just look at it, please, over on to 1576,  
20 consists of a number of comments and in some instances  
21 corrections on the preliminary report. We are grateful  
22 to you for providing these and we will, of course, take  
23 them on board, but I don't propose, sir, to go through  
24 them.

25 THE CHAIRMAN: I have had a look at them. I think that it's

1 relatively easy to see where you are going and we can  
2 adapt to the information you have provided.

3 MS DUNLOP: There is only one that I was going to go to and  
4 it's on the next page, 1577. This is in conclusion,  
5 sir. It's that sentence that we see marked 11.13-11.4:

6 "Fairly crude Factor VIII concentrates had been  
7 available in both Scotland and England and Wales since  
8 at least the mid 60s."

9 I just wanted to ask you one or two questions about  
10 that, Dr Smith, because, I mean no disrespect, but you  
11 are able to reach back for some part of the time on our  
12 behalf and give us a little more information about the  
13 historical picture. Perhaps we could start by looking  
14 at our own transcript for 10 May at page 88.

15 This is Dr Foster on his first attendance at the  
16 Inquiry. I took him to an article which he had provided  
17 for us, an article by Dr Foster from the SNBTS blood  
18 letter. The article was from the spring of 2008 and  
19 I went on to extract certain points from the article.  
20 I.

21 Seem to have managed to create the impression, if we  
22 go down to the transcript, please, that  
23 Dr Drummond Ellis spent 23 years in America, which is in  
24 fact not correct. But anyway, I thought it would be  
25 useful if we just looked again at that publication,



1           which, through lightning processing is now in court  
2           book. I have the number. [\[PEN0172468\]](#).

3           The first section to which I wanted to direct you is  
4           a little bit down the page, please, and it's that  
5           section covering 1951 to 1974 that Dr Ellis travelled to  
6           the United States to study fractionation at Dr Cohn's  
7           laboratory, and this is something we covered with  
8           Dr Foster. We see there a reference to an early version  
9           of Factor VIII, Cohn Fraction I, in 1956, and indeed  
10          Dr Foster told us that one of the bottles in the picture  
11          is a bottle of that early AHF, if we go back up.  
12          I think we are all conscious that it's not terribly easy  
13          to make out the picture and I can tell you it's not  
14          a lot better if you have a hard copy either.

15          You are able to give us a bit of information about  
16          the production of that early AHF, I understand?

17        A. Yes.

18        Q. Cohn Fraction I. How many litres of plasma would go  
19          into a batch for that manufacturing process?

20        A. A batch would be 8 litres, I believe.

21        Q. And you are going really from memory here, Dr Smith?

22        A. I have a vivid picture of the large glass bolt head  
23          bottle in which it was made by dunking in a bath of  
24          glycol to cool it. So I can't remember where the liquid  
25          came on the graduations. It would be somewhere of the

1 order of 8 litres.

2 Q. I should say, Dr Smith, that the other useful  
3 publication which we now have -- and this is something  
4 that we have sought and obtained from Dr Foster -- is an  
5 article by Drs Cumming, Davies, Ellis and Grant, from  
6 Vox Sanguinis in 1965. We will just have a look at that  
7 too. That's [\[PEN0172472\]](#) and we also have hard copies  
8 of it, which are going to be distributed for anybody who  
9 wants to look at the hard copy.

10 (Handed)

11 Trying to get a feel for the donor exposure, which  
12 use of this product will have entailed, which I think  
13 has been underlying the chairman's probing of the issue,  
14 we can see from the very beginning of this article that  
15 in 1960 the volume of fresh plasma fractionated was  
16 320 litres, derived from blood from a total of 1,425  
17 donors.

18 Your feeling, Dr Smith, when we discussed this  
19 yesterday, was that the batch would be about 40 donors.  
20 In fact, if you do the maths on that there, it would  
21 suggest around about 36 donors. So if we can perhaps  
22 compromise on somewhere between 35 and 40 donors, whose  
23 donations would be going into the 8-litre batch, does  
24 that make sense so far?

25 A. Yes, if we say a maximum of 40.

1 Q. Yes, right. And then obviously there is a lot of  
2 description in this article of the process, which  
3 I don't think we need to go through with you, and we can  
4 read it for ourselves, but what would the end product  
5 be? How much product would be achieved?

6 A. It would be six bottles of the size illustrated in  
7 Dr Foster's blood letter article.

8 Q. Right.

9 A. The same size as a blood plasma bottle with a rather  
10 smaller amount of freeze-dried material in them than you  
11 would have if it had been simply plasma.

12 Q. Right.

13 A. But only six bottles from 8 litres of plasma.

14 Q. Right.

15 A. Or 40 donors.

16 Q. Can you capture for us at all, even just an estimate, of  
17 the sort of number of bottles that an adult patient,  
18 needing treatment for a bleed might need, even just  
19 a range, Dr Smith?

20 A. An adult patient would almost certainly need more than  
21 one bottle and if he was being prepared for surgery or  
22 in recovery after surgery, he might require 2, 3, 4  
23 batches, depending you how he was responding.

24 Q. Right. We did see a reference in medical records from  
25 the 1960s to a patient having had four flasks actually

1 of AHG, rather than AHF, prior to a dental extraction.  
2 To take the different initials first, would AHG be  
3 synonymous with AHF?  
4 A. It means anti-haemophilia globulin. That term was in  
5 use more in the States than here.  
6 Q. Right.  
7 A. The "F" can sometimes stand for "fraction" or "factor".  
8 You will find many designations.  
9 Q. But the same stuff?  
10 A. Same stuff.  
11 Q. What about the use of the word "flasks"?  
12 A. That was a bottle. They were sometimes called "MRC  
13 bottles", "MRC flasks".  
14 Q. So that doesn't surprise you, that little anecdote about  
15 a patient having four bottles prior to a dental  
16 extraction?  
17 A. That's a relatively minor operation. In the 60s, we did  
18 not have the kinds of heroic surgery which began to be  
19 attempted in the 70s and 80s to repair damage, for  
20 instance, to haemophilic joints. Treaters were very,  
21 very wary of any surgical intervention but emergencies,  
22 of course, occurred, cranial bleeds, for instance, which  
23 might require much more than preparation for a dental  
24 extraction.  
25 Q. I think the other piece of the jigsaw which I need to

1 ask you about is whether a patient who was receiving  
2 more than one bottle -- whether there would be any steps  
3 taken to try to restrict the number of batches of  
4 product to which that patient would be exposed?

5 A. I believe that even in those days, we were conscious  
6 that -- hepatitis in those days, we would have thought  
7 of it as Hepatitis B but was probably several different  
8 hepatitisides. We were conscious that Fraction I was  
9 capable of transmitting hepatitis and I think we would  
10 have taken what steps we could to make sure that  
11 a patient requiring more than one bottle got it from the  
12 same batch.

13 Q. Which obviously would be up to a maximum of six.  
14 Somebody getting more than six needs to go into another  
15 batch. Yes. Excuse me a moment. (Pause)

16 Yes. I should clarify with you, of course,  
17 Dr Smith, that that product and that manufacturing  
18 process were superseded in the 1970s, when PFC moved to  
19 NY. Is that correct?

20 A. Yes.

21 Q. Yes.

22 A. It was the beginning of the industrial cryoprecipitate  
23 era.

24 Q. Right. So it would be correct to see AHF as having been  
25 around in Edinburgh from 1956 and cessation of that

1 product as occurring in the early 1970s. We do actually  
2 have graphs which show the change from AHF to NY but  
3 that's roughly the sort of time period we are talking  
4 about?

5 A. Yes.

6 Q. But we are a little short on details in terms of annual  
7 amounts, other than for 1960, where luckily we have this  
8 article which gives some figures for that.

9 I suppose the other point which occurs is all this  
10 mention of Edinburgh. Will this have been largely  
11 restricted to patients with haemophilia in Edinburgh and  
12 the East of Scotland or do you think that the material  
13 was in use in other parts of the country?

14 A. I think it would have been available to other -- in the  
15 mid 60s, remember, the SNBTS did not exist. It was  
16 SNBTA, with five local organisations. I am sure that if  
17 Aberdeen or Glasgow had had a patient who would benefit  
18 from the increased potency of AHF, if they had asked for  
19 it, they would have received it. It might have -- we  
20 might have asked that they delay an operation, say,  
21 until we could generate enough extra material. We might  
22 have asked the relevant transfusion centre to provide  
23 some of that plasma, but I'm absolutely certain the  
24 effort would have been made if we had been asked.

25 I think the -- Dr Davies, whose name appears on this

1 paper, was the pioneer of haemophilia treatment but I'm  
2 not sure that -- in fact -- that the same degree of  
3 expertise or ambition to treat haemophilia was present  
4 in all the centres in the 60s.

5 Q. Right. And of course, cryoprecipitate arrives on the  
6 scene in the 1960s and --

7 A. And even before that, fresh-frozen plasma was the  
8 standby for most haemophiliacs in all of Britain, until  
9 cryo and concentrates came through.

10 Q. Right. And I think we are slightly better informed on  
11 the topic of cryoprecipitate. We do have, I think,  
12 a little more information on that than we did have on  
13 AHF or AHG. So your being here and being able to give  
14 us some of these recollections has certainly filled  
15 a bit of a gap in our information. So thank you very  
16 much for that, Dr Smith.

17 THE CHAIRMAN: Could I just follow a little?

18 MS DUNLOP: Yes, certainly.

19 THE CHAIRMAN: Because I do have, as Ms Dunlop said, an  
20 interest in the previous thing. My interest was sparked  
21 by an article by Cash and Spencely and that's the one  
22 that contains the graph, and I would like your comment  
23 on it if I can. It's [\[LIT0010255\]](#). Do we have that?

24 While that's being found, I think I now have  
25 a precise date for the final production of AHF. There

1 is a note of the last production run in September,  
2 I think, 1974. So it clearly was superseded totally  
3 once the commissioning of PFC began to get underway. So  
4 that side of it's easy. But if we go forward a page  
5 until we get the graph, please.

6 You see the bottom graph deals only with the  
7 Southeast of Scotland, of course, but talks about the  
8 preparations that were in use from 1961 to 1975, and  
9 I think that we have very little difficulty in  
10 identifying the different lines since they are tagged.  
11 And what one sees is that fresh-frozen plasma was just  
12 in excess of AHF, 61 and 62, and then AHF begins to  
13 predominate through to 1970, when, according to this  
14 graph, cryoprecipitate came into use.

15 Does this --

16 A. That is single donor cryoprecipitate prepared in the  
17 individual transfusion centres, yes.

18 THE CHAIRMAN: Does this sort of pattern square with your  
19 recollection, Dr Smith?

20 A. Yes, I think perhaps your puzzlement is why the  
21 southeast region should be using so much cryo.

22 THE CHAIRMAN: There is that but of course Dr Cash was just  
23 reporting on the southeast and he perhaps didn't even  
24 have access to data about the other centres. But the  
25 other things that interested me when I saw this include



1 the role that AHF clearly was meeting right up until  
2 1974 and if the quantity in 1960 is still reflective of  
3 practice at the beginning of this graph, it doesn't tell  
4 one that there is a great deal of treatment going on,  
5 does it?

6 A. No, treatment was much patchier. It was -- heavy dosage  
7 was given only in true emergencies and in relation to  
8 the severity of the bleed and the need to keep the  
9 patient up to a certain level for that, surgery was not  
10 lightly undertaken. There was a shortage.

11 THE CHAIRMAN: Coming right through to what does interest  
12 me, and that is whether the haemophilia population was  
13 seriously exposed to the risks of hepatitis, using the  
14 envelope term "B" at that stage, before sophistication  
15 took over, what would your view be? Was there  
16 a material change once one got to 1974 and PFC's  
17 procedures or not?

18 A. For the severely affected haemophiliac, very little.  
19 But I would have to say that for the occasionally  
20 treated haemophiliac, then they were incurring more  
21 donation risks with the large pool product than with the  
22 40 donor pool of Fraction I, but that small pool  
23 material was known to transmit.

24 THE CHAIRMAN: But, of course, we also know that at that  
25 early period, therapy often consisted simply of bed

1 rest, of remaining in hospital for considerable periods  
2 of time, rather than the administration of therapeutic  
3 products at all.

4 A. In fact, as a small anecdote, in the year I arrived in  
5 what was then called the BPU, Blood Products Units, in  
6 the Royal Infirmary, there was news that a haemophiliac  
7 had been found in the Orkneys who had never seen  
8 a doctor, who was kept at home by his family he had  
9 spent his entire life in bed. Just to give you some  
10 idea of how primitive things could be, even in the late  
11 1960s, of how little access some patients had,  
12 tragically to what we could provide in the way of modern  
13 treatment. Quite an incentive to do better.

14 THE CHAIRMAN: Ms Dunlop, I think I am developing a better  
15 picture of what the realities were, and that picture  
16 does include the appreciation that there was relatively  
17 little treatment, that it was patchy and that it had the  
18 characteristics that Dr Smith has described.

19 I think that may be enough for me unless anyone else  
20 develops it further but if you feel you can help  
21 further --

22 MS DUNLOP: I do have some more goodies from Dr Foster but  
23 they are more about the early use of cryoprecipitate and  
24 I'm certainly going to arrange for them to go into court  
25 book, but I wasn't planning to trouble Dr Smith with

1           that because I think that's not so much his area. There  
2           is more reading material but I don't think we  
3           necessarily need more evidence on it.

4   THE CHAIRMAN: That's fine. I'm sure that your judgment on  
5           this will be right so long as the picture that emerges  
6           is clear enough and I will depend on you for that too.

7   MS DUNLOP: Thank you, sir.

8           Mr Mackenzie and I take the view that it would be  
9           better that any questions from other counsel were to  
10          follow Mr Mackenzie's questioning of Dr Smith because  
11          there will be a degree of overlap. So it would seem to  
12          us more sensible just to do it all at one time but  
13          obviously that would be subject to any views to the  
14          contrary expressed by any of my colleagues.

15   THE CHAIRMAN: I was going to ask. So I think this is an  
16          appropriate time.

17          Mr Di Rollo, do you feel that it would be better to  
18          deal with it in two tranches or all at once?

19   MR DI ROLLO: All at once would be my preference.

20   THE CHAIRMAN: Mr Anderson?

21   MR ANDERSON: The same, sir.

22   THE CHAIRMAN: Mr Johnston.

23   MR JOHNSTON: The same, sir.

24   THE CHAIRMAN: It would appear that you have got your  
25          unanimity.

1 Questions by MR MACKENZIE

2 THE CHAIRMAN: Mr Mackenzie?

3 MR MACKENZIE: Thank you, sir.

4 Good morning, Dr Smith.

5 A. Good morning.

6 Q. Dr Smith, we will turn now to the topic C3, please. It  
7 may help, before we look at your main statement, to go  
8 back to your two-page supplementary statement, please,  
9 which is [\[PEN0172198\]](#).

10 What I would like to do is just spend some time  
11 looking at the development, production and introduction  
12 of 8Y and if we go to the second page of that  
13 supplementary statement, please, under "Introduction of  
14 8Y" we see some dates relating to the clinical trial but  
15 I think I would like to start with the development of 8Y  
16 and I'll try and avoid as much duplication as possible,  
17 having regard to your evidence yesterday.

18 Dr Smith, the starting point is perhaps May 1984,  
19 and we saw, for example, your letter of 22 May 1984 to  
20 Dr Foster, where you talked about stumbling, literally,  
21 on an intriguing alternative to zinc. Is that really  
22 the start of the development of 8Y?

23 A. Yes.

24 Q. And we heard evidence that that in short involved the  
25 use of heparin as a precipitant. What was the purpose,

1           remind us, of seeking to make a purer product?

2   A. I'm sorry, I didn't hear your question.

3   Q. Yes, I'm sorry.

4           You were seeking to use heparin as a precipitant,  
5           which would result in a purer Factor VIII concentrate  
6           and what was the purpose of seeking a product of higher  
7           purity?

8   A. Two main reasons. One, that we were always in pursuit  
9           of a product with less fibrinogen in it, which could  
10          therefore be dissolved more readily and given at  
11          a higher potency. That was an ongoing theme since I had  
12          been in the trade.

13          Secondly, and perhaps becoming more salient in our  
14          minds, was the knowledge that pasteurisation would be  
15          a whole lot easier if the -- first of all the volume we  
16          had to deal with was reduced --

17   Q. Why?

18   A. -- and secondly the burden of this nuisance protein,  
19          fibrinogen and fibronectin, were reduced.

20   Q. Just for the avoidance of doubt, why would  
21          pasteurisation be easier with a smaller volume of  
22          product?

23   A. I think the stages which would be -- well, first of all,  
24          the heating stage, the stage at which you have to add  
25          loads of sucrose and glycine, or sorbitol and glycine,

1 to stabilise it, obviously, your heat transfer and  
2 control of temperature is much easier with a small  
3 volume.

4 In particular, I would say, the removal of  
5 Factor VIII from this jam is much more approachable in  
6 even extensions of laboratory-scale equipment than if  
7 you have a 100-litre volume which has to be ultra  
8 filtered or otherwise desalted using technology which  
9 was only in its infancy as far as industrial  
10 exploitation was concerned.

