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Thursday, 27 October 2011

(9.30 am)

DR PETER FOSTER (continued)

Questions by MR MACKENZIE (continued)

THE CHAIRMAN: Good morning.

Yes, Mr Mackenzie?

MR MACKENZIE: Thank you, sir.

Good morning, Dr Foster.

A. Good morning.

Q. I think we had reached page 12 of your statement, question 7, if we could have that up on the screen, please.

Question 7 concerns the dealings between PFC and those south of the border and it's stated:

"There was [clearly] informal contact and exchange of information between PFC and BPL/PFL, in particular, between Dr Foster and Dr Smith."

There is a reference to:

"There appears to have been difficulties with more formal contact, in particular, at a senior or managerial level."

We will come to the documents in a second but in short the document suggests that there may have been difficulties between the directors of BPL and PFC, and the issue in short is whether any such difficulties

1 adversely affected the heat treatment programme
2 generally at PFC and in particular, in respect of the
3 development of Z8, and I should firstly, I think,
4 doctor, take you to the three documents which form the
5 basis of this question. The first document is
6 [\[SNB0043282\]](#).

7 We will see this is a letter from Dr Cash to Dr Lane
8 of 19 December 1980 and this document is referred to as
9 it really forms a precursor to the next letter, but one
10 can see Dr Cash saying in the second paragraph that:

11 "I believe that we should grasp the nettle and
12 arrange a meeting of the appropriate colleagues with
13 regard to arranging a workshop on fractionation aspects
14 of Factor VIII concentrates."

15 Et cetera.

16 So that's the suggestion by Dr Cash. It appears
17 that workshop didn't take place because if we then look
18 at the next document, please, which is [\[SNB0043163\]](#),
19 obviously this is again Dr Cash writing to Dr Lane, now
20 on 17 December 1982. We looked at this letter in
21 a previous hearing. We have looked at it before. It was
22 B3.

23 Page 2. Dr Cash states:

24 "The solution to our problems rests, as I said at
25 the meeting, in thinking and acting very much more

1 positively. I refer to the problem of getting BPL and
2 PFC to work together at all levels. I now deeply regret
3 that the joint PFC/BPL meeting on Factor VIII
4 concentrates that I proposed in a letter to you dated
5 19 December 1980 did not take place. However, we must
6 now surely consider this as water under the bridge and
7 get down to the urgent task of bridge building. I'm
8 bound to conclude that up to the present time we, as
9 professionals, have failed and the time has come for
10 a joint meeting of the top managers."

11 Then we saw before the reference to:

12 "I do not regard the existing ..."

13 What Professor Cash called "furtive arrangements":

14 "... as regards Factor VIII, between Jim Smith and
15 Peter Foster, however good they may be, as a sound basis
16 upon which the NHS fractionators can combat the
17 commercial people."

18 The final document, before I come to your response,
19 is [\[SNB0065138\]](#). This document is again, if we look at
20 the bottom right-hand corner, please, the letters "JDC".
21 Dr Cash is the author. It's dated January 1984 and we
22 can see "Background notes for chairman (on the occasion
23 of the meeting between the ..."

24 Common Services Agency, I think is the reference:

25 "... and CBLA colleagues, 20 January 1984)."

1 If we could then look at pages 2 and 3 and the next
2 page again, please. In the first full paragraph Dr Cash
3 states:

4 "It would be appropriate to conclude that the formal
5 relationships between BPL (originally managed by the
6 Lister Institute) and the SNBTS have not been
7 satisfactory over the years."

8 Could I then, please, scroll down to the second last
9 paragraph, commencing:

10 "Soon after I was appointed NMD, I visited BPL with
11 the express intention of attempting to build bridges.
12 It became evident that Dr Lane was not prepared to
13 liaise with Mr Watt but did agree to my suggestion that
14 liaison could begin between operational counterparts at
15 a subordinate level. This programme of liaison was
16 commenced some six months later and in the subsequent
17 three years, it has proved of considerable value to both
18 institutions. Nevertheless, it repeatedly ran into
19 temporary difficulties when either Dr Lane and/or
20 Mr Watt for their separate reasons, ordered
21 a disengagement of liaison. There can be no doubt that
22 throughout these periodic difficulties, Dr Peter Foster
23 (PFC) and Dr Jim Smith ... did much to keep a measure of
24 momentum going."

25 I'll stop there.

1 Dr Foster, these documents are the background to
2 this question. The question, as I say, in short, is
3 firstly do you accept there were difficulties between
4 the respective directors of the BPL and PFC?

5 A. It's difficult for me to answer because I have no
6 personal experience of that. Whenever I met Dr Lane, it
7 was always a very pleasant experience and I have to say
8 I didn't meet him that often and I was always encouraged
9 by Mr Watt to interact with colleagues at BPL and at PFL
10 quite freely, and that was, to my knowledge, always
11 reciprocated and I was never ordered to disengage this
12 liaison at any time.

13 I was aware that Mr Watt and Dr Lane had different
14 views and that's understandable, that they were -- at
15 this time people did have different views but Mr Watt
16 was very much trying to take forward the plan that
17 English plasma be processed in Scotland and I don't
18 think Dr Lane saw things the same way. So there was
19 a point there, where they clearly disagreed and that's
20 conceivable that that might have led to some friction
21 but that's really all I can talk to. That's all I'm
22 aware of.

23 Q. From your position as head of research and development
24 at PFC, how were your relations with your counterpart or
25 counterparts down south?

1 A. They were always excellent and I think I went over this
2 in the previous B3 session, that in -- shortly after
3 I joined PFC, I was given a task by Mr Watt to lead
4 a delegation from PFC to BPL to help people to meet
5 their counterparts, and there were maybe 10 or 12 people
6 from PFC went down to BPL, they met their counterparts,
7 that was reciprocated by visits from BPL, and we always
8 encouraged our staff to communicate with their
9 counterparts and that was always the situation and
10 remained the situation thought my employment.

11 Q. So there was communication, not only between yourself
12 and Dr Smith but also the staff beneath you as well?

13 A. Yes, very much so. All of my staff were encouraged to
14 deal with their counterparts because we saw ourselves in
15 the wider sense part of the same organisation. We all
16 worked for the NHS and we were in an area where it's
17 really highly specialised.

18 So to find somebody who is dealing with the same
19 problems and same issues is not something that happens
20 every day. So to have, if you like, another branch of
21 the same organisation where you can talk to somebody was
22 really a very good thing to have. So we did encourage
23 that and I think that happened at BPL as well. And I'm
24 not aware of anybody saying, "Please stop doing this,"
25 either at BPL or PFC.

1 Q. So from your perspective, doctor, did any difficulties,
2 if they existed between the respective directors,
3 adversely affect the heat treatment programme at PFC
4 generally or in particular in respect of the development
5 of Z8?