11 Q. How about the pasteurisation step? Would that be  
12 easier --

13 A. That's what I tried to say first, that the heating  
14 stage, the stage at which you would -- the material in  
15 a tank with a heated jacket, you can control -- get to  
16 temperature much more rapidly, which is important, and  
17 maintain the temperature more precisely in a smaller  
18 volume.

19 Q. Thank you.

20 So at this time you are still considering  
21 pasteurisation. I think that is illustrated. You had  
22 a visit, I think, in June 1984 to Dr Foster and you took  
23 photographs of the ZHT process at PFC. Is that correct?

24 A. That's correct.

25 Q. I think for completeness, we can just take you to that.

1           It's [\[PEN0172206\]](#). This has only recently become  
2           available to us but I think this is a letter dated  
3           9 July 1984, Dr Smith, from yourself to Dr Foster,  
4           enclosing prints from the film you took at PFC on  
5           25/26 June 1984.

6           Could we then, please, go to document [\[PEN0172208\]](#)?  
7           One can see there is an index of the photographs.  
8           I don't think we have to go through the various steps.  
9           It's simply to show that you were still interested at  
10          this stage in pasteurisation. I should also give the  
11          reference number for the photographs and perhaps briefly  
12          go to them. They are [\[PEN0172209\]](#). And perhaps we can  
13          just flick through them without considering them in any  
14          detail. We can just see the different photographs which  
15          were taken. Dr Smith, I don't intend to ask you  
16          anything more about this. It all looks quite  
17          complicated.

18          So that's that.

19   THE CHAIRMAN: It doesn't look very automated.

20   A. No. They were still pilot scale, improvised.

21   MR MACKENZIE: Thank you.

22          Dr Smith, we have looked at the heparin  
23          precipitation step. There must have been various other  
24          steps involved in the manufacture of 8Y and we will come  
25          to look at them shortly when we come to a published

1 paper, but presumably in short, from about May 1984, for  
2 the rest of that year, presumably, at PFL you were also  
3 working on the other steps required for 8Y. Is that  
4 correct?

5 A. Yes, in fact we had ready to plug in, after the heparin  
6 precipitation stage, precipitation using glycine and  
7 sodium chloride, which we had already researched.

8 Q. Is that a second precipitation?

9 A. Yes.

10 Q. Given for the purpose of?

11 A. Concentrating the Factor VIII.

12 Q. And removing?

13 A. To some extent removing the heparin, yes.

14 Q. And further removal of the fibrinogen and fibronectin?

15 A. Yes, a further fourfold reduction of the sticky proteins  
16 which was quite important.

17 Q. We will come back to these other steps shortly when we  
18 look at our published paper. Just before you went to  
19 Groningen in November 1984, obviously you had worked at  
20 PFL on developing the 8Y process, you had also carried  
21 out some heating experiments we discussed yesterday, and  
22 certainly you had carried out dry heating experiments.  
23 Had you also been able to carry out wet heating  
24 experiments on 8Y, before you went to Groningen?

25 A. I'm almost certain we would have but I cannot point to



1           any documentation of that.

2   Q.   Yes.

3   A.   However, on Factor IX we were getting the same kind of  
4        results as PFC and I'm not sure we had actually  
5        completed our work on pasteurisation of IX but it was at  
6        an advanced stage.

7   Q.   Okay.  Then in November 1984 you went to Groningen and  
8        heard the same news as the others in respect of the  
9        evidence that heating at 68 degrees inactivated HIV.  
10       What happened when you came back from Groningen?

11  A.   A small group of the people who knew most about the  
12        heating experiments of both kinds and those who would  
13        have to make a decision on what national policy should  
14        be met and reviewed all we knew about the severity of  
15        heating.

16           Dry heating would be applied to our candidate 8Y and  
17        to our candidate 9A and reviewed how far pasteurisation  
18        might have got, and the result of that is summarised,  
19        that PFL would immediately start to scale up from the  
20        chemistry of 8Y to what might be an engineered solution,  
21        which could be applied on a large-scale at BPL, and that  
22        since this would take time, meanwhile, to protect all  
23        haemophiliacs, all regarded at the moment as vulnerable  
24        to HIV, at least, to do what we could by heating our  
25        stocks of intermediate material.

1           I should clarify here that when we say  
2           "retroheating", we did not do what some of the  
3           commercial companies did, which was to recover stocks of  
4           their product from the haemophilia centre and even,  
5           I believe, from the fridges of haemophiliacs, their home  
6           treatment supply. I don't believe we ever went that far  
7           or we even went back to the transfusion centres, which  
8           distributed our material. I believe we only retroheated  
9           the stocks in our own holding rooms.

10    Q.   And sticking with 8Y, I think you said pilot-scale  
11           production of 8Y was commenced at PFL. Why did you  
12           choose heating at 80 degrees when the evidence had been  
13           that HIV was inactivated at 68 degrees?

14    A.   I think we were prompted by the fact that our Factor IX  
15           product appeared to resist 80 degrees very well but  
16           started to peg out a bit at 90. So that was a ceiling  
17           put on the Factor IX.

18           As the 1983 table shows, with Factor VIII it was  
19           a quantitative decision, that whether you went to 60 or  
20           70 depended on just how much loss of Factor VIII and  
21           loss of solubility in some cases you were prepared to  
22           tolerate, and I believe we went in the first place with  
23           60 degrees, probably in order to get more material  
24           available quickly, but we also thought at the same  
25           meeting that, in order to match the conditions for 8Y

1 and 9A, that it might seem at least symmetrical to apply  
2 what appeared to be the same conditions.

3 This is a bit of a cheat because in fact the same  
4 heating applied to two different products with very  
5 different formulations and content may not have  
6 precisely the same effect on viruses but it seemed  
7 intuitive at the time and we took a small hit on  
8 Factor VIII yield in order to push the boundary a bit  
9 and make sure we might be doing a bit more damage to  
10 non-A non-B than you would at 60 or 70.

11 Q. And when the decision was taken to heat 8Y  
12 in November 1984, what was the main reason for heating  
13 the product? Was it to inactivate HIV? Was it to  
14 inactivate NANBH or what?

15 A. Certainly to put our HIV kill beyond all reasonable  
16 doubt and, as I said, the hope was that at least we  
17 could do a bit more damage to non-A non-B but I had no  
18 hopes, to tell the truth, that this would deal with  
19 non-A non-B Hepatitis.

20 Q. And we will come back to that when we come to your main  
21 statement, thank you. But just to finish this point  
22 off, in November 1984 why did you decide to apply dry  
23 heat rather than wet heat?

24 A. Right. (a), because we could do it. We had the  
25 premises and the equipment in which we could make a case

1 for doing it. We did not have the premises, equipment  
2 and resources to make a job of pasteurisation, certainly  
3 of Factor VIII.

4 Although the signs from clinical use of dry-heated  
5 products were not exactly encouraging at that time, at  
6 least it was becoming clear that HIV was being killed by  
7 even 68 degrees, if not 60.

8 Q. So we have, I think, the first pilot-scale production  
9 batch of 8Y at PFL in November 1984. Were there  
10 a number of production batches made at PFL?

11 A. As I recall, it went very smoothly from the 1 litre to  
12 the 10-litre, to the 50-litre, to the 100-litre scale.  
13 Obviously, you don't want to commit 100 litres of  
14 precious fresh-frozen plasma until you have done a bit  
15 at the lower scale; and once we were at 100, it scaled  
16 up very easily to 300 in the same equipment. And  
17 I should add, perhaps, that a feature of our work at PFL  
18 was always the -- the ambition was always to end up with  
19 a product manufactured at the scale which BPL could  
20 start to pick up and using equipment which was  
21 commensurate with the equipment used at the large-scale.

22 So we were fairly skilled in scaling up rapidly from  
23 10 litres to 300, after which it would be BPL's job to  
24 bring out the bigger tanks.

25 Q. And presumably that scaling up at PFL took place over

1 a period of months?

2 A. Very few months. November would be 1 litre and December  
3 would be going from 1 litre to 100, and January would  
4 be -- I think we would be up to 300 by the end  
5 of January with the aim of producing enough material for  
6 a convincing clinical trial or to start off a trial.

7 Q. Thank you. On that point. If we can revert to your  
8 supplementary statement, please, [\[PEN0172198\]](#), and on  
9 page 2, please, under "Introduction of 8Y" we see:

10 "Clinical trial for safety and  
11 efficacy: March 1985."

12 So that's a phase 1 clinical trial. Is that of the  
13 8Y produced at PFL?

14 A. Yes, and just to explain -- I think Dr Foster went  
15 through this or Dr Cuthbertson went through this -- the  
16 material available in March 1985 was probably  
17 fractionated in December or January, very early product.

18 Q. Because the product has to undergo a variety of tests  
19 within the production facility before it can be released  
20 for issue?

21 A. Exactly.

22 Q. I understand. We then see from your supplementary  
23 statement:

24 "Clinical trials for virus safety: from April 1985".  
25 I think that's what we have called the phase 2

1           clinical trial starting in April 1985.  Would that be  
2           again with the 8Y produced at PFL?

3    A.  Initially, yes, and as soon as BPL had produced its  
4           first successful batches, we saw the need to introduce  
5           their batches into trial, not least to answer any  
6           questions about pool size.

7    Q.  Thank you.  When was production of 8Y transferred to  
8           BPL?

9    A.  BPL continued to make the intermediate product up until  
10           the end of March.  Meanwhile very energetically  
11           acquiring the equipment to scale up 8Y.  And there was  
12           a clean break.  There was no intercollation of the two  
13           products.  They moved immediately in April to making 8Y  
14           with a full complement of PFL staff in there helping  
15           throughout the process.  These batches, of course, would  
16           only start to come through in June/July.

17   Q.  Yes.  So really from April 1985 production of 8Y started  
18           at BPL.  Would BPL again scale up their production,  
19           starting with smaller starting volumes of plasma and  
20           ramping up production or ...?

21   A.  No, we had been through that at PFL and we were  
22           confident that the equipment we had used at PFL had its  
23           big brother equivalents at BPL, and BPL went  
24           immediately, as far as I can recollect, to 1500 litres  
25           or maybe even 3,000.

1 Q. I understand and you tell us that 8Y was first issued  
2 for general use in September 1985 and reading your  
3 statement, you say:

4 "Between March and September 1985,  
5 haemophilia centre directors were aware that 8Y was  
6 available for clinical trial, using the Oxford protocol.  
7 However, by this time many of the suitable adult PUPs  
8 and in England ..."

9 Is "and" perhaps redundant in that sentence:

10 "... Many of the suitable adult PUPs in England had  
11 been hoovered up by one commercial trial or another and  
12 were now infected. If a patient presenting himself at  
13 a haemophilia centre was thought to have received very  
14 little or no treatment before, but circumstances were  
15 such that this could not be immediately documented ..."

16 A. The "and" after PUPs is redundant.

17 Q. Yes, thank you. Reading on:

18 "... if the circumstances were such that this could  
19 not be immediately documented, 8Y was not withheld. All  
20 patients submitted in good faith continued to be  
21 supplied with 8Y until general release in September.  
22 From September, BPL allocated supplies directly to RTCs  
23 who became responsible for onward allocation to  
24 haemophilia centres. Clinicians submitting suitable  
25 patients into trial after September would have been

1 encouraged to ask for special trial supplies via Oxford  
2 PFL, where I liaised frequently with Dr Rizza and was  
3 unofficial trial gofer. The aim was to ensure that  
4 a good spread of batches went into trial."

5 I think we saw, Dr Smith, a product information  
6 sheet for 8Y, which was issued by the director of BPL  
7 in July 1985, which suggested that the output production  
8 of 8Y would meet about one third of current demand for  
9 Factor VIII concentrate in England and Wales. Does that  
10 tie in with your recollection at the time?

11 A. I don't have the information with me today to make that  
12 calculation. I think that would have been based on the  
13 limited capacity of the old production plant at BPL to  
14 force any more plasma through the sausage machine.

15 Plasma by that time was not the limiting factor.  
16 The transfusion centres had made a fantastic effort to  
17 supply us with blood. In fact we were building up  
18 embarrassing stockpiles of plasma. The limitation would  
19 have been the capacity of the old coagulation factors  
20 lab to process the plasma to any product, whether it was  
21 8Y or not.

22 Q. We have certainly heard evidence, I think, that when 8Y  
23 was first introduced in September 1985 for routine use,  
24 there was insufficient supply to meet all demand in  
25 England and Wales, and I think in fact that situation



1 continued for perhaps a year or two. Do you have any  
2 recollection of that or is that not something you have  
3 really come here in a position to give evidence on?

4 A. I will try. The trouble is that demand has been defined  
5 in many different ways. I think what was in Dr Lane's  
6 mind in that memo would be the projected demand for all  
7 haemophilia use in England and Wales. The definition  
8 became: we have enough for or we don't even have enough  
9 for those treaters who would prefer to prescribe 8Y.  
10 These were very different quantities.

11 Q. So if one looked at it from the point of view that if in  
12 England and Wales from September 1984 no commercial  
13 products at all were used and only BPL-produced  
14 Factor VIII was used, is it right that looking at things  
15 from that point of view, there wouldn't have been enough  
16 8Y to meet all demand?

17 A. That's to the first approximation, yes.

18 Q. Sticking with that analysis, did that continue for  
19 a number of years or can you simply not remember or  
20 what?

21 A. My recollection is it was no longer my responsibility by  
22 then, that by the time the new plant opened in 1987, we  
23 would not have had quite enough plasma to make 8Y for  
24 the entire demand of the UK, but demand had slipped away  
25 from 8Y already by the commercial companies having

1           persuaded many directors that they needed a new level of  
2           purity to avoid giving their patients disastrous  
3           redundant proteins in 8Y.

4    Q.   Yes, and just in terms of your responsibility, you, of  
5           course, were head of research and development, I think,  
6           based primarily at PFL in this period?

7    A.   At -- yes.

8    Q.   So when --

9    A.   I was not even head of R&D at BPL, but I functioned as  
10           the R&D person for coagulation factors at PFL and there  
11           was an understanding that PFL did most of the research  
12           and piloting for BPL in coagulation factors.

13   Q.   And once BPL were comfortable in producing 8Y and were  
14           able to do so, then essentially matters were handed over  
15           to them to continue doing that?

16   A.   Yes, PFL continued to make 8Y, since we had to remove  
17           cryoprecipitate in order to get at the other things we  
18           were making on behalf of the whole country. Many of the  
19           products we were making, we could do on 300 litres  
20           a week. Fewer sufferers from certain deficiencies.  
21           Therefore we could look after the needs for the whole  
22           country in our pilot plant. Factor VIII --  
23           cryoprecipitate had to come out anyway. We might as  
24           well make our 8Y for it. It gave also a nice comparator  
25           to the large-scale product at BPL, and when we had

1           teething problems or troubleshooting to do at BPL, you  
2           always had that comparator of: how is it doing at  
3           Oxford?

4    Q.   Thank you, Dr Smith.

5           I would like to move on now, please, to the  
6           statement you provided for us on this topic, which is  
7           [\[PEN0171130\]](#). I would like to simply take you through  
8           your statement, pausing at certain times to ask you  
9           various questions or perhaps take to you one or two  
10          documents. We will see from page 1 that your  
11          contribution is in three parts: firstly, responses in  
12          red to specific questions we have put to you; secondly,  
13          an additional note 6, which we will come to, at the back  
14          of your statement; and thirdly, a reference to red  
15          annotations on a C3 chronology. In short the Inquiry  
16          team tried to bring together all of what appeared to be  
17          relevant documents into a chronology. It's about  
18          50 pages. We sent that to you for your information and  
19          any comment. I'll simply provide the reference number  
20          for that without going through it. The reference number  
21          is [\[PEN0171142\]](#).

22          You do say that as in B3, you have no inside  
23          knowledge of SNBTS's activities with the result, of  
24          course, your interpretations must yield to those of  
25          persons intimately involved at the time.

1 Thank you.

2 Then over the page, please. At the bottom of the  
3 page we will see under "Matters to be included in the  
4 statement," the first question one was this:

5 "In note 4.4 to his B3 statement ..."

6 And this is a reference to events post-Groningen  
7 in November 1984. You stated that:

8 "... PFL/BPL had the option of higher temperatures  
9 than PFC".

10 We asked:

11 "Why were BPL able to heat Factor VIII concentrate  
12 at higher temperatures than PFC?"

13 We have explored this to some extent yesterday but  
14 in your written answer you say:

15 "At the time ..."

16 So this is a reference to November 1984, round about  
17 then?

18 A. Yes.

19 Q. "... I believed that the higher temperature was  
20 permitted by the reduction (about 10-fold) of the  
21 sticky, poorly-soluble proteins, fibrinogen and  
22 fibronectin. Such reductions had been our predominant  
23 aim for many years. The Winkelman publication in 1989  
24 still attributed success to higher purification."

25 I'll pause to look at that. Please. It's

1        [\[LIT0010617\]](#). We can see this is a 1989 publication by  
2        Mrs Winkelman and others, including yourself. I think  
3        in short this publication relates to 8Y. Is that  
4        correct?