6 A. No, there was nothing like that at all. But I should
7 add the rider to -- I can understand why Professor Cash
8 perhaps was seeking something more formal because the
9 relationships that we had were to a large extent
10 informal and it did depend on the individual
11 personalities, and if I had left or Dr Smith had left
12 and someone else had come long, things might have been
13 different. So Dr Cash might have wanted something more
14 formal to have a structure in place. So I can
15 understand that but from my perspective it wasn't
16 necessary, but if Dr Cash had said, "Please do this more
17 formally," we would have done.

18 Q. So certainly we saw the use of the words "formal
19 relationships" in Dr Cash's briefing notes and he did
20 recognise in the notes that there was communication,
21 dialogue and liaison between yourself and Dr Smith.

22 A. Yes, and if we had been asked to do it more formally
23 then we would have had no difficulty with that.

24 Q. Thank you.

25 Turning next, please, to page 13 in your statement

1 and question 8, question 8 relates to the Central Blood
2 Laboratories Authority central committee on research and
3 development in blood transfusion, which first met on
4 21 June 1983. We don't have to go to it but the
5 reference to the first minute is [\[PEN0161156\]](#), and we
6 saw yesterday that Dr McClelland attended, I think, in
7 a personal capacity with an observer from SHHD and you
8 also, I think, told us that you weren't aware of this
9 committee at the time and it was only, I think, perhaps
10 as part of this Inquiry that you became aware of this
11 committee. Is that correct?

12 A. That's correct.

13 Q. Have you had a chance to look at any of the minutes of
14 this committee?

15 A. Very briefly.

16 Q. Yes. We asked you various questions about the committee
17 and on page 14 at the top you say you don't believe that
18 PFC representation on this committee would have enabled
19 Z8 to have been introduced earlier. Can you briefly
20 explain why?

21 A. Because I was getting information from Dr Smith and
22 Mrs Winkelman and I was getting this directly from the
23 scientists who were doing the work and leading the work
24 and this committee was secondhand or third hand
25 information. So I was actually in the better place to

1 know what was going on.

2 Q. I understand. Then you go on to say you can:

3 "... only think of two occasions when exchange of
4 information on 8Y may have been influenced by the
5 commercial brief of CBLA, firstly when Dr Smith wrote to
6 [you] on 22 May 1984."

7 And he said:

8 "I'm trying to get a Crown record entered this week
9 and will let you know immediately I have confirmation of
10 this."

11 We looked at that letter yesterday:

12 "... secondly, when details of the method of
13 preparation of 8Y were provided to me only after
14 a patent application had been filed."

15 As you say:

16 "As a wider release of these details could have
17 undermined the validity of the patent application,
18 I believe that it was understandable that I was not
19 given details of the 8Y process earlier ..."

20 In the next paragraph you say:

21 "I don't believe that either of these occasions
22 contributed to any delay in the development or
23 introduction of Z8, as the critical importance of the
24 method of freeze-drying had not been recognised at BPL
25 or at PFC, and details of the freeze-drying method were

1 not included in the patent application for 8Y."

2 We discussed that yesterday.

3 One further question I would like to ask you,
4 Dr Foster, is this: what was the approach of PFC in
5 respect of the sharing of research and development
6 discovery with BPL or PFL; in particular did PFC ever
7 apply for patents in the 1980s and if so, did PFC hold
8 off from giving full details south of the border until
9 the patent application had been lodged?

10 A. I did apply for a patent application for the method of
11 thawing plasma, which I had designed, and that patent
12 was awarded and so it's conceivable that that
13 information wasn't given to BPL immediately but it was
14 published shortly thereafter. The only other example
15 I can think of is when we were working with Dr Johnson,
16 and of course, we had to sign confidentiality
17 arrangements with him and we weren't allowed to discuss
18 that with anyone else.

19 Q. This is a hypothetical question but if in 1985 you had
20 discovered something new and you had decided to lodge
21 a patent, what would have been your attitude to whether
22 you would have given full details to those south of the
23 border or not before the application had been lodged?

24 A. I have been involved in filing patent applications
25 subsequently, maybe not at that point in time but later,

1 and the advice from the patent lawyer always was, "Don't
2 breathe a word of this to anybody," because that could
3 undermine the application because it might be regarded
4 as a prior disclosure, and there are cases where even
5 correspondence between parties, a letter from one person
6 to another, is cited in opposition cases in patent
7 oppositions.

8 Q. It could be fatal to the application?

9 A. Certainly, the patent lawyers are very clear, "Don't
10 breathe a word of this to anybody; don't put it in
11 writing until the patent is filed".

12 Q. Was that a government patent lawyer?

13 A. No, that was a commercial patent lawyer.

14 Q. In private practice?

15 A. Yes, but we -- more recently we had advice from
16 commercial patent lawyers but that seemed to me -- this
17 was very much the situation throughout this period, that
18 patent lawyers would say, "Look, don't disclose any of
19 this to anybody until you have filed your patent".

20 Q. I understand.

21 Question 9, please, doctor. We asked:

22 "Were more formal links between PFC and BPL/PFL
23 desirable and were more formal links eventually
24 established?"

25 You responded that:

1 "From my perspective, scientific communications
2 between ... [the respective facilities] ... were
3 excellent and [you] believe that scientific
4 communications would not have been improved by a more
5 formal arrangement..."

6 And that may in fact:

7 "...have resulted in less effective communication
8 and also a greater degree of administration, and there
9 may have been delay introduced." Top of page 15 you
10 tell us you are not sure that:

11 "... more formal links ... were ever established."

12 Albeit you remind us some joint studies were carried
13 out, in particular involving, I suppose, the Factor IX
14 but also the viral inactivation of BPL products, using
15 marker viruses, and you say you were:

16 "... involved in both of these studies and believe
17 that communications between the respective organisations
18 were generally similar to those that took place with
19 8Y."

20 There is a final document I would like to put to
21 you, please, doctor. I think you have only been shown
22 this in the last day or two. It's SNB0083036. It
23 doesn't appear to be in the system yet. That's okay, we
24 can rectify that. I think what I might do, doctor, is
25 ask for hard copies to be made. That can be done now

1 and we will come back to it in perhaps half an hour at
2 the end of your evidence.

3 A. Okay.

4 Q. So don't let me forget this one?

5 THE CHAIRMAN: Can I understand just what it's about?

6 MR MACKENZIE: Yes, it's to do with joint research between
7 England and Scotland.

8 THE CHAIRMAN: In a particular area?

9 MR MACKENZIE: Actually we have got the letter,
10 I understand. Sorry, it's my wrong reference. It's
11 [\[SGH0083036\]](#), I apologise.

12 Doctor, I put this to you because I think it's
13 referred to in one of the other witness statements.
14 Perhaps Mr Macniven who is coming next week.

15 If I go to page 2, please, we can see it's a letter
16 from Mr Duncan Macniven of the SHHD. Back to page 1,
17 please. It's to a Mr Harris of the Department of Health
18 and it's dated 17 January 1989. We have a slight
19 difficulty in that I don't know the context of this
20 letter but I understand you have had a chance to look at
21 it and can help us with what it relates to, but it's
22 headed "Blood Transfusion Service research, PFC and
23 BPL."