5        A. Yes.

6        Q. And we can see from the abstract, it provides:

7                " ... a new method for the manufacture of a heated  
8        Factor VIII concentrate of a high specific activity  
9        (2-6 IU Factor VIII per milligramme) ..."

10               Does that relate to the purity of the product,  
11        doctor?

12        A. Yes.

13        Q. Just for comparison purposes, if we go to the left-hand  
14        column, please, at the bottom we can compare that purity  
15        with the purity of the BPL intermediate purity  
16        Factor VIII, the bottom left-hand paragraph:

17                "Heating of the blood products laboratories'  
18        intermediate purity concentrates (less than 0.5IU/mg  
19        ..."

20                That's a reference to the purity of the intermediate  
21        concentrate?

22        A. Yes.

23        Q. Thank you. Then going back to the abstract, I think we  
24        can just read that for ourselves. (Pause)

25                We don't have to say anything more about that. Then

1           returning again, please, to the bottom left-hand column  
2           and picking up where we left off:

3           "Heating of the intermediate purity concentrates in  
4           the dried state at over 70 degrees centigrade resulted  
5           in a substantial loss of Factor VIII activity and  
6           unacceptable loss of solubility. This poor performance  
7           during severe heating may have been due to the presence  
8           of impurities, particularly to high concentrations of  
9           fibrinogen and fibronectin. We report here a method for  
10          substantial reduction of fibrinogen and fibronectin  
11          concentrations that allows preparation of a high purity  
12          Factor VIII concentrate in high yield. This paper  
13          describes the stability of this new concentrate to  
14          severe dry heating and the exploitation of the method  
15          for the manufacture of high purity, heat-treated  
16          Factor VIII (product code 8Y) ..."

17          Et cetera. Over the page I think we see quite  
18          a nice summary of the different manufacturing steps of  
19          8Y. In the right-hand column, please, towards the  
20          bottom we can see:

21          "Production of 8Y concentrate ..."

22          And I'm not going to go into the different steps in  
23          detail but perhaps, looking at the heading of each one,  
24          firstly we see "Cryoprecipitate Extraction" and  
25          underneath that we see "Heparin Precipitation" and we

1           have discussed that. And then over the page, please,  
2           the next step we see is "Precipitation of Factor VIII".  
3           Is this essentially the second precipitation step?  
4    A.   Exactly. After the heparin stage, the Factor VIII is in  
5           the supernatant and therefore of quite large volume.  
6           It's always an advantage if you can get the Factor VIII  
7           into a small volume and you do that by making sure it  
8           goes into the solid phase and the unwanted material  
9           stays in the supernatant.  
10   Q.   Yes, and that second precipitation takes place with  
11           glycine and sodium chloride?  
12   A.   Yes. That is something we had been working on as  
13           a second stage to another primary precipitation stage.  
14           We could just slot that in.  
15   Q.   I see. The next step is "Removal of Saline", that's  
16           just salt, is it?  
17   A.   Yes.  
18   Q.   The last stage is "Finishing", which no doubt involves  
19           various things but also in particular I think involves  
20           freeze-drying and also then the heating in a dry state.  
21           Is that correct?  
22   A.   Yes.  
23   Q.   I will come back to ask you just a little bit about  
24           freeze-drying in the next question but if we could for  
25           present purposes, please, go to the page 0621, the start

1 of the discussion. In the first sentence under

2 "Discussion" it states:

3 "The key step in this new manufacturing process is  
4 the use of heparin at temperatures above ambient to  
5 precipitation fibrinogen and fibronectin. These two  
6 proteins are the main constituents of cryoprecipitate  
7 and a substantial reduction in their concentrations is  
8 an essential part of any high purity Factor VIII  
9 preparation."

10 Over the page, please, finally at the bottom  
11 left-hand column, the final paragraph commences:

12 "The ability of the 8Y concentrate to withstand very  
13 severe heating in the dried state is probably a result  
14 of increased purity."

15 Actually, Dr Smith, a reference back to your written  
16 answer, that even in 1989 the ability to heat severely  
17 was still attributed to higher purification?

18 A. Yes, mainly.

19 Q. Mainly, yes. Just the last point in this paper, please,  
20 the final paragraph. We have at the right-hand column  
21 at the bottom, the reference to:

22 "The 8Y concentrate has now been in use since 1984."

23 Is that correct?

24 A. I think what was intended there was we had been using  
25 the process.



1 Q. Oh.

2 A. Plainly we did not -- we knew that it had not been into  
3 patients before early 1985.

4 Q. Thank you. We can put that paper to one side, please,  
5 and return to your written statement, if we may?

6 A. Could I just --

7 Q. Yes.

8 A. -- give you another reason for stating that?

9 With hindsight, in respect of some of the objections  
10 being made to the success of 8Y, it was important to get  
11 the date at which the plasma for the first pools was put  
12 in because over this period, for instance, anti-HIV  
13 testing was being introduced and it was a moving target,  
14 if you like, for virus inactivation. So that's another  
15 motivation for being specific.

16 Q. Yes, we know that in October 1985 HIV screening was  
17 introduced in the UK, so --

18 A. Yes.

19 Q. I understand. Back to your written statement, please.

20 THE CHAIRMAN: Could I just ask, while there is something  
21 which again has interested me incidentally. You refer  
22 to some of the objections that have been raised to the  
23 success of 8Y and I seem to have read somewhere  
24 a comment that people, fractionators around the world  
25 were amazed at what had been achieved partly because

1           they couldn't replicate it. Do you remember anything to  
2           that effect?

3    A. Not at the time. I know the amazement was that two men  
4           and a boy working in a dustbin under socialised medicine  
5           could have come up with a solution before large  
6           pharmaceutical companies.

7    THE CHAIRMAN: That's not unique. That's what they think  
8           about everything that happens in Britain, is it not,  
9           Dr Smith?

10   A. I did not know in detail about PFC's difficulty. I did  
11           not even know if they had any motivation to try 8Y at  
12           any time --

13   THE CHAIRMAN: I'm not thinking of PFC. I'm thinking of  
14           other fractionators.

15   A. I am not sure at what date that refers to.

16   THE CHAIRMAN: I'll follow it up and see if I can give you  
17           the reference.

18   A. 8Y was adopted by several other countries around the  
19           world eventually.

20   THE CHAIRMAN: I think it's in the report of another  
21           Inquiry. Yes, I'll come back to it.

22   MR MACKENZIE: Thank you.

23           Dr Smith, returning, please, to your written  
24           statement, we have got, I think, to three lines from the  
25           top of the page. You say:

1           "Today I freely accept that other influences may  
2           have been at work, and that we could have been fortunate  
3           that other aspects of 8Y manufacture did not mask the  
4           benefits of increased purification. In this context  
5           I must emphasise that high purity in the early 1980s  
6           meant 5-10IU Factor VIII/mg protein not the much higher  
7           purifications later achieved by chromatographic  
8           methods."

9           To pause there, when you say today you:

10           "... freely accept that other influences may have  
11           been at work, and that we could have been fortunate that  
12           other aspects of 8Y manufacture did not mask the  
13           benefits of increased purification ..."

14           What do you mean by "other influences" and "other  
15           aspects"?

16    A. I think to some extent 8Y had a charmed life through its  
17           development and its early introduction. We seem to have  
18           had very few teething problems, even in the scale-up at  
19           BPL, which could not be handled very quickly.  
20           Unusually, I am reminded that we did hit a rough patch,  
21           1986/1987, when BPL was having trouble with solubility  
22           of 8Y, and at some point in 1886 it became a major  
23           project between my freeze-drying and 8Y experts at PFL  
24           and everyone who could help us at BPL to try and solve  
25           this. This uncovered far more potential variables to

1 the success of dry heating than we had suspected at the  
2 time.

3 The point I suppose I'm trying to make is that if we  
4 had made unfortunate choices in 1985 in our  
5 freeze-drying conditions, we might very well have been  
6 discouraged. I think you reminded me of a very large  
7 amount of work done in 1987 to try and put  
8 freeze-drying, especially at Elstree, on a more  
9 consistent footing. This, however, was against  
10 a background when BPL was having to accept a very wide  
11 variety of plasma qualities, ranging from plasma from  
12 Edgware, which was literally about four hours old, to  
13 material which had been stored for some time, perhaps  
14 frozen under very different conditions. A variation in  
15 plasma quality which led to a twofold variation in the  
16 amount of protein in a vial.

17 In turn, the amount of protein in a vial influences  
18 the moisture content, which you get when you freeze-dry  
19 under particular conditions. And although we knew there  
20 was some variation in moisture content, partly,  
21 probably, as a result of the different qualities of  
22 plasma, we had not at that time fully explored the range  
23 of moisture contents in which we could both get  
24 acceptable virus kill and acceptable Factor VIII yield  
25 and solubility. So some of the -- what we might call

1 the development work -- was done a bit late on 8Y. But  
2 that is standard for almost any concentrate.

3 Q. Yes. In answer to the question why was 8Y able to  
4 withstand such severe heating at the time in 1984/1985,  
5 you thought it was primarily because it was a high  
6 purity product.

7 A. Yes. I should perhaps explain another relationship  
8 between yield and solubility. If the material in your  
9 vial is predominantly sticky fibrinogen and fibronectin,  
10 these being proteins very readily damaged by heat,  
11 unless you have suitable stabilisers, the product is  
12 difficult to redissolve and there is no use the  
13 Factor VIII being in there if the fibrinogen and  
14 fibronectin, claggy mass, is masking it. It just does  
15 not come out to be assayed, so you appear to be losing  
16 yield. It is particularly relevant when you are talking  
17 about home treatment, where a haemophiliac is getting an  
18 aura, a sensation, that he is bleeding into his joint,  
19 or about to, and wants to get the stuff dissolved fast.

20 Under these conditions we know that patients are  
21 almost bound to try and take shortcuts and it's -- the  
22 effective yield, the effective amount of material going  
23 into the patient is therefore likely to be a bit less  
24 than we thought, because time has not been given to get  
25 all of it into solution. It is not the haemophiliac's



1 both native and heated, we keep coming across this  
2 tension between yield and solubility. The solubility is  
3 important not just for the convenience of the doctor,  
4 nurse or haemophiliac making up the product but if the  
5 preponderance of sticky proteins, like fibrinogen and  
6 fibronectin, is such as to mask the Factor VIII, to hide  
7 it in fact from the solvent in which you are trying to  
8 dissolve the dry product, you do not get the true amount  
9 of Factor VIII back, either into the tube from which you  
10 are going to assay the Factor VIII, or from the vial in  
11 which the haemophiliac is going to get his dose.

12 So if a product is not perfectly soluble, you are  
13 not going to get into solution all of the Factor VIII  
14 which is actually in the vial.

15 Q. So in a way are you explaining that there are a number  
16 of benefits of a high purity product?

17 A. Benefit of a very highly soluble product.

18 Q. The emphasis is on solubility, I see. Thank you,  
19 doctor --

20 THE CHAIRMAN: Can I just be sure I do understand? We are  
21 talking at this stage of the use of the product, the end  
22 use, are we?

23 A. Yes.

24 THE CHAIRMAN: Yes. The convenience of the administrator,  
25 that's relatively straightforward, but what one has to

1 take on board, I think, is this notion that if there is  
2 a high proportion of fibrinogen and fibronectin, then  
3 the purified water used to dissolve will not necessarily  
4 dissolve all of the Factor VIII?

5 A. No, you will get a suspension, if you like, which in  
6 fact may be quite tolerable on infusion but in most  
7 cases would not get into the patient because it would be  
8 retained in the filter element of the needle used to  
9 administer the product.

10 THE CHAIRMAN: Yes, well, before we get down to the sharp  
11 end, as it were, I think my problem is this: I can  
12 understand that the fibrinogen and fibronectin would  
13 resist dissolution, as it were, they are much less  
14 soluble. What I find a little difficult at the moment  
15 is to see why the FVIII that's there is not dissolved  
16 when it is soluble.

17 A. The Factor VIII which was distributed throughout the  
18 product originally because it was in solution, is in  
19 fact being sequestered in small lumps, if you like, of  
20 insoluble material, and although it's alive, it is not  
21 getting out.

22 THE CHAIRMAN: It is not getting out.

23 A. And it's being administered before it has been  
24 completely dissolved.

25 THE CHAIRMAN: I think I can see the physical way in which



1           that could happen, if you have bunching, as it were, of  
2           the various molecules and some of the FVIII is hidden  
3           within a blob, then it can't be attached. Is that the  
4           notion?

5   A.   Yes.

6   THE CHAIRMAN: Thank you.

7   A.   Sorry, I have made a meal of that. Almost as good as my  
8           Factor VIII explanation.

9   THE CHAIRMAN: No, not at all.

10  MR MACKENZIE: Thank you, sir.

11           Thank you, Dr Smith.

12           Could we then, please, turn to question 2 in your  
13           main written statement? We asked:

14           "Does Dr Smith agree that the reason why 8Y was able  
15           to be severely heat-treated was because of the  
16           freeze-drying process used and the resulting crystal  
17           structures which formed during that process? To what  
18           extent did any of the other manufacturing steps,  
19           including the fact that 8Y was a high purity  
20           concentrate, explain why it was able to be heated at  
21           80 degrees for 72 hours?"

22           Before we look at your written answer, Dr Smith,  
23           I don't think we have looked at the freeze-drying step  
24           at all and I wonder whether you can give us a very  
25           simple or basic understanding of how the freeze-drying

1 step was carried out at PFL in the production of 8Y?

2 A. I have said elsewhere that we had only one rather  
3 elderly freeze dryer at PFL, dating from about, oh,  
4 certainly 1965. Originally a dryer for bottles, the MRC  
5 bottles we talked about earlier, it had been adapted to  
6 dry vials. The geometry of the dryer and the vial  
7 header, into which we put the vials, was such that  
8 drying was uneven. There was a gradation of drying  
9 efficiency from the top to the bottom shelves of the  
10 header unit. Consequently, even with the preceding  
11 products, we had learned to freeze-dry very carefully,  
12 very conservatively and to finish the freeze-drying over  
13 a long period of time, in order essentially for the  
14 bottom vials to catch up with the top ones, and in that  
15 way to have to have a more homogeneous batch of product.  
16 If you would like me to go into the processes of  
17 freezing and freeze-drying.

18 Q. Just so that we can have some sort of visual picture or  
19 some understanding of what goes on inside the freeze  
20 dryer.

21 A. Right. I'm wondering whether it is best to describe the  
22 PFL -- I'll describe the PFL system first.

23 This freeze dryer would not freeze the vials on the  
24 shelves of the dryer. We had to freeze the vials  
25 offline and load them frozen at minus 30 into

1 a pre-cooled header. Once in the freeze dryer header,  
2 the vials are resting directly on shelves, which can be  
3 electrically heated. In a first stage you apply the  
4 vacuum to the chamber and a small amount of heat into  
5 the shelves.

6 Q. And how is heat applied to the shelves?

7 A. It is applied electrically in the case of the PFL dryer.

8 Q. So the shells are heated --

9 A. The shelves are heated gently and as evaporation  
10 occurs -- in fact sublimation. There is never any  
11 liquid phase; you go straight from the solid ice phase  
12 to the vapour stage -- as evaporation occurs and the  
13 vapour is condensed in another part of the machine, the  
14 product naturally cools. Therefore you keep adding  
15 a little more heat to balance the rate of evaporation  
16 which you are getting. This is called the sublimation  
17 phase, and the intention is that every vial should have  
18 lost nearly all the water originally present.

19 Q. And at that stage the heat is being conducted from the  
20 shelves to the vial to the product. Is that correct?

21 A. Yes, since this is a high vacuum, there is no question  
22 of convection, heating by convection, so the only source  
23 of heat to the product is from the heated shelf through  
24 a layer of glass in the bottom of the vial.

25 Q. To the product?

1 A. Yes.

2 Q. There is no question of -- is it convection --

3 A. There is no convection. It has to be done rather  
4 carefully. It's a slow process. After you have removed  
5 the bulk of the water, you are left with water which is  
6 physically adsorbed to the protein and therefore in  
7 a further phase you apply a higher temperature and, of  
8 course, still vacuum, and you drive off more and more of  
9 the adsorbed water to end up with a product with the  
10 moisture content you believe to be appropriate.

11 In our case, because we were drying very  
12 conservatively, and we had to wait a long time for the  
13 bottom vial to catch up with the top one, playing safe,  
14 our product would end up usually being dryer than  
15 perhaps a comparable freeze dryer elsewhere would have  
16 produced. Moisture content is critical to both the  
17 survival of Factor VIII during heating and the action of  
18 heat on the target viruses.

19 Q. Yes. So that is the freeze-drying step at PFL?

20 A. Yes.

21 Q. What was the --

22 THE CHAIRMAN: Could I --

23 MR MACKENZIE: Yes.

24 THE CHAIRMAN: I think what interests me is not the detailed  
25 discussion of what happens once you get into the

1           Usifroid freezer but the need to reduce it to minus 30  
2           as a preliminary step? Does that mean that in effect  
3           your freeze-drying process at PFL was indeed a two-phase  
4           operation with both important contributors to the  
5           ultimate outcome?

6    A.    In hindsight they could have been because the way in  
7           which you freeze is critical to the crystal structure  
8           you get, which is in turn critical for the solubility of  
9           the product.

10   THE CHAIRMAN: I know you say "in hindsight" and I know  
11           there is quite a lot of history that lies behind that  
12           but that wasn't in the Winkelman specification as  
13           a factor, was it?

14   A.    Not in the specification, no. In the paper, a little  
15           more detail.

16   THE CHAIRMAN: Yes, but not in the specification.

17   A.    No.

18   THE CHAIRMAN: So those plagiarists that you have described  
19           around the world who were looking at the patent for  
20           inspiration would not get a hint of what you were  
21           actually doing.

22   A.    We were not really going to proselytise for our way of  
23           drying Factor VIII. Put it that way.

24   THE CHAIRMAN: That's roughly the point I was interested in  
25           before the break.

1 MR MACKENZIE: Thank you. Just to sidetrack a little,  
2 doctor, to look at the full volume of material in the  
3 vial, I think from different sources we understand that  
4 for the PFC NY Factor VIII, it was freeze-dried from  
5 40 ml of solution. Z8 was freeze-dried from 15 ml of  
6 solution and I think the NYU higher purity product, it  
7 was perhaps envisaged that it would be freeze-dried from  
8 perhaps 2 to 3 ml of solution. What was the fill volume  
9 of 8Y when you were undertaking the freeze-dried step at  
10 PFL back in late 1984/beginning of 1985?

11 A. During development, and I think for several years  
12 thereafter, the only presentation we offered was a 10 ml  
13 fill. That would be 250 units, I believe.

14 Q. And is the fill volume of the product a relevant factor  
15 in the process and in particular the ability of the  
16 product ultimately to withstand severe dry heating?

17 A. It is not so much the volume per se. Depending on what  
18 the geometry of the vial is, you are aiming to have the  
19 thinnest possible layer of product. So if you had  
20 a tall vera(?) vial, obviously you would have a deep  
21 layer and a deep plug. The disadvantage of this, having  
22 a deeper plug, is that during freezing this is going to  
23 occur much more slowly; it is going to occur unevenly  
24 from the outside in, as it were.

25 Then again in the drying phase, the freeze-drying,

1 the evaporation is all occurring from the top of the  
2 vial. It dries from the top, and the heat is coming in  
3 from the bottom, and of course it takes time for the  
4 heat to come through to where it's going to be used to  
5 evaporate the water from the Factor VIII.

6 Q. Yes.

7 A. So it's a disadvantage to have a thick layer. You would  
8 aim to have the thinnest possible layer within reason.

9 Q. I understand. Then you --

10 A. If you go too thin, you get the -- we have an industrial  
11 vial here. The bottom is not very even and if you have  
12 it too thin, you have uneven thicknesses of your frozen  
13 mass across the individual vial.

14 Q. Thank you. And the freeze-drying step at BPL, did that  
15 differ in any material way from this undertaken at PFL?

16 A. The most significant difference, perhaps the only one,  
17 was that in BPL the vials filled in the dispensing area,  
18 the aseptic dispensing suite, went directly into the  
19 freeze dryer on trays with a false bottom. There was no  
20 offline freezing. The vials were frozen by removing the  
21 bottom of the tray, letting the vials fall directly on  
22 to the shelves, and in the case of the large-scale  
23 equipment, at BPL, the shells were cooled and then later  
24 heated by circulating fluid in the five or six shelves  
25 in the instrument, rather than by electric heating.

1 Q. Thank you.

2 THE CHAIRMAN: That's a washing machine approach to it at  
3 that stage, is it, introducing liquid at an appropriate  
4 temperature?

5 A. It means you can go from freezing to cooling -- I'm not  
6 sure if it was the same fluid but without having to  
7 pre-freeze.

8 MR MACKENZIE: But, doctor, the liquid, is introduced within  
9 the shelves like a radiator, a closed system, or is it  
10 circulating around about the vials?

11 A. No, the vial is sitting dry on the dry shelves and as  
12 you aptly point out, it is like heating five or six  
13 radiators on top of each other, on each of which sits  
14 a batch of vials.

15 Q. Yes. Simply for completeness, I think we have  
16 a photograph of the freeze dryer at PFC. It might be  
17 worth just looking at that for completeness. It's page  
18 18 of [\[PEN0121695\]](#). The first page, if it helps, is  
19 1695.

20 I don't have a date for this photograph, doctor --

21 A. That's at either PFC or BPL.

22 Q. Yes, I think it's PFC. Is the freeze dryer shown in  
23 these photographs similar to the type of freeze dryer,  
24 at least in looks, as that at BPL?

25 A. The geometry of the chamber seems to be very similar.



1           There is some evidence that it's circulating fluid in  
2           the shelves because of the nature of the plumbing.

3   Q.   There seem to be pipes going into the shelves?  Yes?

4   A.   Yes.

5   THE CHAIRMAN:  I think there is some evidence that PFC had  
6           an Usifroid also.

7   A.   Yes.

8   THE CHAIRMAN:  So it would be the same machine, the same  
9           type of machine.

10  A.   Same type of but very different from the Usifroid at  
11       Oxford, which is a very primitive top-loading machine,  
12       like a top-loading washing machine.  The geometry of  
13       a freeze dryer like the one you show on the screen gives  
14       minimum distance from top to bottom and with each shelf  
15       being heated independently, it is designed to give  
16       homogeneous drying.  Our dryer was vertical, with quite  
17       a tall header, twice the height of that array of  
18       shelves, and the arrangement of the cooling condensers  
19       were such that it did not have the same homogeneity of  
20       heat application.

21  Q.   Thank you.

22           Moving back, please, doctor, to page 3 of your  
23       written statement and your written reply to question 2  
24       was:

25           "Here too, I remain agnostic.  It is conceivable

1           that the traditional freezing and drying conditions  
2           which we transferred to 8Y and 9A (without too much  
3           brain activity or choice, given the capability of our  
4           equipment) were crucial to its success but the arguments  
5           for that come from PFC, not from PFL or BPL."

6           You refer to an event in about 1986. You:

7           "... tweaked freeze-drying conditions at BPL ...  
8           their more modern driers to optimise performance and  
9           avoid occasional failures (attributable at the time to  
10          the variable quality of plasma), but these adjustments  
11          did not include a supercooling phase recommended by PFC.  
12          This never featured deliberately in the design of our  
13          freeze-drying programmes for 8Y or any of the half dozen  
14          other delicate products we dry-heated successfully in  
15          those years. It may well have determined success for  
16          other companies' Factor VIII concentrates with a similar  
17          purity but different constituents."

18          When you refer in the second last sentence to "this  
19          never featured" and in the final sentence, "it may  
20          well", is that a reference to supercooling?

21        A. Indeed.

22        Q. When you say in your answer that you remain agnostic, is  
23          that really in relation to the necessity of supercooling  
24          as part of the freeze-drying process?

25        A. Essentially, yes.

1 Q. Yes. If I were to ask the question in a different  
2 way -- do you accept as a general principle that the  
3 freeze-drying step is a relevant factor to  
4 a concentrate's ability to withstand severe dry  
5 heating? -- what would your answer be to that more  
6 general question?

7 A. That ...

8 Q. That freeze-drying step --

9 A. That freeze-drying and indeed freezing were important,  
10 the variables were important -- yes. And indeed, I feel  
11 I have answered the wrong question. I have given the  
12 wrong answer to question 2. I was looking over my  
13 shoulder at Dr McIntosh, who was a proponent of  
14 supercooling, and I see the question actually asks, was  
15 it because of the freeze-drying process and the  
16 resulting crystal structures -- I can go along with  
17 that, that it was important, but I was rather  
18 anticipating a bid from PFC that ...

19 Q. I understand. Two documents may help just to finish  
20 this issue. Could we, please, go firstly to  
21 [\[PEN0171426\]](#)? This is a memo dated 7 August 1986 from  
22 Dr Evans to Mr Kinnarney and others, including yourself,  
23 Dr Smith, on the question of freeze-drying of 8Y and BPL  
24 and I think in short, consideration is being given at  
25 this time to the freeze-drying process at BPL. Is that

1 correct?

2 A. In response to occasional failures.

3 Q. And I think anyway, the better document perhaps is the  
4 next one please. [\[PEN0171438\]](#). If we go to page 5,  
5 please, which is 1442, we can see the date and authors  
6 at the bottom. The date is March 1987. The authors,  
7 I think, are Dr Winkelman and Dr Evans. Could we then,  
8 please, go back to the front page? We can see the title  
9 is "Freeze-drying 8Y: progress report, April 1986  
10 to March 1987". We can see the background in  
11 paragraph 1:

12 "Investigation of the freeze-drying stage of  
13 Factor VIII processing has only begun to come under  
14 close scrutiny in the last 12 months."

15 Et cetera. At page 2, I think, an interesting  
16 paragraph. In the third paragraph:

17 "Once a fix was found, we began a more wide-ranging  
18 investigation of the freeze-drying process. A major  
19 difficulty was choosing where to start when there are so  
20 many controllable variables (and plenty of  
21 uncontrollable ones), all of which are potentially  
22 interrelated (eg freezing, cooling, primary drying  
23 temperature, secondary drying temperature, time and  
24 pressure, final moisture content, formulation). The  
25 only possible approach was to seize clues from each

1 experiment as it was done and to control as much  
2 identifiable variables as possible in every experiment."

3 I think also of interest, please, 1442, under 4  
4 "Further Work":

5 "We have obviously only scratched the surface of the  
6 extremely complicated process of freeze-drying. Even  
7 the few experiments described here point out how much  
8 there is to find out, how seemingly small changes in  
9 procedure can produce different end results and how  
10 interrelated the various stages are."

11 Without going into the details, doctor, in short  
12 this document suggests that freeze-drying was  
13 a complicated process, involving many interrelated  
14 variables. Is that fair?

15 A. It was more complicated than we had thought.

16 Q. I see.

17 A. But having opened the can of worms we were going to try  
18 and make a job of making sure that the difficulties  
19 didn't recur.

20 Q. Yes. I should ask you: were there any changes to BPL's  
21 freeze-drying process of 8Y between the initial  
22 production of 8Y in April 1985 at BPL and subsequently?  
23 Were any changes made?

24 A. Again, you would have to perhaps distinguish the  
25 controlled ones from the ones which happened by drift or

1 plant aging or changes in the specification of the  
2 drying programmes. But the one which springs to mind  
3 and which is mentioned in this is that we did increase  
4 slightly the concentration of sucrose in the  
5 formulation, and I do recall that because I was afraid  
6 that that increase in sucrose to protect the Factor VIII  
7 might also protect viruses, and at that time I know we  
8 had the good fortune to send product to Dr Cuthbertson  
9 at PFC, who kindly reassured us that there was not much  
10 difference in the amount of virus kill he was getting.

11 Q. I see. Moving on, please, to the next question in the  
12 statement, question 3. We asked about the patent  
13 application for 8Y and we asked whether:

14 "... the fact that the 8Y process was subject to a  
15 patent application inhibit disclosure by BPL to PFC of  
16 the manufacturing process for 8Y, including the severe  
17 heating regime?"

18 You explain your:

19 "... dim recollection is that you were disappointed  
20 that a swift Crown record did not in fact provide  
21 protection."

22 I forget, Dr Smith, if we have considered the  
23 question of Crown records before but in case we haven't,  
24 could you explain briefly what you mean by "Crown  
25 record"?

1 A. It was our assumption, I think, in the public service --  
2 I don't know if this was shared by PFC -- but when  
3 I would ask about why must we patent, can we not share  
4 knowledge equally with our partners in PFC, I was  
5 assured that a Crown record would protect us and allow  
6 us to have priority without attack on prior disclosure  
7 to, for instance, PFC. So I believe the advice we got,  
8 as far as we got into this with the patent lawyers, was  
9 that this was not so. It was an illusion that this  
10 would protect us.

11 Q. And what did one have to do to get a Crown record?

12 A. I can't really recall. I think one wrote down the  
13 substance of the invention and presumably there is  
14 a Crown patent office or ...

15 Q. And --

16 A. I'm not sure, it was forestalled in any case.

17 Q. Okay. You go on to explain that:

18 "... full description to any other party  
19 (unfortunately including even our friends at PFC) would  
20 constitute prior disclosure. This was the first time  
21 that BPL had been required to file a patent -- curiously  
22 at the time through the Ministry of Defence's patent  
23 lawyers -- and we had been severely cautioned in this  
24 respect."

25 You explain:

1            "This was much regretted but I was reassured that  
2            PFC, although adopting a different procedure to protect  
3            intellectual property ..."

4            And the reference to [\[SNB0074479\]](#) we don't have to  
5            go to. I think it's Dr Foster in July 1984 writing to  
6            Research Disclosure, an American publication, with an  
7            invention. But you explain that PFC understood your  
8            embarrassment and that:

9            "... it cannot be sufficiently stressed that, in  
10           early 1985, PFC were pursuing their own, much more  
11           promising pasteurisation policy against NANBH and were  
12           not beating at my door for an 'English solution'."

13           And:

14           "The Inquiry has found no evidence that PFC felt  
15           they were slighted or delayed. In any case, the patent  
16           application was filed in record time and immediately  
17           communicated to PFC. This was a courtesy obligation; I  
18           did not expect PFC to express rapt interest, nor does  
19           the record reveal any. There is evidence that a visit  
20           to PFC (on 19 February 1985) may have bridged any  
21           interim gaps in what they needed to know."

22           In short, Dr Smith, we can look at the evidence of  
23           Dr Foster as to what his reaction was on receipt of the  
24           8Y patent application. But in short, his view was that  
25           he had a better option, he wished to pursue the NYU



1 Johnson project and the receipt of the patent  
2 application didn't cause him to change direction. Would  
3 you have expected him to have expressed a lot of  
4 interest or changed direction on receipt of the 8Y  
5 patent application?

6 A. In his shoes, no. And even knowing what I did about 8Y,  
7 we knew nothing about whether it would withstand  
8 sufficient heat to inactivate non-A non-B Hepatitis.

9 Q. Thank you.

10 The next question, please, is question 4. We asked:

11 "When did it seem likely, from evidence of its  
12 clinical use, that the heating regime for 8Y resulted in  
13 a product which did not transmit NANBH?"

14 There is a reference to footnote 3, if we can scroll  
15 down to that, please. In short, doctor, we had set out  
16 all the documents we had found that provided evidence of  
17 the safety for NANBH of 8Y; really with a view to seeing  
18 at what point in time you thought the evidence was such  
19 that one could say it seemed likely that the heating  
20 regime for 8Y worked, and you explain in your written  
21 answer that -- before we get to that I should ask, do  
22 you remember, Dr Smith, I think you said earlier that  
23 you were the gofer for the 8Y trials. So you were quite  
24 heavily involved in organising it or you were quite  
25 heavily involved in it, put it that way?

1 A. To be specific, I had no role in designing the protocol.

2 Q. Yes.

3 A. My role would be to receive calls from a clinician who  
4 thought he had a suitable patient, either having had no  
5 previous treatment or a few cryos, to explain that we  
6 were not offering freedom from virus transmission,  
7 explain the named-patient system, if he did not already  
8 understand that, obtain his signature for that and  
9 rather quickly to get the product to him, since quite  
10 often it was a patient presenting for the first time.

11 After that, I would be in nagging role, reminding  
12 the centre at fortnightly intervals that we were due an  
13 enzyme test, and if I had not received it within two or  
14 three days of the due date, nagging again to make sure  
15 that it was done within the leeway allowed around the  
16 fortnightly or monthly testing.

17 Receiving the results each month on a new photocopy  
18 of an ongoing record, to give me a cumulative view of  
19 what was happening, to initiate investigations as far as  
20 possible to determine the possible sources of any  
21 suspicious rise in ALT, assisted where appropriate, by  
22 Dr Rizza next door, to assemble the data, again in  
23 consultation with Dr Rizza, for any report which we were  
24 invited to produce. That would be it. And eventually  
25 to assist in the publication, presentation, of a script

1 for publication.

2 Q. Thank you. The phase 2 trials start in April 1985. Do  
3 you remember whether you reported the results to PFC  
4 and, if so, when?

5 A. I never formulated a report directly for PFC. I assumed  
6 first of all that they were rather preoccupied, and if  
7 their haemophilia directors were particularly interested  
8 in what we were achieving or not achieving, then they  
9 would have transmitted that too to PFC. There was no  
10 aim to keep them out of the loop. There was no reason  
11 to keep them in the loop given they had so many  
12 opportunities to learn from their own directors.

13 Q. And presumably, if the trial started in April 1985, and  
14 one was undertaking testing of raised transaminase in  
15 recipients, one would have to wait a certain period  
16 before any results could carry any weight at all. Is  
17 that correct?

18 A. Exactly, and I would not, for instance, have copied to  
19 Peter Foster the preliminary and interim results we  
20 reported to the haemophilia centre directors, for  
21 instance, because I would not think we were ready to  
22 make a case for or against. I'm almost certain that  
23 when it came to a publication, from courtesy I would  
24 have posted these off, at least to Dr Foster, if not to  
25 Dr Perry.