24 Mr Macniven states:

25 "I'm writing about two unrelated aspects of the

1 Blood Transfusion Service -- first, the question of
2 research; second, future arrangements for
3 fractionation."

4 It's the question of research that may be of
5 relevance today.

6 In paragraph 2, Mr Macniven states:

7 "When last we met, I said that we were considering
8 a proposal from the SNBTS to conduct a great deal more
9 research. The SNBTS line is that they now realise that
10 too little attention has been given to this in the past;
11 so they are behind the game, both in refining existing
12 products and in developing new ones which were (or were
13 expected to be) required for the health service in
14 Scotland. The SNBTS proposal was based on the
15 assumption that in most key areas of research, they
16 would develop their own expertise. I was sceptical that
17 this represented good value for money and felt that
18 there should be the maximum cooperation with NBTS/CBLA,
19 (mainly the latter, since the proposals principally
20 involved fractionated products); and more consideration
21 of the option of manufacturing, under licence,
22 commercially developed products."

23 Paragraph 3:

24 "When we met you agreed that that general attitude
25 and said that you were already taking steps to learn

1 more about, and possibly bring under closer control, the
2 CBLA research effort. I suggested that the time might
3 be ripe to relaunch the abortive national research
4 discussions which were tried a couple of years ago.
5 I believe that the SNBTS would be prepared to
6 participate (because of their greater realisation,
7 compared with two years ago, of shortcomings in their
8 research effort) ... "

9 Et cetera.

10 Are you able to help us, doctor, with what this
11 letter is dealing with and in particular its relevance,
12 if any, to the question of Z8?

13 A. Yes, the key -- I'll just say, I haven't seen this
14 before but I'm fairly familiar with the subject matter.
15 The key hint here is the date of the letter, which
16 was January 1989, and in the first paragraph there are
17 a number of points I could comment on. The first says
18 that:

19 "The SNBTS line is they now realise too little
20 attention has been given to this in the past."

21 And "they are behind the game," and I think this is
22 referring to the high purity Factor VIII, and at this
23 point in time one commercial company was beginning to
24 introduce a high purity Factor VIII into the UK and that
25 was Armour, who had Monoclone-P. That wasn't licensed

1 until December 1989 but it was already available on
2 a named-patient basis and for clinical trials.

3 I think if you check the records, you will find
4 that Dr Ludlam was already using it for some patients.
5 As we had been over yesterday, we had done a lot of work
6 developing this high purity work with Dr Johnson but we
7 had shelved that work in order to focus on severe dry
8 heat treatment. Other organisations had not done that.
9 They had continued to develop this idea of a high purity
10 product. So in that respect we had fallen behind as it
11 says here.

12 But I should make it -- just point out that the
13 organisations who were developing these high purity
14 products had not achieved a product safe from
15 Hepatitis C before we did. We were maybe some two years
16 before them. So although this says we are behind the
17 game, I'll leave it for you to judge who was behind and
18 who was ahead.

19 The other issue, of course, that was driving this
20 idea for high purity products was the concern that
21 patients might be having their immunity depressed in
22 some way, and this was the idea of immuno-suppression or
23 immune disturbance that was caused by Factor VIII
24 concentrates. And there was a considerable amount of
25 attention given to this during this period. There were

1 conferences on it, many articles, there was research in
2 Glasgow, research in Edinburgh and it was a main area of
3 activity.

4 Certainly the haemophilia directors very much wanted
5 a high purity product to deal with that issue.

6 Now, this is not my area of expertise but my
7 understanding is that that immune suppression that was
8 taking place was actually a result of Hepatitis C
9 infection. In fact, in making the products safe from
10 Hepatitis C, we had dealt with that also. So in fact
11 this concern that existed, which was the driving force
12 for high purity Factor VIII, had actually already been
13 dealt with in the Z8 project.

14 So the reality was, though, that we did have to take
15 notice of what haemophilia directors wanted and we
16 didn't have the luxury of distributing our products
17 elsewhere. So we did move on and develop a high purity
18 product relatively quickly. So we did, if you like,
19 catch up, even though I accept that we were behind at
20 that point in time in developing that type of product.

21 The next area here is about developing new products,
22 and certainly at this time we were looking at the
23 possibility of a whole range of new plasma products
24 emerging. So Dr Cash is right -- I should say, these
25 ideas come from Dr Cash. He was right in that we would

1 need more research effort to be able to develop these
2 new products, and what Dr Cash was wanting to do at this
3 point in time was to obtain funding to develop his own
4 laboratory. He had a research laboratory that was
5 called the "headquarters laboratory" and that -- he
6 obtained extra resources for that, which are described
7 at the bottom of paragraph 3 as "modest", and that then
8 became the National Science Laboratory and it did
9 provide us with some more capability for doing early
10 research in the area of plasma products. So that is
11 what that was dealing with.

12 Q. I see. Mr Macniven is coming next week and no doubt we
13 can put the letter to him as well but in short, I think
14 your position is that the contents of this letter relate
15 to a later period than the period we are looking at in
16 relation to Z8?

17 A. That's correct.

18 Q. I think I have already asked you many questions about
19 the liaison between England and Scotland in respect of
20 Z8 during the relevant periods. We will put that to one
21 side for now, thank you.

22 Back to your statement, please. We are at question
23 10. We asked the question which to a fractionator may
24 seem daft. The question was:

25 "Why was PFC able to make available for use clinical

1 Factor IX concentrate that had been severely treated in
2 October 1985 but Factor VIII concentrate subjected to
3 a similar heat ... regime ... was not available for
4 clinical use until ... [later] ... "

5 You explain the reason for this difference in timing
6 was primarily due to two factors, firstly, differences
7 in the ability of the established Factor VIII and IX
8 concentrates to withstand severe dry heat treatment, and
9 secondly, to changes in the strategy of the SNBTS in
10 response to new information, et cetera.

11 Is the answer in short, doctor, that it's easier to
12 heat Factor IX than it is Factor VIII?

13 A. Yes, I think that's a simple way to put it, although it
14 wasn't entirely straightforward, it was easier to do
15 that.

16 Q. Then over the page -- we don't have to go through all of
17 the events but at the bottom of the page 16 you explain
18 in subparagraph (v):

19 "The PFC Factor VIII concentrate was unable to
20 withstand dry heat treatment at temperatures higher than
21 68 degrees centigrade. By contrast it was found that
22 the PFC Factor IX concentrate could withstand dry
23 heating agents at 80 degrees centigrade for 72 hours if
24 a small change was made to the composition of the
25 product (the addition of the protein antithrombin 3).

1 As this change to the composition of Factor IX
2 concentrate was relatively straightforward, the
3 timescale for the introduction of severe dry
4 heat-treated Factor IX concentrate was primarily
5 determined by the time taken to carry out a safety study
6 concerning the risk of thrombotic reactions."

7 You have previously provided evidence on this in
8 relation to B3. The further events narrated on pages 17
9 and 18 are simply a repetition of what we went over
10 yesterday. So I'm going to skip them and go on to
11 question 11, please.

12 Question 11 relates to something Dr McIntosh is
13 noted as having said but Dr McIntosh is coming next
14 week, so I'm going to ask him that question. I think
15 that would be the best evidence. So again I'm going to
16 skip pages 19 and 20.

17 The top of page 21, the reference to a memo we
18 looked at yesterday. It's a letter from yourself to
19 Dr Smith dated 13 November 1985 and some questions are
20 asked about that, but again I have covered all this
21 yesterday so I'm going to carry on skipping.

22 Similarly, page 22. That refers to your memo of
23 18 December 1985 to Dr Perry and I had asked what is
24 meant by the high ionic strength of NYU product, and
25 I think we will just take the answer as read without

1 going into that in detail. I think it's a point of
2 detail really.

3 Go on to page 23, please, sub-question (b). We
4 asked about difficulties in adopting or adapting the BPL
5 methods and why PFC did not decide to simply adopt/adapt
6 the BPL method at that time. Again, we discussed all
7 that at length yesterday, so I think we can skip page 24
8 to avoid repetition and go on to page 25, please. The
9 last paragraph on page 25, I think, brings things
10 together a little by stating:

11 "The method for the preparation of 8Y had been
12 adapted from the method devised at the PFC for the
13 pasteurisation of Factor VIII (ie the ZHT process). The
14 Z8 process was also adapted from the ZHT process and can
15 therefore be regarded as an indirect adaptation of the
16 8Y process, using the zinc precipitation rather than the
17 heparin precipitation, for the reasons given above."

18 Go over the page, please. The first paragraph
19 states that:

20 "This interrelationship between the 8Y and Z8
21 processes illustrates how fractionators could learn from
22 each other, but utilise the knowledge gained in a manner
23 that was compatible with their own manufacturing
24 operation."

25 At question (c) we asked:

1 "What work, by whom and when had previously been
2 undertaken at PFC into investigating/adopting/adapting
3 the BPL process?"

4 Is the answer, in a way, not much because that
5 wasn't an option you wanted to pursue?

6 A. The answer is none, because it wasn't really a practical
7 option for us.

8 Q. For all the reasons we discussed yesterday?

9 A. For all the reasons that we have been through.

10 Q. Again, to avoid repetition, I think we can then happily
11 go on to page 28. Question 11 is a new question we
12 haven't yet dealt with, and we asked you:

13 "When were commercial manufacturers able to produce
14 and supply Factor VII concentrates that were
15 sufficiently treated to inactivate NANBH/hepatitis C,
16 and by what methods of viral inactivation?"

17 It seemed to us there was a helpful publication by
18 Kasper and others in 1993, which is reference
19 [\[SGH0021947\]](#). We don't actually have to go to that
20 quite yet. We will come to it in a second. I think we
21 simply suggested it may be helpful for you to look
22 through the products in this publication and identify
23 those which you considered were safe from the point of
24 not transmitting Hepatitis C. At page 29 of your
25 statement, doctor, you say, in your opinion:

1 "... a number of commercial coagulation factor
2 concentrates were sufficiently treated to inactivate
3 NANBH/hepatitis C."

4 You go on to list these according to tables 1 to 5
5 in Kasper. You then say:

6 "I do not know precisely when manufacturers were
7 able to produce and to supply these products but
8 I believe that the dates would closely equate with (a),
9 the date that either a USA FDA licence or a UK licence
10 was granted, whichever was the earlier (produce) ..."

11 What do you mean by "produce"?

12 A. It should be "product".

13 Q. I'm easily confused:

14 "... and (b), the date that a UK licence was
15 granted for supply in the UK, although any supply in the
16 UK for clinical trials and for named-patient use would
17 have been earlier.

18 "You have given the dates for the granting of a UK
19 licence," to the best of your knowledge, based on
20 information from the UK Medicines and Healthcare
21 Products Regulatory Agency.

22 Then the next paragraph. I propose then just going
23 through and looking at the Factor VIII products firstly,
24 which you identify as having been safe from the
25 perspective of Hepatitis C. So firstly products from

1 Armour, a pharmaceutical company, Humate-P.

2 This was pasteurised product at 60 degrees
3 centigrade for ten hours. FDA licence, May 1986. This
4 is the Behringwerke product, manufactured in Germany, a
5 UK licence in 1984 but you stated it was not generally
6 available in the UK due to very low levels of exports
7 from Germany. We have heard about that product,
8 I think, in previous hearings.

9 Then at the very bottom of page 29 you refer to
10 products from Alpha Therapeutic Corporation?

11 A. After Humate-P, there is Monoclade-P, and I should point
12 out I made a mistake here. When I say it was licensed
13 in the UK in December 1999, that of course, should be
14 1989.

15 Q. Yes, I understand, thank you.

16 A. That's relevant to the letter that we have just covered
17 from Mr Macniven.

18 Q. Monoclade-P, was that also the Behringwerke method?

19 A. No, this was Armour's own product, which they had
20 developed and it was a pasteurised version of that
21 product and it was a high purity product.

22 Q. Was that manufactured in America?

23 A. Yes, it would have been.

24 Q. Thank you. Then at the bottom of page 29 you go on to
25 table 2, which looks at products from Alpha Therapeutic

1 Corporation, and at the top of page 30, we see, sticking
2 with Factor VIII products, Profilate SD, treated with
3 solvent-detergent. I will come back to ask you a
4 question about that shortly. FDA licence, July 1989.
5 You don't know if the product was available in the UK.
6 Another product, Profilate OSD, again solvent-detergent.
7 FDA licence, May 1990, and you don't know if that was
8 available in the UK. Then Alpha-8, again
9 solvent-detergent, FDA licence pending as at November
10 1992. And you don't know the date a UK licence was
11 granted but you do have a UK patient information leaflet
12 dated December 1992, which is probably the date from
13 which the product was supplied in the UK.

14 Then going down the page, table 3, products from
15 Hyland Division, Baxter and their Factor VIII product
16 Hemofil M, again solvent-detergent, receives an FDA
17 licence in February 1988, a UK licence in June 1994.

18 Then products from table 4 from Cutter Biologicals,
19 Miles Corporation. Their Factor VIII product, Koate-HS,
20 a pasteurised product at 60 degrees for ten hours,
21 received an FDA licence in April 1986 but not available
22 in the UK to the best of your knowledge. Was that the
23 Behringwerke process or something different?

24 A. It was different but very similar.

25 Q. And manufactured in America?

1 A. It was manufactured in America.

2 Q. Thank you. Then Koate-HP, a solvent-detergent product,
3 FDA licence, March 1989, UK licence, June 1994.

4 I would now like to ask you, doctor, about the
5 solvent-detergent method. Could we now go to the Kasper
6 paper? Thank you.