1 Q. Yes. On that last point, could we please go to  
2 a document [\[SNB0015484\]](#).

3 What this is, Dr Smith, it is an addendum by  
4 Dr Perry to a report he had drafted for a meeting which  
5 was still to take place between the SNBTS and  
6 haemophilia directors in Scotland. And in January 1985,  
7 I think, Dr Perry drafted this addendum. In the first  
8 paragraph he states:

9 "The heat treatment procedure now being applied to  
10 Factor IX concentrates (PFC and BPL) and to Factor VIII  
11 (BPL) may well be effective in ensuring non-infectivity  
12 of products --"

13 A. Excuse me, I think you said "January 1985".

14 Q. January 1985, yes.

15 A. But this can't be written in 1985. It's new, "Products,  
16 1985/87".

17 Q. I think it's a reference to new products PFC are  
18 intending to develop --

19 A. I see.

20 Q. -- in a later period. But I think it's fairly clear  
21 that this addendum is written in January 1985. It's  
22 really just to make the point, Dr Smith, certainly by  
23 that time, either the end of -- I'm sorry,  
24 it's January 1986, I'm sorry, I'm confusing myself.

25 It's January 1986 this is written, because there was

1 a meeting at PFC on 23 December 1985, where it was  
2 decided to change priority and this memo was written  
3 in January 1986. So you are quite right, thank you, you  
4 are quite right.

5 So certainly by early 1986 it appears that you had  
6 communicated with Dr Perry initial results of the 8Y  
7 trial. Do you have any recollection of that?

8 A. Not especially. It would have been quite inconsistent  
9 of me, I think, to have suggested in so many words that  
10 it may well have been effective. I think that's going  
11 a bit further than I would have --

12 Q. We don't know whether you had offered the results at  
13 this time or Dr Perry had requested them.

14 I was also going to ask: would you have agreed at  
15 that time with that choice of words, that the heat  
16 treatment procedure "may well be effective in ensuring  
17 non-infectivity of products"?

18 A. I don't recognise the direct quotations.

19 Q. And I think that perhaps takes us back quite nicely to  
20 your written answer, if we may. You say:

21 "Likely it would depend on who is writing/speaking  
22 and who is listening. The references in footnote 3 are  
23 intended to be helpful but I accept no responsibility  
24 for opinions which do not have my mark on them.  
25 Subjectively, I started to surmise (for public

1 consumption at least) in mid 1986 that it was looking  
2 quite good and I probably eased up on plans to revert as  
3 soon as possible to pasteurising or even to explore the  
4 solvent-detergent option with more determination."

5 So, Dr Smith, can one take it then that throughout  
6 1985 and in early 1986, you still had a plan to revert  
7 to wet heating?

8 A. Yes.

9 Q. Does that mean then that during 1985 and early 1986 work  
10 was still ongoing at PFL on pasteurisation of  
11 Factor VIII?

12 A. No, by that time we would have been fairly happy with  
13 updates on our own interpretation of pasteurisation from  
14 PFC if we had had to adopt it. We were not doing  
15 positive work on it. It was being retained as a very  
16 lively option. But this time an alternative, very  
17 potent, method of inactivating lipid envelope viruses  
18 was becoming known and in fact available under licence,  
19 and that would have competed with pasteurisation.

20 Q. That's the solvent-detergent method?

21 A. Yes. Had we been driven to admit defeat on 8Y, for  
22 instance, these two approaches, pasteurisation, picking  
23 up on PFC's advances, and solvent-detergent, would have  
24 been competing in my mind in 1986.

25 Q. Yes. Because the use of the word "revert "in this

1 statement is perhaps interesting, doctor, in that it may  
2 suggest that during 1985 at least you regarded dry  
3 heating as essentially an interim or temporary solution.  
4 Is that a reasonable inference?

5 A. I saw it as less likely to be wholly successful,  
6 especially against hepatitis, than would pasteurisation.

7 Q. So you kept an open mind on alternative heating regimes?

8 A. Exactly.

9 Q. And then reverting to your written answer -- we don't  
10 have to go to it, [\[SNF0011123\]](#). We have looked at it  
11 before. It's your written interim report of  
12 30 December 1986, you say:

13 "That was a little more upbeat but not much. Even  
14 then, tentative exposure of our NANBH clinical data  
15 throughout 1986-87 was heavily criticised (see,  
16 typically [\[SNB0017768\]](#)... "

17 We don't have to go to it but we have seen before  
18 these are the minutes of the UKHCDO meeting on  
19 25 September 1987 and I think we will recall a reference  
20 from Dr Kernoff to the data being "soft" data rather  
21 than "hard" data. You go on to say that:

22 "It was gratifying that more England and Wales  
23 clinicians were supporting our new, more rigorous trial  
24 by 1987. Following a wave of NANBH and even HIV  
25 failures in dry-heated commercial products, 8Y became

1 briefly the best game in town and they may have sensed  
2 some risk if they did not fall into line. However,  
3 using the only product which hasn't failed yet does not  
4 necessarily denote confidence that it's going to be  
5 100 per cent successful. Note the extremely cautious  
6 wording of the Colvin publication in 1988 more than  
7 three years into trials."

8 We have looked at that before:

9 "Until anti-HCV testing became available in 1989,  
10 I woke each morning thinking 'This is the day some  
11 patient on 8Y or 9A will throw a non-specific ALT  
12 elevation, and it will all be in vain.' Or that we would  
13 hit a plasma pool with an unusually high titre of NANBH,  
14 and even severe dry heating would not have sufficient  
15 margin to cope with it."

16 Putting the question another way, doctor, at the  
17 beginning of 1985, what degree of confidence did you  
18 have that 8Y would not transmit HIV and separately  
19 NANBH, at the beginning of 1985?

20 A. HIV -- there was word coming through from the US  
21 products that even 60 degrees for 72 hours or 68 degrees  
22 for 24 hours in the hands of respectively Baxter and  
23 Cutter, appeared to be successful so far in inactivating  
24 HIV in a plasma supply which was almost certainly, by  
25 that time, heavily infected. The natural inference is,



1           therefore, that if you can go to 80 degrees for  
2           72 hours, you are going to be home and dry with HIV or  
3           at least you have introduced an additional margin of  
4           safety for what that's worth. If you get hepatitis or  
5           HIV, you have got it and the margins don't matter to you  
6           very much.

7           Non-A non-B Hepatitis, a completely different  
8           picture. I had no confidence whatever that dry heating,  
9           even at 80 degrees, would inactivate what was obviously,  
10          from clinical exposure of the commercial concentrates,  
11          proving to be a much hardier, tougher nut to crack than  
12          HIV.

13        Q. Could I ask the same question but as at the end of 1985?  
14          So at the end of 1985, what degree of confidence did you  
15          have that 8Y inactivated HIV and NANBH?

16        A. A little more, very little more, only gratitude that so  
17          far it didn't seem to have allowed hepatitis.

18        Q. Thank you.

19          The next question, please, if we go on, if we may,  
20          doctor, to page 5 of your statement. This is to do with  
21          the contact and exchange of information between PFC and  
22          PFL/BPL. During this period. It's a topic we have  
23          covered at some length in the Inquiry, Dr Smith.

24          I don't want to take too much time on it, which is why  
25          I think I propose taking your answer on page 5 (a),

1 simply taking that as read but asking you two points.

2 The first point is this: you say:

3 "As early as 1980, and with a persistence much to  
4 his credit, Dr Cash had been trying to persuade BPL  
5 to have formal meetings ..."

6 Et cetera. I think we have heard on a number of  
7 occasions how a number of ways and a number of times,  
8 doctor, now Professor Cash, did I think, try to  
9 encourage greater degree of working together between  
10 those north and south of the border. Is that a feature  
11 that you wish to comment on at all?

12 A. Yes, I think I possibly owe Professor Cash an apology  
13 for any nuance there may be in some of my replies to the  
14 effect that Dr Cash's interventions were unwelcome in  
15 the communications between Dr Foster and myself. The  
16 impression might be given from that that we saw him as  
17 trying to control the situation and I would like to  
18 clarify that that was not in my view the case.

19 Dr Cash may have felt that he was being kept at  
20 arm's length from some developments at PFC and in  
21 Mr Watt's time there may have been some justification in  
22 that feeling. But Dr Cash is a very responsible  
23 National Medical Director, as well as National Director.  
24 He would naturally have felt responsible for the quality  
25 and in particularly the safety of any product coming

1 through PFC and being issued with SNBTS's name on it.  
2 So it was not at all my view that Dr Cash's vanity or  
3 potential to control-freakery caused his interest and  
4 lasting interest in getting around the problem between  
5 the two respective directors.

6 I would say also that this kind of persistence on  
7 Professor Cash's part in getting more and more  
8 cooperation between Scotland and England in all  
9 transfusion matters was very important and bore fruit  
10 a few years later in the development of a red book,  
11 a book of standards to be met by any plasma or blood  
12 component issued in the UK. And it was very largely due  
13 to Dr Cash's energy that that got off the ground and was  
14 sustained through to a result which was the envy of many  
15 larger countries.

16 If you will indulge me just a small time more, I do  
17 wonder whether the Inquiry has fully appreciated the  
18 towering achievements of Dr Cash as the first National  
19 Director of SNBTS, when he took over as first director,  
20 the transfusion service was national in name only. It  
21 was to his credit that it was forged into a truly  
22 unified service, bringing evidence-based transfusion  
23 medicine to Scotland first and secondly -- and one kind  
24 of example, at least, to England of how it can be done.

25 I'm particularly grateful for his achievements in

1 bringing together a world class group of scientists in  
2 his central R&D lab and I have referred several times in  
3 my testimony to the assistance received not just from  
4 PFC but from Dr Prowse, Dr Pepper, Dr Dawes, in fact  
5 almost all the people in the central lab. That central  
6 lab would never have been set up, would never have  
7 existed to help us and the rest of the world if it had  
8 not been for Dr Cash's energy.

9 The particular area in which I have to be  
10 particularly grateful to him was the initiation and the  
11 nurturing of the dog DIC model which was absolutely  
12 critical to ensuring that our Factor IX and PFC's was  
13 safe from thrombotic consequence when given to patients.

14 Thank you for indulging me.

15 Q. Thank you, doctor. Some of what you said, I think,  
16 touches upon the second point in this answer I wish to  
17 ask you about. You say:

18 "During much of this period there was no central  
19 NBTS in England and Wales to be represented at the  
20 table, only individual RTCs."

21 I'm not sure we have really heard about this but we  
22 have heard about the structure in Scotland, where  
23 essentially there were a number of transfusion  
24 directors, a national medical director and a director of  
25 PFC, who I think all essentially were responsible to one

1 body, the Common Services Agency.

2 Am I right in thinking that in England the structure  
3 was that each Regional Blood Transfusion Service  
4 reported to its own Health Board. Is that correct?

5 A. Yes.

6 Q. So that essentially in England one had as many bosses or  
7 employers as there were health boards?

8 A. Indeed.

9 Q. And as regards the CBLA, I think it had no formal links  
10 to the regional transfusion centres and it was simply  
11 responsible for BPL and PFL and also, I think, the Blood  
12 Group Reference Laboratory. Is that right?

13 A. Exactly.

14 Q. Yes. I think that simply forms part of the background  
15 to our consideration of looking at the links between  
16 Scotland and England.

17 At the bottom of the page we have another question  
18 about the CBLA, the Central Blood Laboratories Authority  
19 Central Committee on Research and Development in Blood  
20 Transfusion, which first met on 21 June 1983. Doctor,  
21 were you aware of this committee at the time?

22 A. I knew it existed.

23 Q. Yes.

24 A. And I'm fairly sure I was invited to assist Dr Lane, who  
25 was a participant, to prepare reports or mini reports,

1           for that.  Until the Inquiry has revealed these  
2           documents, I don't think I ever saw a minute of the R&D  
3           committee.

4    Q.  Thank you.  And on the next page of your statement,  
5           please, we ask you another question about the committee  
6           and you reply that:

7                    "I do not recall knowing the membership of the  
8                    committee; its precise remit; whether it had any new  
9                    money to disburse or its clout to make policy."

10                   And you are reading the minutes for the first time.  
11                   I think we can perhaps take the rest of your answer as  
12                   read because we have spent quite a lot of time looking  
13                   at this committee.  I think answers are perhaps starting  
14                   to become clear about its relevance, if any, to the  
15                   topic we are looking at.

16                   The next page of your statement, please.  The  
17                   passage commencing:

18                            "These tempests need not detain the Inquiry too  
19                            long.  In practice, the minutes do not reflect much  
20                            active interplay or debate between Scottish and English  
21                            ideas.  BPL's current progress was reported to the CCRD  
22                            regularly ... there appears to have been no active  
23                            discussion of that progress, or even any discreet touch  
24                            on the tiller.  The CCRD received the reports rather  
25                            passively ... There is no record of CCRD being invited

1 to advise on comparable reports from PFC. This is  
2 exactly as one would expect from its original remit to  
3 advise CBLA -- not CSA ..."

4 In the final paragraph, one of the questions you had  
5 been asked was whether, if there had been PFC  
6 representation on this committee, is that likely to have  
7 led to an earlier or fuller exchange of information as  
8 regards 8Y, and you say:

9 "The short answer is: no. Had there been more  
10 active fractionation-oriented participation of SNBTS on  
11 the CBLA's committee ... it would not have advanced  
12 PFC's virus-safe concentrates by a day. PFC scientists  
13 had reliable access to anything we knew ... and  
14 evaluated it against their own strong policies, at least  
15 as rationally and rigorously as I would have in their  
16 position."

17 That completes, Dr Smith, the written answers to the  
18 questions posed. You have also added a helpful  
19 supplementary note 6, which I would like to look at as  
20 well, please. It's the four and a half page note. So  
21 I will take parts of it as read, if I may. The initial  
22 paragraph I propose taking as read, subject to two  
23 matters. Just to note that we are now dealing with the  
24 involvement of Mr Hamill in, I think, 1988. I'll  
25 provide the reference for the SHHD internal minute which

1 we looked at previously in the Inquiry, it's  
2 [\[SGH0024677\]](#). But we should perhaps go to  
3 Dr Forrester's response.

4 We haven't looked at that yet and it's [\[SGH0024672\]](#)  
5 and we will see this is Dr Forrester's memo or minute to  
6 the chief medical officer in Scotland. It's dated  
7 30 August 1988 and this is the Punch and Judy minute and  
8 it's paragraph 1. Mr Hamill had raised the point why  
9 are those in the SNBTS meeting with representatives from  
10 Finland and Holland? Why aren't there closer links  
11 between England and Scotland on the R&D front? And  
12 Dr Forrester's reply is in the second paragraph:

13 "It should be remembered, as I pointed out to  
14 Mr Donald some time ago, that the picture of Punch  
15 (England?) and Judy (Scotland?) at blows is only what is  
16 presented to the Department of Health and to the SHHD.  
17 If you go behind the scenes after the show, the two are  
18 in bed together. For instance, PFC are conducting virus  
19 elimination research for BPL now by mutual arrangement."

20 We will leave that now. You refer to that memo in  
21 your note 6. Then the subheading B in your written  
22 note, I think, I propose simply taking that as read.  
23 Subsection C I think is quite helpful. It's headed  
24 "Limitations of BPL/PFL in pursuing pasteurisation and  
25 contributing to PFC's efforts".



1           I think, again, I'll simply propose taking this as  
2           read because I think we have covered, I think, much of  
3           the ground set out there. I think it's an interesting  
4           and important response but as I say, I think with a view  
5           to avoiding unnecessary repetition, I'll simply take  
6           that as read.

7           Then over the page, please, there is something  
8           a little new. You touched upon yesterday, at the top of  
9           the page, subheading D, "Endemic constraints on national  
10          fractionators' responsiveness to new challenges." You  
11          did, I think, touch upon this yesterday, doctor, as to  
12          why perhaps national or, I think, socialised  
13          fractionators, to use your expression from earlier, were  
14          perhaps always a little behind the game compared to  
15          commercial fractionators, or certainly found it harder  
16          to move as quickly when planning ahead for future  
17          developments.

18          Again, I think I'll largely take this as read other  
19          than perhaps just providing some of the references. So  
20          if we go about ten lines down, we pick up, "This  
21          certainly happened with the new PFC at Liberton", and  
22          you say:

23                 "See [\[SGH0018783\]](#)."

24          Just to explain for the record, that is a document  
25          relating to PFC revenue development proposals for 1982

1 and 1983, including in particular expansion and work  
2 required as a result of the medicine inspectors' report.  
3 You also go on to refer to annual reports. I think  
4 that's a reference to annual reports of BPL and PFL.  
5 I think we have previously clarified with the SNBTS that  
6 PFC did not at this time produce annual reports.

7 A. It's bad proofreading on my part. The annual reports  
8 were supposed to go into the next bracket but ...

9 Q. I see, and when you do then refer in the next bracket to  
10 "see annual reports, eg [\[DHF0021590\]](#)), that is  
11 a reference to the 1985/1986 annual report from the  
12 director of BPL and PFL to the CBLA. I think we can  
13 read the rest of that for ourselves.

14 I should provide one further point of detail. In  
15 the paragraph commencing:

16 "In these circumstances ..."

17 Then the next sentence:

18 "Once a settled pattern has evolved ..."