7 We can see this is a paper from Kasper, Lusher and
8 the transfusion practices committee. I think it comes
9 from various centres in America. Could we, please, go
10 to page 426 of the paper, which is 1951 in our
11 reference. So page 426, the left-hand column, three
12 lines from the top. This concerns solvent-detergent.
13 The paper states:

14 "Inactivation of lipid coated viruses, including
15 Hepatitis, with a solvent-detergent combination that
16 allowed clotting factor activity to be well preserved
17 was reported in 1984. The Factor VIII concentrate
18 treated by a solvent-detergent combination, (tri-n-butyl
19 phosphate and sodium chlorate) was licensed in 1985."

20 That must be in America?

21 A. That's correct.

22 Q. "HIV, which has a lipid envelope, also proved highly
23 vulnerable to such treatment. Solvent-detergent virus
24 inactivation methods quickly gained popularity. Further
25 licences were granted in 1988 and 1989 for treatment of

1 other Factor VIII concentrates with combinations of
2 tri-n-butyl phosphate and such detergents as
3 polysorbate 80 (Tween 80) and Triton X-100. No
4 transmission of hepatitis virus or of HIV has been seen
5 in any of the several formal trials of various
6 solvent-detergent-processed concentrates but the protein
7 coated B19 parvovirus can be transmitted."

8 Can we then go to page 430 of this paper, which is
9 1995 of our records. Table 5 we can see is headed
10 "Concentrates Marketed by Other Manufacturers,
11 1981-1992". If we look in the left-hand column which
12 details the type, manufacturer and brand name, about
13 four lines down we see a reference to
14 NYBC/Melville Biologics coagulation Factor VIII-SD."

15 The "NYBC". Is that the New York Blood Centre?

16 A. It is, indeed.

17 Q. Who are Melville Biologics?

18 A. It was also the New York Blood Centre but they built a
19 facility and called it Melville Biologics, I don't
20 really understand why.

21 Q. We see a licence or release date of this product in
22 1985. What I simply wondered, doctor, is whether this
23 product was safe for Hepatitis C transmission?

24 A. I would say, looking back, yes, and I did not include it
25 in my response to you because your question concerned

1 commercial companies, they were not a commercial
2 company. They simply supplied material to the New York
3 area. It was not a product that was commercially
4 available.

5 Q. I understand. So this product wouldn't have been
6 available for purchase in the UK?

7 A. No.

8 Q. I understand. There is a wider question of what
9 consideration was given by the PFC to solvent-detergent
10 as a method of viral inactivation in 1985 and 1986?

11 A. We did consider it quite seriously and I was aware of
12 this work and I had actually met Horowitz who was
13 developing the product -- the technique in 1984.
14 I think I mentioned that in my previous evidence. But,
15 as this article explains, the solvent-detergent method,
16 which was a chemical treatment, was only effective
17 against certain types of viruses that have a lipid
18 envelope. There are viruses that have a lipid envelope
19 and viruses that don't.

20 By the time this was being developed in late 1984,
21 it was known that HIV was a lipid-enveloped virus and
22 therefore that was the driving force for the development
23 of this technique. It wasn't known what the agents for
24 non-A non-B were in terms of their viral structure,
25 because the viruses responsible hadn't been discovered.

1 There were some publications that suggested that it
2 might be enveloped or it might not be, or there might be
3 more than one agents. So it was conceivable that there
4 might have been an agent that was responsible for non-A
5 non-B that was non-enveloped, and it wouldn't have been
6 addressed by solvent-detergent treatment at all. So, in
7 considering solvent-detergent treatment, we decided not
8 to pursue that at the moment as an immediate option but
9 to be aware of it, and if it did emerge that it was
10 effective against non-A non-B Hepatitis, it might be an
11 option to pursue, and ultimately we did pursue it and we
12 did move away from severe dry heat treatment to a high
13 purity Factor VIII that was solvent-detergent treated in
14 1991, once that information was available.

15 Q. For completeness, would it have been feasible to have
16 introduced solvent-detergent treatment of any of the PFC
17 Factor VIII concentrates in 1985 or 1986?

18 A. The method that was used at New York -- and you can see
19 it here to some extent -- had a problem with it, and the
20 problem was how do you remove these chemicals, because
21 they are toxic chemicals. You can't inject them into
22 the patient, and the procedure that was being used at
23 New York was -- in our judgment -- not really adequate
24 for a large routine manufacturing operation. It was
25 a kind of oil extraction that we wouldn't have wanted to

1 get involved in, and it was only subsequently, when high
2 purity Factor VIII was developed, that the techniques
3 that were used to purify the Factor VIII also removed
4 these chemicals and that became a technically acceptable
5 process.

6 Q. Thank you.

7 Returning to your statement, please, page 31, you
8 state:

9 "I believe that three methods of virus inactivation
10 provided treatment of coagulation factor concentrates
11 that was sufficient to inactivate NANBH/hepatitis C:
12 pasteurisation at 60 degrees centigrade for 10 hours;
13 solvent-detergent treatment; dry heat treatment at
14 80 degrees centigrade for 72 hours."

15 You go on to say that:

16 "Despite the general safety from transmission of
17 NANBH/hepatitis C, coagulation factor concentrates,
18 prepared either by pasteurisation or by
19 solvent-detergent treatment have been associated with
20 occasional transmission of viruses."

21 I think I'll take the next two pages as read in that
22 we can't spend time going into all of the details.
23 I think it's enough to note the point that you make,
24 that pasteurisation and solvent-detergent have been
25 associated with occasional transmission of the viruses,

1 as you then list in more detail.

2 Going, please, to the bottom of page 32 of your
3 statement, the next question, we then ask:

4 "As it turned out (dry) heat treatment at 80 degrees
5 centigrade for 72 hours ..."

6 That should perhaps be "or 75 degrees centigrade for
7 72 hours":

8 "... was required to inactivate NANBH/hepatitis C in
9 Factor VIII and IX concentrates. Why was severe (dry)
10 heat treatment required for these blood products when,
11 in respect of albumin, a lesser heating regime, ie (wet)
12 heating at 60 degrees for ten hours, inactivated
13 NANBH/Hepatitis C."

14 Is the answer in short that the explanation is that
15 albumin was wet heated, whereas the Factor VIII
16 concentrate was dry-heated and a lesser severity of
17 heating is sufficient for wet heating?

18 A. Yes, that's correct.

19 Q. You go on to explain why, giving a scientific
20 explanation -- I think I will simply take that as read
21 for those who are interested in it.

22 Dr Foster, on a separate point, we can see
23 a supplementary statement you provided. It's
24 [\[PEN0171127\]](#).

25 This point arises from Professor Cash's statement.

1 We will be hearing from Professor Cash this afternoon
2 but in short, Professor Cash had raised as a potential
3 issue whether the difficulties which arose in the
4 development of in vitro virus inactivation validation
5 studies at PFC may have contributed to any delay in
6 respect of the development or introduction of Z8. So
7 it's slightly the cart before the horse because we
8 haven't heard from Professor Cash but we did ask you for
9 your response to this and we said:

10 "In particular, do Drs Foster and Perry consider
11 that these difficulties contributed in any way to
12 a delay in the introduction of Z8?"

13 We gave you a copy of Professor Cash's references
14 and what was your response?

15 A. That I was very familiar with the issue and that we were
16 very -- certainly very interested and very keen in
17 obtaining the type of data that he describes, these in
18 vitro studies using HIV, and there was a delay in
19 getting that done for the reasons -- they are not really
20 fully explained here but it didn't actually interfere
21 with the introduction of Z8; it was something that we
22 would be expected to produce at some point in the future
23 by the regulatory authority and we were trying to get
24 ahead of the game and get this information in good time,
25 and we did have the information when it was required.

1 So it didn't actually hold anything up.

2 Q. Certainly, I don't think any of the documents we looked
3 at yesterday mentioned a concern that any delays in
4 carrying out in vitro virus inactivation validation
5 studies were causing any delay in the development of Z8.

6 A. There was nothing of that type and BPL didn't have that
7 type of data either because we were doing the work for
8 them. So it was not an issue.

9 Q. Dr Foster, that completes Factor VIII.

10 I can deal with Factor IX briefly because I think
11 you have given evidence on it in topic B3 in relation to
12 HIV. Now perhaps we will look at the Hepatitis C angle
13 but the HIV angle, I think, was covered in your B3
14 evidence. I can perhaps, simply for the record, also
15 refer to your briefing paper at pages 1359 to 1360.
16 Perhaps we can take them as read.

17 For completeness, perhaps, could we go to
18 [\[SNB0103401\]](#). This is really vouching of the dates of
19 introduction of heated Factor IX. We can see these are
20 the minutes of a meeting of heads of department and
21 section managers at PFC, held on 16 August 1985. Can we
22 go down the page, please?

23 Under (c):

24 "Heat treated Factor IX. Dr Perry reported that the
25 product had now been issued for routine use at Edinburgh

1 centre and further issues would be made to remaining
2 centres in September/October 1985."

3 Does that accord with your understanding?

4 A. It does, yes.

5 Q. We can put that to one side, thank you.

6 Finally, doctor, I would like to return to your
7 statement and go back to the question at page 28 of when
8 were commercial manufacturers able to produce and supply
9 Factor IX concentrates that were safe for Hepatitis C.
10 So could we go back, please, to your statement at
11 page 29? Is the answer to that in short, doctor, that
12 the blood transfusion services in Scotland and England
13 introduced Hepatitis C safe Factor IX before any of the
14 commercial manufacturers?

15 A. Yes, I think that's probably the case.

16 Q. Because that thought occurred to me when looking at your
17 detailed answer. Could we perhaps look at the bottom of
18 page 29? So this is table 1 of Kasper looking at Armour
19 products. So Factor IX Mononine, FDA
20 licence, August 1992. Over the page at page 30, looking
21 at the Alpha product. Middle of page 30. Their
22 Factor IX Alphanine SD. FDA licence, August 1992. Then
23 table 4, the Cutter Biologicals product, Konyne 80, FDA
24 licence, April 1991. That's it, I think. Thank you,
25 Dr Foster.

1 Sir, I have no further questions.

2 THE CHAIRMAN: Mr Di Rollo.

3 MR DI ROLLO: Sir, Mr Mackenzie has been good enough to

4 incorporate in his questions, the question that we

5 wished to ask and I have no questions for Dr Foster.

6 MR ANDERSON: I have no questions.

7 MR JOHNSTON: I have no questions either.

8 THE CHAIRMAN: Is Dr Foster coming back?

9 MR MACKENZIE: Never say never but I don't think so.

10 THE CHAIRMAN: Dr Foster, I would like to say publicly thank

11 you very much. You have applied a great deal of

12 diligence to assisting us. We are all very grateful.

13 Also very grateful for the way you have given your

14 evidence, which we found very, very helpful.

15 A. Thank you very much.

16 MR MACKENZIE: Sir, the next witness is Dr Cuthbertson, who

17 we asked to come at 10.30. So our timing is pretty

18 spot-on today. But it may be helpful to have a 15 or 20

19 minutes' break.

20 THE CHAIRMAN: I was about to suggest we should have a break

21 now.

22 MR MACKENZIE: I'm grateful.

23 (10.32 am)

24 (Short break)

25

1 (10.59 am)

2 DR BRUCE CUTHBERTSON (continued)

3 Questions by MR MACKENZIE

4 THE CHAIRMAN: Yes, Mr Mackenzie.

5 MR MACKENZIE: Thank you. Sir.

6 Good morning, Dr Cuthbertson.

7 A. Good morning.

8 Q. Dr Cuthbertson, I think you were the PFC microbiology
9 manager between 1980 and 1985 and then you were the
10 quality manager between 1985 and 2003. I think from
11 2003 to date you have been the quality director of
12 SNBTS?

13 A. That's correct.

14 Q. I think we have looked at your CV before, so I'm not
15 going to go back to it but for the record, it's
16 WIT0030196.

17 Dr Cuthbertson, for the topic we are looking at
18 today, we are looking at the development of Z8, in
19 particular in the period 1985/1986/1987. I think,
20 doctor, I'm not entirely clear what a quality manager at
21 PFC did in that period. Could you perhaps help us?

22 A. Yes, it was interesting times, I think. The role of
23 quality manager was multiple, I think. Firstly, we did
24 have a quality control laboratory which numbered about
25 20 people, who did testing on the various blood products

1 that we manufactured. So I was in charge of those. But
2 we also had a team of -- a small-ish team of people then
3 but growing ever since, who were actually looking after
4 the quality assurance of the whole process, the plant,
5 to ensure that the procedures that we followed were
6 defined, documented and that there was evidence that
7 things were being done correctly.

8 Ultimately, as quality assurance manager at that
9 time, I signed off that the batches of products that
10 were manufactured were fit for clinical use.

11 Because of my previous experience as a virologist
12 developing virus systems, I still had a scientific
13 interest in the development of virus validation systems
14 for the monitoring of the effectiveness of the processes
15 that we used.

16 Q. Thank you.

17 Am I right in thinking, doctor, that your role
18 during this period was mainly related to the production
19 side at PFC, rather than the research and development
20 side, or would that be wrong on my part?

21 A. That would be correct. It was ultimately my role to
22 ensure that the products were manufactured correctly and
23 that the processes that were developed in the R&D
24 department were transferred appropriately into
25 manufacturing.