19 The next one:

20 "Ideas for a new product are therefore developed  
21 over months or years, the originators mindful ... of how  
22 the process may be implemented in their particular  
23 manufacturing environment."

24 And to pause to explain the reference to  
25 [\[SNB0073635\]](#), that is a reference to Dr Foster's memo to

1 Mr Watt of 3 May 1983 in respect of a possible  
2 acceleration of the heat treatment programme in response  
3 to AIDS.

4 Then three lines up from the bottom of that  
5 paragraph, you say:

6 "The fractionator must look very scrupulously at the  
7 overall chances of success in adopting his own or  
8 another project within a practical timescale before  
9 making a decision. (See, eg [\[SNB0074867\]](#))."

10 Which is a reference to a document we will, I think,  
11 come to shortly, which is Dr Foster's progress report  
12 in February 1985. As I say, I will take you to that  
13 shortly. Then the next subheading, E, "Sharing  
14 Information". Again, I think it's an important and  
15 interesting response but I'll take that as read, if  
16 I may.

17 The top of page 10, please. There is a reference at  
18 the top of page 10 to, I think, staffing, employment and  
19 remuneration aspects. I think in short, Dr Smith, we  
20 note all that you say and while staffing, et cetera, may  
21 have been a factor in events at PFC, it doesn't seem  
22 from the evidence we have heard so far that it was  
23 a determining factor or indeed was at the forefront of  
24 decision-making. So I think, for that reason we will  
25 simply take what you say at the top of page 10 as read

1 and no doubt, if anyone disagrees with what I say, then  
2 a point can be made in submissions to the chairman in  
3 due course about that issue.

4 A. Could I just say that I was pointing to conceivable  
5 things in PFC's mind at a particular point in time, when  
6 they might have asked themselves "Why not?" Not that  
7 any of these things actually was important, since I know  
8 nothing about that.

9 Q. I understand.

10 Then subheading "F. Why didn't PFC just copy  
11 England's successful 8Y?" I think you had referred to  
12 that in your B3 statement but you go on to expand upon  
13 it here. Paragraph 1.1:

14 "A priori objections."

15 We can see what you say and there is an element of  
16 repetition, I am afraid, in some of this, which I think  
17 is inevitable, given the overlap between the topics B3  
18 and C3 we are looking at. You reply in paragraph 1.2:

19 "PFC would be unable to evaluate, even at bench  
20 scale, the promise of that first step ..."

21 This is the heparin as a precipitant:

22 "... since a high residual concentration of heparin  
23 would invalidate the type of Factor VIII assay available  
24 at that time in SNBTS ... "

25 We have looked at that but it's the next point:

1           "The supply of reliable Factor VIII assays has  
2 always been the most serious limitation on every  
3 laboratory's development of improved concentrates ... "

4           Then the next sentence:

5           "Too many variables, not enough capability to  
6 quantify their influences."

7           I think I understand the first sentence, "the supply  
8 of reliable Factor VIII assays", but that last sentence,  
9 "too many variables", what does that mean?

10 A. At every stage, whether it is the investigation of  
11 precipitation methods or taking freeze-drying to pieces,  
12 you are confronted with far more variables than you can  
13 pursue systematically, if you only have a handful of  
14 Factor VIII assays on which to base your evaluation of  
15 the results.

16 Q. I understand. Thank you.

17 THE CHAIRMAN: I think that I am interested in the first  
18 sentence. As an outsider looking in, one possible  
19 response would be that, well, the assays are really  
20 checking what's happening; what's fundamental is the  
21 process. But this suggests that the assays are actually  
22 integral parts of the process to the extent that unless  
23 you can do them reliably, you can't go ahead. How does  
24 one resolve it?

25 A. You are waiting for the assays to confirm that what you

1 intended to achieve by changing a variable has in fact  
2 had that result, and you cannot proceed until you have  
3 rationally -- until you have determined that. It slows  
4 down progress.

5 THE CHAIRMAN: So it is truly sequential. Each element in  
6 the sequence requiring validation before you can  
7 properly go forward to the next, or how should one  
8 understand it?

9 A. It's a bit of both. One might be trying, say, the Latin  
10 square approach, where you do a patchwork of more than  
11 one variable, where you do not have the time or assays  
12 to pursue each one systematically one at a time. So you  
13 may be trying to get inferences at least from having  
14 changed more than one variable at a time. No one likes  
15 doing that but if you only have a few results to depend  
16 on, you sometimes do have to change more than one  
17 variable at a time and rely on inference rather than on  
18 proof.

19 THE CHAIRMAN: And quite of a lot of it requires a great  
20 deal of imagination as well as just practical  
21 application of successive chemical set-type activities.

22 A. This is where the art comes in.

23 THE CHAIRMAN: I think it is important for us to get a sense  
24 of it, Dr Smith, certainly if we are going to try to  
25 communicate this to others in due course. An

1 appreciation of the nature of the exercise is very  
2 important.

3 A. Well, no scientist likes to do other than systematically  
4 attack one variable at a time.

5 THE CHAIRMAN: At the moment there seems to be holes in your  
6 patchwork on this approach.

7 A. One always feared that there would be holes in the  
8 patchwork. So your experience of what might have worked  
9 in the past or what in the past has not been too  
10 important a variable, you might draw inferences from the  
11 few results you had -- not watertight inferences but the  
12 best you could do to permit you to move on to the next  
13 set of variables.

14 THE CHAIRMAN: But you must always have been worried about  
15 the unknown unknowns.

16 A. The unknown unknowns and also having settled on what  
17 appears to be a sequence of validations, find that the  
18 optimum which you found at stage 7 starts to have an  
19 interference with your conclusions about stage 1  
20 validation.

21 THE CHAIRMAN: Right. Yes, thank you.

22 MR MACKENZIE: Thank you, sir.

23 Dr Smith, in paragraph 2 it's headed "Obstacles  
24 evident from practical investigation of 8Y methodology  
25 at PFC."

1           You explain the difficulties in attempting to  
2           quickly duplicate methods from another laboratory, even  
3           provided with a lot of detail. You say:

4           "The equipment used in such attempts may not mimic  
5           exactly that used by the originators, equally probably  
6           the originators may have failed to identify hidden  
7           variables ..."

8           That's back to the unknown unknowns perhaps:

9           "... which in fact had been imported in their  
10          apparent success, and the low priority accorded to 8Y by  
11          Dr Foster in his February 1985 review of options was  
12          probably attributable to both factors, and this was even  
13          before the challenges of freeze-drying had surfaced.  
14          The issue of the Factor VIII assay preferred in Scotland  
15          complicated many of our shared interests ..."

16          Could I perhaps pause, doctor, to look at  
17          Dr Foster's February 1985 progress report, please? It's  
18          [\[SNB0074867\]](#). I'm going to take you through it but the  
19          question I'm going to ask shortly, if I may, is, if  
20          Dr Foster had sent you a copy of this report in early  
21          1985 and asked "do you think we are on the right lines  
22          or would you suggest any change of direction," what  
23          would your response have been given what you knew in  
24          early 1985 about 8Y?

25          If we could perhaps start at page 6 of the report.



1 I think, doctor, you have had a chance to look at it  
2 previously, although it may have been some time ago in  
3 preparation of your statement. Is that correct?

4 A. Yes.

5 Q. To perhaps refresh your memory, it is page 6 of 4872,  
6 Dr Foster sets out the ZHT process and in the third  
7 paragraph we see:

8 "Following the completion of small scale laboratory  
9 studies, a number of experiments have been carried out  
10 at pilot scale."

11 Under 3.1.1:

12 "Results from zinc precipitation step 1 are  
13 disappointing compared to the earlier laboratory data."

14 Could we perhaps go briefly to page 4881, we see  
15 table 6 is headed "ZHT process, summary of pilot scale  
16 experiments."

17 I'm not going on ask you about the details, doctor,  
18 but I think in short one can see the different process  
19 stages and the target for the efficiency of Factor VIII  
20 and the results of the experiments, I think, all with  
21 a view to seeing how much Factor VIII was lost at each  
22 step in the process and whether yield levels could be  
23 maintained with the ZHT process, and Dr Foster referred  
24 in the body of the report we just looked at to results  
25 from the zinc precipitation step, "step 1:

1           disappointing", but I think we can see for ourselves  
2           that in fact in all of the steps, if one takes an  
3           average of the figures, the recovery of Factor VIII is,  
4           I think, less than the target figures. So I really just  
5           put that to you to put it into the record of the Inquiry  
6           rather than ask you to comment in detail on it.

7           But if I may then, please, go back to the body of  
8           the report and in particular page 4873. At the very  
9           bottom of the page:

10           "Work on the ZHT process was suspended  
11           in October 1984 to give priority to a new process which  
12           promises a higher purity product and high yield."

13           This is the NYU, Professor Johnson project. Over  
14           the page, please. It's headed:

15           "Much of the knowledge gained in the ZHT programme  
16           will be valuable in the alternative process and some of  
17           the key steps may remain."

18           Which may link in with what you were saying earlier,  
19           doctor, about fractionators for understandable reasons  
20           preferring familiar processes, rather than adopting  
21           something unfamiliar.

22    A. Yes.

23    Q. Then various texts on the high purity product, the NYU,  
24           Professor Johnson product, and under 4 we see:

25           "Pasteurisation. Heating in solution with sorbitol

1 as a stabiliser is the preferred option at the moment  
2 but severe heating of the freeze-dried powder may be  
3 possible (Dr Smith unpublished results) and may be of  
4 interest."

5 So pasteurisation is the preferred option but not  
6 closing one's mind to dry heating. Then the heat  
7 treatment programme is set out in paragraph 4, which  
8 states:

9 "At the time of the last meeting of the study group,  
10 our preferred option for viral inactivation was heating  
11 in solution, as opposed to heating the freeze-dried  
12 powder for the following reasons: 1. It is likely to  
13 achieve a greater degree of viral kill ...

14 "2. Preliminary animal and clinical data from  
15 heated dried products suggested little effect on HBV and  
16 incomplete inactivation of NANBH.

17 "3. In theory, the procedure is difficult to  
18 control ..."

19 Then:

20 "Although heating in solution would seem to be still  
21 the preferred option, recent information concerning  
22 HTLV-III has led to the introduction of a dried heating  
23 procedure for the existing product."

24 This is really post-Groningen explaining the  
25 evidence based approach to introducing dry heating at

1           that time. I think, in short, Dr Smith, from this  
2           report Dr Foster is explaining the introduction of dry  
3           heating of the intermediate PFC product in late 1984 but  
4           also that the research work would continue to seek to  
5           develop a high purity Factor VIII concentrate with  
6           pasteurisation being the preferred heating method but  
7           not closing one's mind to dry heating.

8           So going back to the rather lengthy question at the  
9           beginning, if Dr Foster had sent you a copy of this  
10          report in February 1985, even with your knowledge of 8Y,  
11          would you have tried to dissuade him from prioritising  
12          research into the high purity product with  
13          pasteurisation being the primary heating method?

14        A. I would have had no justification in pushing dry heating  
15          at all in February 1985. The report would indicate to  
16          me that all possible angles had been pursued, all the  
17          right issues had been addressed and that I would have  
18          come to the same conclusion.

19        Q. And would that have remained your view --

20        A. Pasteurisation being the better horse to back if the aim  
21          is to inactivate non-A non-B Hepatitis.

22        Q. Would that have remained your view throughout 1985 or  
23          would your view have changed at some point in 1985?

24        A. Not during 1985. There were not sufficient patients to  
25          be able to hold up any promise of non-A non-B kill.

1 Q. Thank you. Could I return then, please, to your written  
2 response. I think we had come to 3, "Limitations in  
3 PFC's resources."

4 You do say that:

5 "Our respective non-scientific local difficulties  
6 were not a subject for discussion between Dr Foster and  
7 myself but I will speculate from what the Inquiry has  
8 unearthed."

9 I think you explained at the outset that when you  
10 wrote this statement, you didn't know which other  
11 witnesses would give evidence to the Inquiry. So  
12 I think you erred on the side of being generous in your  
13 answers than keeping them unduly narrow.

14 In paragraph 3.1 we can see what is said there.  
15 Paragraph 3.2, you explain:

16 "The 8Y process at full-scale was essentially  
17 continuous and could not be interrupted at a stable  
18 position," and, "This implies at least two shifts of  
19 skilled operatives ..."

20 Et cetera. At the top of the next page, please, you  
21 explain, 3.3:

22 "Two important centrifugation steps in 8Y relied on  
23 technologies which PFC's chemical engineers would  
24 rightly have regarded as retrograde and therefore  
25 unattractive to copy."

1           At what stage in the 8Y process were these  
2           centrifugation steps used? Was that during the initial  
3           extraction from cryoprecipitate or ...?

4    A. We would be using essentially the same technology for  
5           centrifugation of the cryoprecipitate. The steps I was  
6           referring to here were the collection of the heparin  
7           precipitate, which we were doing in centrifuges  
8           reminiscent of the blood bottle centrifuges used in the  
9           transfusion centre but scaled up somewhat to 12 litres.  
10          This is not very elegant technology but we retained it  
11          in moving to BPL because it could be done fast and we  
12          did not want to wait to solve the chemical engineering  
13          problem of recovering that precipitate in order to get  
14          on fast with 8Y.

15          When we precipitate Factor VIII from the heparin  
16          supernatant, this is a very, very fine precipitate. The  
17          instrument we had at PFL and which we knew was available  
18          at BPL in a big brother copy was a tubular centrifuge  
19          dating right back to Cohn in Boston during war time.

20          BPL had always preferred to stick with a different  
21          design of centrifuge, the Westfalia, primarily for  
22          recovery of heavy precipitates on the way to gamma  
23          globulin and albumin but had also adapted them and found  
24          them suitable for recovery of cryoprecipitate and other  
25          precipitates.

1 I do not know in fact whether PFC had a Sharples  
2 centrifuge on the premises. They would therefore have  
3 had to learn how to collect this fine precipitate in  
4 a Westfalia centrifuge, which is not ideally adapted for  
5 this task. Both these centrifugation steps would  
6 therefore have caused PFC trouble.

7 Q. And also delay if they had sought to change to them?

8 A. Indeed.

9 Q. Yes, and then paragraph 3.4, doctor, you refer to:

10 "At an important desalting stage ..."

11 I think there were differences. In short, am I  
12 right in thinking that BPL used gel filtration, whereas  
13 PFC used ultra filtration. Is that correct?

14 A. Yes, simply because we were comfortable with gel  
15 filtration because we had used it with other products  
16 like antithrombin 3.

17 Q. I don't think we need to know the details of that, other  
18 than this presumably again would have caused some  
19 difficulties to PFC to change to gel filtration?

20 A. Yes.

21 Q. And paragraph 3.5 we can see what you say and  
22 paragraph 3.6 again, going back over some ground we have  
23 been over before. 3.7, a point of detail in the text in  
24 italics. You asked you do not know at what point PFC  
25 ordered commissioned and validated precision ovens, and

1 I think the answer is the ovens were ordered  
2 in January 1985 and were delivered in July 1985. And  
3 our reference for that is Dr Foster's briefing paper,  
4 page 38. That's a point of detail.

5 Then 3.8:

6 "Perhaps most importantly, 8Y's yield ... only just  
7 held its own against our earlier intermediate purity  
8 concentrate, dry-heated. I don't think we ever claimed  
9 more than 200 IU/kg. Ever mindful of national  
10 self-sufficiency, PFC were hoping for 300 IU/kg and  
11 could not easily contemplate lowering that aspiration by  
12 one third."

13 Then in the last paragraph there you say:

14 "It was never a case of, 'Jim Smith has finally  
15 smuggled out the recipe for a hepatitis-free Factor  
16 VIII. Stop everything you have been doing for three  
17 years, we start on Tuesday'."

18 Then finally, Dr Smith, subparagraph G. You ask:

19 "What could convince PFC that dry heating (even  
20 80 degrees centigrade) was effective against NANBH?"

21 We see what you say in the first paragraph. I think  
22 we will take that as read, if we may. Then you say:

23 "In the wake of seemingly endless failures of dry  
24 heating between 1983 and 1985 ..."

25 I assume that's to inactivate NANBH.



1 A. That would also include some HIV failures.

2 Q. I see.

3 A. The Armour product, for instance.

4 Q. "... and reputable doubts about its efficacy against  
5 even AIDS virus ... "

6 A. Sorry, that's part of the --

7 Q. Yes. So is the first part, "In the wake of seemingly  
8 endless failures of dry heating between 1983 and 1985",  
9 a reference to NANBH?

10 A. Indeed.

11 Q. I understand. Et cetera.

12 There is one final document I would like to take you  
13 to in that regard, please, Dr Smith. I should perhaps,  
14 for completeness say the reference to [\[SNB0074867\]](#) is  
15 Dr Foster's February 1985 progress report we have just  
16 looked at; the reference to [\[LIT0010330\]](#) is Dr Colvin  
17 and others in the Lancet in 1988, reporting on the trial  
18 of 8Y.

19 The final document, please, if I may, is  
20 [\[LIT0010648\]](#). We see this is a paper published  
21 in June 1987 by Dr Prince and others. If we look at the  
22 abstract, we will see, just half way through the  
23 first paragraph:

24 "This review summarises detailed information which  
25 is now available establishing the viricidal potency of

1 these procedures, particularly with regard to the  
2 contaminating viruses of most concern: Hepatitis A,  
3 non-A non-B Hepatitis and the AIDS virus."