1 Q. Thank you.

2 The other really general introductory question I had
3 for you was this: again, sticking with this period,
4 1985/1986/1987, after a batch of Factor VIII concentrate
5 had been produced at PFC, what testing was then carried
6 out at PFC before the batch was released for issue?

7 A. If you don't mind I would like to elaborate on that
8 question very slightly and just give you a history of
9 what happened from the start to the finish.

10 The actual process of producing the Factor VIII
11 obviously ended up with a freeze-dried product. At the
12 time in question there was still an issue about whether
13 or not an individual batch might tolerate 80-degree heat
14 treatment. So each batch was then subject, a small
15 number of vials, to trial heat treatment, and these were
16 then tested for solubility and residual Factor VIII
17 content, and if that individual batch met the
18 appropriate characteristics, then the batch went on to
19 heating. So that process probably took about
20 a fortnight.

21 Then the actual heating itself took about three
22 days. So from the date that it has been filled until
23 the time that it is available to start the QC testing,
24 already three weeks or so have elapsed.

25 Then each lot was tested for a range of biochemical

1 and microbiological assays. There were obviously tested
2 for Factor VIII content. It was tested for various
3 chemical parameters, simple things like pH and salt
4 content. Then in terms of microbiology, the most
5 lengthy process was a sterility test, whereby samples of
6 each batch were subjected to microbial growth-promoting
7 tests to see if there was any evidence of bacterial or
8 fungal contamination.

9 Samples of each lot, as I think I said in my
10 previous testimony, were sent to independent
11 laboratories for confirmation that there was no presence
12 of Hepatitis B surface antigen, and the other test that
13 sometimes took a lengthy period of time was that each
14 lot was subjected to animal testing in guinea-pigs and
15 in rabbits, to be sure that there wasn't either
16 a pyrogenic response or an acute toxicity response from
17 individual batches, and that was a test that was
18 mandated by the European pharmacopeia.

19 Q. Did the animal testing apply to Factor VIII concentrate
20 in this period?

21 A. Yes.

22 Q. Thank you.

23 A. All of our plasma products, to meet the requirements of
24 the pharmacopeia, were animal tested. So I think I have
25 given an impression of an overall large number of tests

1 that were performed and as a minimum that would take
2 three weeks. So three weeks would be fast tracking,
3 typically four to five.

4 Once the testing had been completed, then we could
5 actually package the product, because we didn't package
6 it until the testing was complete partly because in each
7 batch we declared the potency so that the treating
8 clinicians would know how much Factor VIII was in the
9 vial. So that didn't happen until the end and then that
10 would take another, possibly a week or so and then
11 finally there would be a QA review of the entire
12 documentation before we put our signature on the batch
13 and said it was fit for release.

14 With a fair wind we could do that in two months but
15 typically it took three.

16 Q. The various steps you have just outlined for us, did the
17 Z8 product, which was manufactured at PFC in the second
18 half of 1986, go through all of those steps before being
19 made available for issue?

20 A. Yes.

21 Q. Thank you.

22 We will come back to look at some particular
23 documents shortly, but that's helpful background. Thank
24 you.

25 Could I now, please, turn to your statement, doctor,

1 which is [\[PEN0171200\]](#). At question 1 we asked:

2 "When and how did the SNBTS/PFC first become aware
3 of BPL/PFL's research and development work on 8Y."

4 Also, when was their awareness that the product was
5 able to heated at 80 degrees centigrade for 72 hours?

6 We have asked Dr Foster questions on this as well,
7 doctor, but do you have a recollection of when you
8 personally first became aware of these developments?

9 A. I think my answer to this is a sort of statement of
10 retro-- trying to fit the facts. So I am afraid the
11 answer to that, probably not and in fact, my last
12 sentence says that I'm not sure exactly when PFC became
13 aware of the development but I assume it was around the
14 time that I stated in my statement.

15 Q. Yes. So you think during late 1984/early 1985?

16 A. It was a very fast-moving time, as I'm sure you are
17 aware. There was a lot happening and we were getting
18 information on all fronts almost, and that particular
19 fact I can't really recall with absolute precision.

20 Q. Thank you. So you don't think you can add to your
21 written response?

22 A. I am afraid not.

23 Q. Over at page 2, question 2, we asked:

24 "When did it seem likely from ... [clinical
25 evidence] ... that the heating regime for 8Y ...

1 resulted in a product which did not transmit NANBH."

2 Can I ask, in a way, a precursor to that question:

3 were you made aware in 1985 and perhaps early 1986 of

4 the preliminary clinical data which was becoming

5 available in respect of 8Y's use?

6 A. Yes, I'm sure that as soon as that was available, that

7 was made known to all the PFC senior managers.

8 Q. How would you become aware of that preliminary clinical

9 data, do you remember?

10 A. Almost certainly from conversations with Dr Foster, who

11 was basically the principal conduit of such information,

12 and Dr Perry possibly also.

13 Q. Did you yourself have dealings with the fractionators

14 down south?

15 A. Oh, yes, I mean, I think, as I have said in the previous

16 evidence, we had regular dealings with Dr Smith, who

17 would pop into PFC from time to time, and although the

18 meetings were principally with Dr Foster and

19 Dr McIntosh, other senior managers would regularly meet

20 with them and share information.

21 Q. Thank you.

22 A. As things progressed, we got into closer and closer

23 formal collaboration.

24 Q. Thank you. Then your written response to question 2.

25 You state:

1 "This is a very difficult question to answer since
2 information on this topic was accrued fairly slowly and
3 there were complications surrounding the protocol for
4 following up susceptible patients who were fairly rare."

5 You then say:

6 "The letter from Dr Smith ... "

7 [\[SNF0011123\]](#). We don't have to go to it but this is
8 Dr Smith's interim report of 30 September 1986, and you
9 say that is the first evidence that you were aware of
10 that:

11 " ... 8Y could be potentially effective in
12 significantly reducing the risk of NANBH."

13 A. Hm-mm.

14 Q. You say that:

15 "The data available in Dr Smith's letter
16 of September 1986 ... clearly showed a reduction in
17 infectivity with NANBH, but was not yet conclusive of
18 a lack of infectivity."

19 Do you have a recollection of seeing this paper at
20 the time, doctor?

21 A. Absolutely, yes.

22 Q. Absolutely yes?

23 A. Yes. It was such a pivotal paper that anyone in the
24 industry would have seen it. I would have looked to see
25 it as soon as it was put on the desk.

1 Q. Was this really the first report in writing of the
2 clinical evidence and perhaps before this you would have
3 received more verbal updates?

4 A. I think that -- I mean, I think, to put this into
5 context, if I might, the question is: when did it result
6 in a product which did not transmit non-A non-B
7 Hepatitis. So clearly there is a difference between the
8 product which has a reduced risk from one which is
9 absolutely free of evidence of infectivity. I think
10 that's the point I was trying to get over in this text,
11 that from the early work, it was clear that the risk of
12 non-A non-B Hepatitis from the product was substantially
13 less than from conventional unheated products.