4 Then may we, please, go to page 108, which is 0653?  
5 I'm looking at this paper to compare the results from  
6 wet heated, pasteurised products and dry-heated  
7 products. The bottom left-hand corner, "Heating in the  
8 liquid state", this is pasteurisation. We see the final  
9 sentence there:

10 "Treatment under these conditions will, however,  
11 inactivate viruses, albeit more slowly than in the  
12 absence of stabilisers."

13 The next column, "Process efficacy" -- we will come  
14 to table 3 in a second:

15 "Clinical studies have revealed no virus  
16 transmission, with the possible exception of two cases  
17 of NANB."

18 Can we then, please, go over the page? Table 3 is  
19 headed, "Efficacy of processes involving heating in the  
20 liquid state."

21 The first entry, I think, relates to Factor IX, so  
22 we can put that to one side perhaps, but then the next  
23 entry relates to Behringwerke's Factor VIII. If we then  
24 go to the right-hand columns, in terms of the proportion  
25 of patients infected in the clinical studies, we can see

1 for this product, for NANB, two out of 31 patients  
2 infected, although I think there may have been later  
3 a question mark about that, but below that 0 out of 21  
4 in another trial and, for the Hepatitis B virus, 0 out  
5 of 31 patients and then 0 out of 11, and for HIV one can  
6 see 0 out of 21 patients and then 0 out of 18.

7 If one then compares that data -- back to the  
8 previous page, please -- with the information available  
9 about dry heating, we can see, bottom right-hand corner,  
10 "Heating in a lyophilised state." Then over the page,  
11 please. We can see, under "Process efficacy, table 4":

12 "Unfortunately, despite the appeal of simplicity,  
13 results of chimpanzee and clinical studies document  
14 a relatively limited process efficacy, with the possible  
15 exception of the English 'severe heat' process.  
16 Dessication appears to stabilise not only Factor VIII  
17 but also the potentially contaminating viruses. The  
18 process failed to inactivate HBV in chimpanzee studies  
19 and inactivated only modest amounts of HIV in tissue  
20 culture studies of the 60°C process. Dry heat-treated  
21 US products transmitted NANB and possibly HIV in  
22 clinical studies. However, administration to  
23 13 patients of the product heated at 80°C produced no  
24 indication of hepatitis or HIV transmission."

25 Over the page, please, finally, look at table 4.

1 Table 4 is headed, "Efficacy of processes involving  
2 heating in a lyophilised state".

3 Going through the Factor VIII products, the  
4 first one, Factor VIII Hyland -- I think that's  
5 a reference to Hemofil -- dry-heated at 60 degrees for  
6 72 hours, and we can see in the clinical studies 11 out  
7 of 13 patients reported as infected with NANBH, albeit  
8 zero patients in respect of HIV.

9 Two boxes down, please, Factor VIII Armour, I think,  
10 is Factor VIII at 60 degrees for 30 hours, and the  
11 clinical studies report two out of two patients infected  
12 with NANBH and also a report of perhaps some infection  
13 with HIV.

14 The next one down is Factor VIII Cutter, 68 degrees  
15 for 72 hours. In the clinical study for NANBH one of  
16 six patients reported as infected but none in the HIV.

17 Finally we see the box referring to 8Y. 0 of  
18 13 patients infected with NANB, Hepatitis B or HIV.

19 That's another quite long preamble, doctor, to this  
20 question, which is really: what would a fractionator  
21 take from these results when considering in 1985/1986  
22 whether wet or dry heating was preferable?

23 A. He would see that, as far as non-A non-B transmission  
24 was concerned, (inaudible) product's heated in solution  
25 (inaudible) the only product heated in solution -- had

1           been more effective in inactivating non-A non-B  
2           Hepatitis than any of the dry-heated concentrates  
3           investigated so far, the only one to have a clean sheet  
4           still being 8Y.

5           It would not be regarded as terribly conclusive.  
6           All these Hepatitis B data are unreliable because around  
7           about 1985 all patients being treated with haemophilia  
8           product would have received the Hepatitis B vaccine.

9    Q.   Is there anything else you would like to add in respect  
10       of this paper, doctor?

11   A.   Sorry?

12   Q.   Is there anything else you would like to add in respect  
13       of this paper?

14   A.   Can you tell me the date of publication again?

15   Q.   Yes, it was June 1987.

16   A.   Yes.  You see, the data included in that paper would  
17       have been obtained at least six months, perhaps a lot  
18       more, before June 1987, and the picture is perhaps of  
19       late 1986.  In particular, the Armour concentrate, which  
20       is shown as having perhaps one or two dubious HIV  
21       transmissions -- have been shown to have caused many  
22       more transmissions than that.

23   Q.   I see.

24   A.   This would not have encouraged any fractionator to go  
25       with dry heat.

1 Q. Thank you. Doctor, I've really finished -- yes, sir,  
2 I was going to say I really have finished with the rest  
3 of Dr Smith's statement. I think I'd propose simply  
4 taking that as read. So really --

5 THE CHAIRMAN: Perhaps you had better just keep your --

6 MR MACKENZIE: Powder dry.

7 THE CHAIRMAN: -- options open over lunch. Inspiration may  
8 fall upon you or be thrust upon you over lunch.

9 (1.10 pm)

10 (The short adjournment)

11 (2.00 pm)

12 THE CHAIRMAN: Dr Smith, I mentioned this morning that I had  
13 read somewhere that the world of fractionators viewed  
14 your development with astonishment. That's in the  
15 Lindsay report under reference to evidence given by  
16 yourself and one or two others. The report also  
17 comments that throughout 1985/1986 and 1987, no other  
18 fractionator was producing dry heat-treated Factor VIII  
19 according to the protocols you had developed in England.  
20 Does that square with your recollection? You mentioned  
21 that some did eventually do it.

22 A. By 1986/1987 the exploitation of the patent would be in  
23 other hands than mine and therefore I simply have no  
24 recollection of what the uptake was elsewhere.

25 THE CHAIRMAN: That's fine. My source was Lindsay and if

1           you can't add to that, I'm content. Thank you very  
2           much.

3           Yes, Mr Mackenzie?

4 MR MACKENZIE: Just to follow up that one point, Dr Smith,  
5           we know that BPL produced a dry-heated 8Y at 80 degrees,  
6           we know that PFC produced a dry-heated Z8 Factor VIII  
7           concentrate at 80 degrees. Do you know whether any  
8           commercial manufacturer ever produced a dry-heated  
9           Factor VIII concentrate at 80 degrees?

10 A. I believe that briefly the Alpha company in the US may  
11          have reached 80 degrees with a dry-heated product. But  
12          that is -- I can't confirm that with documentation.

13 Q. Do you know whether that product was ever issued for  
14          use?

15 A. If it was, it would not be for very long because most of  
16          the American companies took up the solvent-detergent  
17          patent and applied it very quickly.

18 Q. Thank you, Dr Smith. I have no further questions.

19 THE CHAIRMAN: Mr Di Rollo?

20                                 Questions by MR DI ROLLO

21 MR DI ROLLO: Thank you, sir.

22           Dr Smith, I think in the last day or two, amongst  
23          other things, we have been looking at the development of  
24          Factor 8Y in England and some of the reasons why PFC did  
25          not develop a similar product until a bit later on.

1           What I would like to ask you about is the question of  
2           whether or not 8Y might have been made available in  
3           Scotland -- that is to say English 8Y -- and the  
4           knowledge that Scottish fractionators and clinicians  
5           might have had in relation to the safety margin that 8Y  
6           may have had in early 1986.

7           If we look at one document, [\[DHF0030476\]](#) -- I think  
8           reference has already been immediate to this. This is  
9           the issue of 8Y in England.

10          This document is indicating that the 8Y is being  
11          issued or to be made available generally, and if we look  
12          further down, we see that clinical trials at six  
13          haemophilia centres are in progress to gain evidence of  
14          reduction or elimination of the viral transmission and  
15          several patients have safely passed the point at which  
16          first evidence of NANBH virus transmission would  
17          normally occur with unheated Factor VIII.

18          Then it goes on to say that:

19          "Factor 8Y will be issued through regional blood  
20          transfusion centres unless special provisions exist by  
21          agreement for product to be sent direct to the  
22          haemophilia centre."

23          Then the final paragraph on that page says:

24          "It is recognised that until the new production unit  
25          at Elstree is completed, output of 8Y will meet about



1 one third of current demand for concentrate. For this  
2 reason, attempts have been made to define those patients  
3 likely to benefit most from the security inherent in  
4 8Y."

5 Just go over the page. I think that is all I want  
6 to put to you there.

7 That's the situation as at July to haemophilia  
8 doctors and the next document I want to show you before  
9 asking you some questions is dated 10 January 1986 and  
10 it's [\[SNB0015469\]](#). Paragraph 3.1 is the relevant  
11 paragraph. Again, this is a document we have seen  
12 before with another witness.

13 It's in the fourth paragraph on the page that we  
14 see:

15 "Directors will be aware that the Blood Products  
16 Laboratory are currently issuing a Factor VIII product,  
17 which has been heated at 80 degrees/72 hours and  
18 preliminary clinical data indicates that this material  
19 is non-infective with respect to HTLV-III, NANB and  
20 Hepatitis B."

21 Then there is a reference to looking at PFC  
22 producing a similar product.

23 On this section the final document I want to put to  
24 you is --

25 A. Excuse me, could I just catch the date of that again,

1 please?

2 Q. The date for this document was 10 January 1986. This is  
3 a draft of a report by Dr Perry for the SNBTS  
4 haemophilia directors for their annual meeting, which  
5 was to be held a number of weeks later.

6 The next document I want to put to you is  
7 17 March 1986, which is [\[SNB0075664\]](#). I think this is  
8 a meeting at PFC on 17 March 1986 and we see that  
9 a number of people appear to have been present, I think  
10 including yourself. Is that right?

11 A. Yes.

12 Q. And if we scroll down, I think it's over the page.  
13 Carry on. At paragraph 5 but it may be further up,  
14 sorry:

15 "Dr Smith outlined clinical trial results of the 8Y  
16 ... product so far. While results cannot be considered  
17 conclusive at the stage, he indicated that no cases of  
18 virus infection had occurred (attributable to 8Y  
19 material) after 12 months' experience of 8Y in virgin  
20 haemophiliacs."

21 The report of that meeting, I think, is dated  
22 24 March 1986 but this is in relation to a meeting on  
23 17 March.

24 What I would like to ask you, looking at these  
25 documents, is obviously there is a difference between

1           asserting publicly that something is safe or anything of  
2           that kind, but it does appear that from the information  
3           available there was likely to be an increased margin of  
4           safety insofar as non-A non-B Hepatitis is concerned in  
5           using 8Y as opposed to other products. Is that  
6           a reasonable proposition?

7    A. Not really. If you had said HIV, yes, I would have  
8           agreed, but there was reasonable prospect of there being  
9           an increased margin of safety; that is that zero  
10          transmission would be more certain. To move from that  
11          to say that the evidence for inactivating non-A non-B  
12          could be called a reduction in incidence, I think is  
13          probably going too far.

14   Q. So what are we to make of the idea, for example, in  
15          issuing the product in England? Particular patients are  
16          identified as being patients that might be suitable as  
17          benefiting from the increased margin of safety. And  
18          from what's indicated in the earlier document from  
19          Dr Perry and what we see here, is it not right to think  
20          that 8Y does appear to be something which does, at least  
21          up until this point, look as though it would be  
22          beneficial?

23   A. Paragraph 5, you will see Dr Perry's words. He is  
24          interpreting perhaps a five minute review and his take  
25          on that is in terms of, while results cannot be

1 considered conclusive at this stage, I don't think in  
2 any forum at this time I would have come out so much in  
3 favour of optimism.

4 Q. So you wouldn't --

5 A. The first -- could I?

6 Q. Yes.

7 A. The first part of your question.

8 Q. Yes, indeed.

9 A. That is what was BPL's attitude to patients who might  
10 particularly benefit. Clearly, this was with a first  
11 eye on non-A non-B Hepatitis, that -- no, I'm sorry, on  
12 HIV, the aim being to protect those patients who had not  
13 yet -- maybe thought not yet to have been infected.  
14 That is the distinction between all patients and those  
15 patients most likely to benefit. The dogma at that time  
16 was that people who had already been infected with non-A  
17 non-B Hepatitis would not suffer any further experience  
18 of that virus on being reinfused with a contaminated  
19 product. Therefore, those who are still vulnerable are  
20 the ones who are most likely to benefit.

21 Q. So are you saying that it would not be reasonable to  
22 think that at this time -- this is March 1986 -- that 8Y  
23 provided -- and this is insofar as non-A non-B Hepatitis  
24 is concerned; that's when we are interested in  
25 specifically -- an increased margin of safety over, say,

1 the available Scottish product at that time, which was,  
2 I think, known definitely to transmit non-A non-B.

3 The point I'm trying to get at is that you have one  
4 product which you know will give the patient non-A non-B  
5 Hepatitis and you have got another product which looks  
6 as though, up until now, insofar as we can tell, there  
7 has been no recorded case of it giving a virgin  
8 haemophiliac non-A non-B. Are you saying that there is  
9 no increased margin of safety in relation to 8Y in that  
10 situation?

11 A. Again, a distinction between HIV and non-A non-B, if  
12 I may. With HIV there was evidence that a jump from  
13 60 degrees to 80 degrees was beneficial. With regard to  
14 non-A non-B Hepatitis, what we could say in the  
15 beginning of 1986 -- the best we could say -- is that  
16 there may have been -- the improvement may have been of  
17 the order of 30 per cent but statistically speaking,  
18 that does not give a very high probability of the  
19 product being safe.

20 Q. I understand that you cannot say it's safe.  
21 I understand that. What I'm asking you to do is to look  
22 at one product, 8Y, and say, one, the existing Scottish  
23 product will definitely give you hepatitis, non-A non-B  
24 Hepatitis, but the English product will not definitely  
25 do that. One can't know whether the English product

1 will do that and there has not been any recorded case up  
2 until that point, despite 12 months of use. I'm asking  
3 you which one has the best margin of safety or the  
4 better margin of safety?

5 A. You start with the premise that any of the mildly heated  
6 Scottish batches would have transmitted hepatitis.

7 Q. Yes, I do.

8 A. It is, I don't think, the case that every infected batch  
9 of -- every batch of Factor VIII, infected with non-A  
10 non-B Hepatitis, transmitted that virus to all patients.

11 Q. All right. But I mean, I think my premise is not really  
12 seriously undermined by that as a premise in terms of  
13 choosing one to the other.

14 A. Provided you do not press me to give a quantitative  
15 answers, then logically there is a slightly larger  
16 margin of safety indicated by these preliminary results.  
17 Whether that margin is of any statistical significance,  
18 I think we would disagree on.

19 Q. There comes a point in the course of 1986, does there  
20 not, at which the optimism in relation to 8Y, if there  
21 is any optimism, becomes much more or even more -- there  
22 are more grounds for optimism as 1986 goes on because  
23 the longer time goes on that patients that have received  
24 this product do not get non-A non-B Hepatitis. Is that  
25 right?

1 A. More patients exposed, more batches exposed.

2 Q. And at what point would you say that there becomes  
3 a worthwhile statistical benefit, if you like, of having  
4 8Y as opposed to the existing Scottish product? What  
5 does that --

6 A. Worthwhile to whom?

7 Q. Worthwhile to a previously untreated patient?

8 THE CHAIRMAN: I think it must be assumed that both products  
9 are available in the same market for this hypothesis,  
10 Dr Smith; otherwise, you know, one doesn't know what the  
11 comparison is.

12 But maybe you have to make it clear, Mr Di Rollo,  
13 what the assumption is.

14 MR DI ROLLO: I am assuming that there is a choice clearly,  
15 a realistic choice, a practical choice, between the two.

16 A. I think you are asking why did I become a little more  
17 convinced during the course of 1986 that things might be  
18 looking better than at the beginning of the year. Would  
19 that --

20 Q. At what point, I suppose I'm asking.

21 A. There was no single point. More patients, more batches  
22 exposed and, although I cannot recollect the precise  
23 timing of this, by 1986 Dr Cuthbertson at PFC would have  
24 in vitro evidence that our 80 degrees treatment was  
25 leading to a significantly larger kill of laboratory

1 viruses.

2 Q. Can I ask you about one or two documents in relation to  
3 1986? Maybe that will help. If you go to [\[SNB0075799\]](#).  
4 Can you just put this document into some sort of  
5 context?

6 A. It's copied to me. I have no exact recollection of  
7 that. I think it would be a preamble to our sending  
8 Dr Cuthbertson our unheated material in order for him to  
9 spike the product with viruses and determine the degree  
10 of inactivation of these viruses after applying as near  
11 as possible our protocol.

12 Q. Right. What was the purpose of doing that?

13 A. That was to offer us laboratory evidence, clinical  
14 evidence being very slow to collect, that we might be  
15 increasing the virus inactivation of perhaps  
16 hepatitis-like viruses by the higher temperature.

17 Q. When was that done?

18 A. I have no detailed recollection of these dates. As  
19 I have said in my previous answer, it is possible that  
20 one of the reasons for my greater optimism by the end of  
21 1986 was that these experiments may have been done and  
22 we had received the results.

23 Q. Right. We see that this has been discussed obviously in  
24 correspondence on 9 May 1986. If you just go to  
25 [\[SNB0075801\]](#), as I understand it, this is what's



1 appended to this document. It's the protocol. Again,  
2 if you just scroll down, that's dated 30 April 1986. Am  
3 I right in thinking that this is the same process that  
4 you have just described in terms of testing --

5 A. Yes, exactly.

6 Q. So that has obviously been discussed in April,  
7 presumably with a view to seeing whether the optimism --  
8 some optimism that we have heard about -- discussed at  
9 the meeting in March referred to by Dr Perry in his  
10 annual report, that this is with a view to testing that  
11 out in the lab in Scotland. Is that right? To  
12 testing --

13 A. With a variety of surrogate viruses.

14 Q. Indeed.

15 THE CHAIRMAN: Would you look back, please, at [\[SNB0075664\]](#),  
16 their note of the meeting on 17 March, at PFC? We may  
17 have to scroll through it because I can't remember the  
18 precise page that one is concerned with. But could you  
19 go through it, please, until we see where there are  
20 references to some experimental work to be done by  
21 Dr Cuthbertson. Go to the next page. Yes. The  
22 paragraph:

23 "It was agreed that Dr Smith would liaise with  
24 Dr Cuthbertson with a view to establishing a level of  
25 virus inactivation achieved by BPL 8Y material. This

1 would involve the transfer of samples between BPL and  
2 PFC and the development of a protocol which accurately  
3 simulated routine BPL formulation and treatment  
4 conditions."

5 Does that anticipate, do you think, what is being  
6 referred to in the two documents we have just been  
7 shown?

8 A. Exactly.

9 THE CHAIRMAN: So this is part of a programme of using  
10 facilities that Dr Cuthbertson had, that aren't  
11 available to you down south, to use model viruses and  
12 things of that kind to test infectivity.

13 A. Exactly.

14 THE CHAIRMAN: Yes. I hope that helps, Mr Di Rollo.

15 MR DI ROLLO: It does, thank you.

16 Just as in the middle of 1986, do you have  
17 a recollection of a request being made for 8Y to be made  
18 available to Scotland for previously untreated --

19 A. I do.

20 Q. Can you just tell us what you recall about the  
21 circumstances of that?

22 A. I was telephoned, I believe, by Mr Pettet, who was  
23 Dr Lane's right-hand man in the business of allocating  
24 resources and who I took would be relaying Dr Lane's  
25 wishes. Mr Pettet was asking me to send, I think, about

1 50 vials of 8Y to Dr Perry. My understanding was that  
2 this was to provide material should any  
3 haemophilia centre in Scotland acquire a patient in the  
4 category we have spoken about, who might benefit most  
5 from what we regard as our safest product at the time.

6 I'm fairly sure that I included in the package  
7 a message and the protocol which I expected to be  
8 studied should such a patient present themselves. I do  
9 not believe that I was given chapter and verse on the  
10 reasons why any particular patient had received it or  
11 was thought to be going to receive it. As I remember,  
12 it was to provide a stock against such eventualities.  
13 Precisely the same eventuality in which any  
14 haemophilia centre director in England would have been  
15 directed to me to request stocks of 8Y for trial.

16 Q. Right. Would it be reasonable to think that it appeared  
17 then, by that stage at least, that somebody thought that  
18 8Y would provide a worthwhile increased margin of safety  
19 for a previously untreated patient, as opposed to the  
20 existing Scottish product?

21 A. That was probably the inference to be drawn from the  
22 request but I do remind you that back in 1984 we had  
23 a request for heated intermediate material at a time  
24 when, if it had not been from specially vetted donors,  
25 the product might very well have transmitted hepatitis.

1 It comes again to your definition or your understanding  
2 of a "margin of safety". It may be more imagined than  
3 real. It would become more real perhaps during the  
4 course of 1986.

5 Q. It does appear that from your point of view or your  
6 organisation's point of view, there might be something  
7 in this for you because would it assist if previously  
8 untreated patients in Scotland received this product,  
9 your product, 8Y, and it was discovered that they did  
10 not develop non-A non-B. That would increase the number  
11 of people to whom that had been given, previously  
12 untreated patients to whom it had been given, and they  
13 had not developed the disease and therefore increase  
14 your research abilities?

15 A. Absolutely, and of course it had been already  
16 established principle that English centres would be  
17 prepared to try out Scottish products if they came  
18 through faster than our own.

19 Q. Indeed. I think there is some contemporaneous material  
20 relative to this and perhaps we should have a look at  
21 that. [\[SNB0075980\]](#). I'll just take you through this.  
22 This is a letter from, is it, Dr Pettet or just  
23 Mr Pettet?

24 A. Mr Pettet.

25 Q. To Dr Perry. Referring to Factor 8Y to PFC:

1           "Following your letter on your requirements for  
2           'virgin' haemophiliacs in Scotland and Northern Ireland,  
3           I tried to contact you by telephone last Thursday in  
4           order to begin supply as soon as possible. As you were  
5           down in London, it was obviously difficult.

6           "However, with Dr Lane's agreement I had spoken to  
7           Jim Smith and he hoped to see you last Friday with a  
8           novel proposal: perhaps Scotland would like to  
9           participate in our trial of Factor VIII-Y!

10          "Provided that you are agreeable and that the  
11          patients met the criteria, and given agreement by the  
12          haemophilia directors involved, Jim Smith can provide 8Y  
13          from batches set aside for trial purposes. I assume  
14          that everything went well as I have not had any adverse  
15          comment from Jim.

16          "In case there are some patients who do not strictly  
17          meet the criteria for trial, now or in the future,  
18          I have put aside some 8Y for immediate dispatch to PFC  
19          (or any other destination), if you require it. I can  
20          arrange same day delivery if necessary. Would you like  
21          this additional product to be set to PFC now, or have  
22          you made adequate arrangements for cover with Jim?

23          "Please do not hesitate to phone me in order to save  
24          time, and we can take it from there."

25          Then he goes on:

1            "There is one point, however, that you need to  
2            consider. Current batches of 8Y on issue, are not made  
3            from certified anti-HIV screened donations. The first  
4            individually screened product will not be released for  
5            issue until August. Subsequent batches will all be made  
6            from screened plasma."

7            It does appear from that that a request having been  
8            made for the purpose that you have outlined in your  
9            evidence, there doesn't appear to have been any  
10           practical problem in the supply of 8Y to Scotland for  
11           the treatment of previously untreated patients.

12          A. No, but could I return to the first page, just to  
13           clarify something?

14          Q. Of course.

15          A. Right, the fourth paragraph, "or any other destination".  
16           That does not refer to myself or anyone else in England,  
17           simply sending 8Y to any haemophilia centre.

18          Q. No, I understand.

19          A. It would always be under the cloak of Dr Perry, who was  
20           the person who allocated product within Scotland,  
21           wherever that came from.

22          Q. Right. So it would be down to Dr Perry to distribute  
23           from there?

24          A. Yes, Mr Pettet is trying to say that if you, Dr Perry,  
25           would prefer that for speed, it goes straight to

1           Aberdeen haemophilia centre; it would go on the plane.  
2           But our understanding will be that we will be in full  
3           touch about this and you will have blessed the transfer  
4           of this material straight to the haemophilia centre,  
5           instead of it going through the official routes through  
6           the PFC stocks --

7    Q.    I understand.

8    THE CHAIRMAN:  What does the expression "do not strictly  
9           meet the criteria for trial," mean to you?

10   A.   Our trial protocol at that point still allowed entry of  
11          patients who had had small amounts of exposure to  
12          cryoprecipitate and even if the period of administration  
13          were right, perhaps even to one our two vials of  
14          concentrate, the strict protocol would have excluded  
15          these people.

16                I think Mr Pettet is saying that if a patient turns  
17          up who perhaps it is not certain that he meets these  
18          criteria, we are not going to withhold the material  
19          while you go through all the records of three  
20          haemophiliacentres to find out.  This is precisely the  
21          understandings on which I would issue trial material in  
22          England, without asking for cast iron proof of the  
23          number of cryos previously received.

24   MR DI ROLLO:  Just to follow some correspondence through,  
25          just so that we see it, 28 July 1986, [\[SNB0075986\]](#).

1 I think just here we have a letter from Dr Perry to  
2 Mr Pettet and he says:

3 "Thank you for your helpful letter of 24 July.  
4 I have indeed spoken Jim and have confirmed locally that  
5 supply of 8Y should be conditional on users  
6 participating in the clinical trial of your product, at  
7 least until a PFC lookalike product is available (two  
8 months' time approximately)."

9 It sounds as though that might have been a little  
10 bit optimistic in retrospect. But anyway:

11 "I have now written to Jim confirming these points  
12 and I have asked if he can now send immediately 50 vials  
13 to PFC as a contingency stock of non-infective material  
14 ... "

15 Again, the phrase "non-infective" is quite an  
16 interesting one:

17 " ... in the unlikely event that a virgin  
18 haemophiliac presents for treatment in the near future."

19 Then if we go to the next letter, 1 August 1986,  
20 [\[SNB0075990\]](#), I think this is a letter from you on this  
21 occasion:

22 "Dear Bob,

23 "As requested in your letter of 24 July and agreed  
24 verbally by Dr Lane, I'm sending the 50 vials of 8Y  
25 3312, in case you wish to protect category 1 patients



1 before your Z8 is ready."

2 What did you understand category 1 patients were?

3 A. These would be pure virgins, previously untreated --

4 Q. Right. Again, it does look as though your

5 understanding in this letter is that this was to protect

6 these against, presumably non-A non-B Hepatitis; is that

7 right?

8 A. And incidentally HIV, but I don't believe that the

9 current Scottish product would have transmitted HIV

10 either.

11 Q. Yes. We are principally concerned with non-A non-B

12 Hepatitis. You say:

13 "Please issue one of the attached copies of the

14 trial protocol to the responsible physician in each

15 event and let me know whom I should nag for data."

16 The quid pro quo from your point of view or the

17 English point of view here is that data is going to be

18 obtainable on virgin patients not having developed non-A

19 non-B, which is the best data you could possibly have.

20 A. Just to qualify that, I'm not exactly sure what our

21 category 1 would have included. It may have included up

22 to a certain number of cryos, maybe about ten but as

23 I sit here, I cannot give an exact definition.

24 Q. I understand that, Dr Smith, I'm grateful to you.

25 A. Good prospects for a clean trial --

1 Q. Indeed. Did you get any Scottish data?

2 A. I don't believe -- I can't remember -- our publications,  
3 I think, never included any data from Scotland. I would  
4 have to -- would you give me a minute to check?

5 Q. Of course.

6 A. I have a feeling that Dr Ludlam may have been -- could  
7 it have been one of those? The publications contained a  
8 list of the contributing clinicians. There are no  
9 Scottish patients included in the 1988 publication.

10 I am afraid I don't have a copy of the Rizza 1992.  
11 Mr Mackenzie perhaps can find that.

12 Q. Perhaps we can clarify that shortly but I don't believe  
13 there to have been any Scottish patients --

14 A. In the 1987 update given to the HCDs, less official  
15 thing, I see no Scottish clinicians on this list.  
16 Therefore, the assumption must be that we received no  
17 information from Scotland.

18 Q. Thank you for that, Dr Smith.

19 Could I ask you, did BPL supply 8Y to any other  
20 country during this period at all? Did you get requests  
21 from abroad?

22 A. I don't think so. If they had been for trial purposes,  
23 they would have gone through me at some point.

24 Q. Right.

25 A. And appeared on the list of people to be acknowledged in

1 the papers.

2 Q. So --

3 A. They would have appeared --

4 Q. They would have appeared and you don't think there is  
5 anyone?

6 A. I can't recall anyone.

7 Q. Right.

8 Thank you, Dr Smith.

9 THE CHAIRMAN: I think, Mr Di Rollo, if you look at Lindsay,  
10 you will find that there is a discussion of contact made  
11 with BPL to see whether there could be supplies obtained  
12 for Ireland, but it may have foundered on the fact that  
13 you wanted to charge 10p or 20p -- I can't remember  
14 which -- a unit but you won't find that before about  
15 1987/1988, I think. I don't pretend to have all the  
16 page references for you, but -- no, in fact I can't.  
17 I can only give you it up to 1987, which is page 105,  
18 but it's not far after that you will get an account of  
19 what happened.

20 MR DI ROLLO: I'm obliged sir.

21 THE CHAIRMAN: Mr Anderson?

22 Questions by MR ANDERSON

23 MR ANDERSON: Good afternoon. I only want to discuss one  
24 discrete matter with you.

25 Do you remember this morning Mr Mackenzie was

1           discussing the general issue of 8Y in England for  
2           clinical use in about September 1985. Do you recall  
3           that?

4    A. Yes.

5    Q. He sought your views on the proposition that upon  
6           introduction, effectively only about one third of the  
7           demand was being met. Do you remember that?

8    A. Yes.

9    Q. In your response to Mr Mackenzie's questions, you talked  
10          of satisfying the needs of the UK --

11   A. I'm sorry.

12   Q. I wonder if that's a slip and you meant England and  
13          Wales?

14   A. Absolutely. I apologise for that.

15   Q. Just for the record, sir, that's page 33, line 22 and  
16          just after that at page 34, line 16, again, I think you  
17          made reference to the whole country and I take it again  
18          that's a reference to England and Wales?

19   A. That's a slip.

20   Q. I'm obliged to you.

21   THE CHAIRMAN: Even expatriate Scots make that mistake, do  
22          they?

23   MR ANDERSON: So it would appear, sir.

24                  Just related to that, Dr Smith, finally, can you  
25          look with me at the final paragraph of your statement,

1           which we find on page 12 of [\[PEN0171130\]](#). You say  
2           there, reading short, that:

3           "PFC ... to produce its own, robust and severely  
4           heated Z8 which did not transmit non-A non-B Hepatitis.  
5           It is to the credit of the whole of the SNBTS, and its  
6           donors, that Scotland can rightly claim to have been  
7           first to provide virus-safe concentrates of Factor VIII  
8           and Factor IX for all its haemophiliac patients."

9           Which you underline and then go on to say:

10          "[This] phrase is far from trivial".

11          Can I just be clear that when you say "first" there  
12          and you go in the final line of that paragraph to talk  
13          of the first country, is that a comparison with England  
14          or are we to understand that in a more global sense?

15   A.   Global.

16   Q.   I'm obliged. Then you may recall that my learned friend  
17          Mr Di Rollo was asking you about the point in 1986 where  
18          things began to look better, as it were, in relation to  
19          8Y. Do you remember that?

20   A.   Yes.

21   Q.   I think in your answer you said there was not a single  
22          point. Is that right?

23   A.   Exactly.

24   Q.   I say that simply because it has been transcribed as --  
25          I think what you said was a "single point"?

1 A. I meant a single point, in any case.

2 Q. I'm obliged to you.

3 THE CHAIRMAN: Mr Johnston?

4 MR JOHNSTON: I have no questions, thank you, sir.

5 Further questions by MR MACKENZIE

6 MR MACKENZIE: Sir, there is one point of detail.

7 Dr Smith, in relation to the question as to Scottish

8 participation in the clinical trial of 8Y, were you

9 looking at one point for the later paper by Rizza and

10 others, the 1993 paper?

11 A. Indeed.

12 Q. We can bring that up. It's [\[SNB0045996\]](#). If we look at

13 the bottom left-hand part of the paper, we can see

14 a list of names --

15 A. No, I'm sorry, that was 1983, no?

16 Q. Is that a different paper? This is 1993?

17 A. Yes, that's it. Same authors.

18 Q. I think the one name I recognise is Dr Hann, who had

19 been at Yorkhill but I think at this point he was down

20 in London at Great Ormond Street. I don't think

21 I recognise any other Scottish names but I may be wrong.

22 A. The difficulty is they did move around a bit, especially

23 the younger directors in those days, and several of them

24 had experience in both Scotland and England.

25 Dr Franklin, he would have been only in Scotland.

1 Q. I think Dr Franklin may have been in England at that  
2 stage, I think.

3 A. Then it's inconclusive.

4 Q. Yes, thank you.

5 A. Dr Ludlam's name does not appear.

6 THE CHAIRMAN: Dr Smith, thank you very much. As you know,  
7 your name appeared many times before your appearance and  
8 I think we were all looking forward to hearing what you  
9 had to say, you have been very helpful. Thank you very  
10 much.

11 A. My privilege.

12 MR MACKENZIE: Sir, there are no further witnesses today but  
13 we have a fuller day tomorrow. We have Dr McIntosh and  
14 then Mr Murray and Mr Macniven tomorrow.

15 THE CHAIRMAN: I don't think we can anticipate any of that.  
16 We will rise now.

17 (2.55 pm)

18 (The Inquiry adjourned until 9.30 am the following day)

19

20

21 I N D E X

22 DR JAMES SMITH (continued) .....1

23 Questions by MS DUNLOP (continued) .....1

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