14 The infection rate with them was close to
15 100 per cent, whereas from the early evidence, a number
16 of patients had not developed clinical evidence of non-A
17 non-B Hepatitis. But to actually demonstrate freedom
18 from infectivity is a very difficult process and takes
19 time -- or certainly took time then, when we were
20 relying on indirect biochemical tests as a means of
21 assessing infectivity.

22 Q. Yes. You then, in the next paragraph in your statement,
23 go on to say that:

24 "It is perhaps noteworthy that this ongoing evidence
25 of freedom from infectivity was not widely acknowledged

1 outwith the UK, nor was the process adopted by any other
2 mainstream fractionator."

3 You explain:

4 "This was partly due to the fact that the regulators
5 were never comfortable with it as a process, following
6 the wide variability in inactivation of HIV seen in
7 experimental studies of Factor VIII heat-treated at 60
8 or 68 degrees centigrade."

9 You say:

10 "Control of the process was believed to be difficult
11 and Z8 was never formally licensed by the UK regulatory
12 body, due to these concerns."

13 Then in the next paragraph --

14 THE CHAIRMAN: Dr Cuthbertson, I have a slight difficulty in
15 the linkage between the first and second paragraphs.
16 You end up the first paragraph by talking about 8Y. You
17 then say:

18 "Perhaps it's noteworthy that this ongoing evidence
19 was not widely acknowledged."

20 But you end that paragraph by a reference to Z8, and
21 I'm not quite following what's being referred to in the
22 several parts.

23 A. Okay. I suppose what I was trying to say in a condensed
24 way is that the issue is why did individual
25 fractionators not kind of develop an 8Y lookalike more

1 rapidly, and I think what I was trying to point out was
2 that in the sort of period of 1986 or so, publications
3 had come out which shed -- cast some doubt on the
4 effectiveness of dry heat treatment, even to inactivate
5 HIV, and that by and large most people were trying to
6 work out how to move away from dry heat treatment. It
7 was the UK that was the outlier that continued to
8 develop with that particular process, and that that
9 feeling of unease wasn't just amongst fractionators; it
10 transmitted itself to the regulators who, as I say,
11 ultimately our Z8 licence application, which, when it
12 was made in 1989, was good enough to allow us to
13 continue issuing it but the licence application itself
14 drew dust on the desk of a particular regulator until we
15 finally withdrew it when we moved on to an alternative
16 product.

17 So I think I was just trying to say that we were
18 actually in difficult times and that SNBTS were moving
19 along a route that was perhaps not typical of mainstream
20 thinking.

21 THE CHAIRMAN: Was 8Y in the same position as you understand
22 it, or not?

23 A. 8Y was ultimately licensed by the regulators because
24 unlike us, they didn't have a pre-existing licence on
25 which to hook the authorisation to continue release.

1 THE CHAIRMAN: This recurrent technical problem of
2 substitution of one for another?

3 A. Yes.

4 THE CHAIRMAN: Thank you.

5 MR MACKENZIE: Thank you, sir.

6 Doctor, in the next paragraph you refer to a paper
7 by Professor Ian Franklin, submitted to the
8 Archer Inquiry. I'll simply, for the record, give the
9 reference without going to it. That is page 9 of
10 [\[PEN0171200\]](#). Then, moving on to question 3, please,
11 doctor, we noted that:

12 "In October 1985, PFC discovered that their existing
13 intermediate NY Factor VIII product withstood heating at
14 80 degrees centigrade."

15 And we asked:

16 "Why was such heating of the existing product ...
17 not introduced immediately?"

18 You then corrected us by stating that the question
19 was actually based on an incorrect assumption and that,
20 as stated in your earlier statement:

21 "The NY Factor VIII product manufactured at
22 full-scale in the PFC manufacturing plant could not
23 withstand dry heat treatment at 80 degrees centigrade.
24 The NY product was studied extensively to maximise heat
25 treatment, whilst still retaining adequate quality

1 characteristics, in particular potency and solubility."

2 And that:

3 "The time/temperature combination of 68 degrees
4 centigrade for 24 hours was the most severe conditions
5 that the NY product could withstand and still retain
6 adequate potency and solubility characteristics. The
7 material which tolerated heat treatment at 80 degrees
8 centigrade was a small vial produced in PFC's R&D
9 laboratories. The good results from this accidental
10 discovery were part of the stimulus to identify the
11 characteristics of a Factor VIII product which could
12 reliably tolerate severe heat treatment."

13 The issue of which vial was inserted as a control,
14 I think Dr Foster told us yesterday that it was a small
15 sample taken from the routine NY intermediate purity
16 product. Would you defer to him in that regard or ...?

17 A. Yes, my understanding is exactly as he has described,
18 that this was some control material from routine
19 manufacture that was dispensed in small volumes as
20 a control.

21 Q. It's just, doctor, you state in your statement that:

22 "It was a small vial produced in PFC's research and
23 development laboratories."

24 I understood from Dr Foster that the product hadn't
25 been manufactured in the R&D laboratory; rather, it had

1 been manufactured in the main plant?

2 A. I had indeed perhaps slightly misled you there. It was
3 manufactured in the main plant and then redispensed in
4 a small volume within R&D --

5 Q. That's what you mean by "produced in R&D laboratories"?
6 I'm sorry, it's my misunderstanding.

7 A. No, it's a slightly misleading use of language.

8 Q. Then over the page, please, page 3. At the top of the
9 page we asked:

10 "Why did it take until May 1987 before intermediate
11 Factor VIII manufactured by PFC and dry-heated at
12 80 degrees centigrade for 72 hours was available for
13 clinical use?"

14 You explain:

15 "In actual fact, this product was available
16 considerably earlier than May 1987 but was not released
17 for routine clinical use until it had been evaluated for
18 tolerability and effectiveness (recovery) in a small
19 scale clinical trial. This was necessary because there
20 was concern that heat treatment could reduce the
21 tolerability or efficacy of the Factor VIII product.

22 "This clinical trial was in itself delayed over
23 issues of clinical indemnity. In effect, if SNBTS had
24 taken the huge risk of making an unproven product
25 generally available, then Z8 would have been available

1 for clinical use from December 1986."

2 You then refer to a previous witness statement
3 provided to the Inquiry, where you explain that:

4 "The development of a new product is a very detailed
5 process ... nowadays, it's believed that the development
6 of a new process from development through clinical
7 trialing to final licensing and routine issue will take
8 of the order of five years. In those days, the
9 regulatory requirements were not so rigorous ..."

10 You then set out the steps required to implement
11 a new process, and at the bottom paragraph you say:

12 "It has been noted in the chronology ..."

13 Which was produced:

14 "... that the decision to manufacture a PFC product
15 heated at 80 degrees was proposed at an internal PFC
16 meeting on 23 December 1985. To successfully transfer
17 this process to manufacturing scale in a 12-month period
18 is actually a very commendable achievement, given the
19 technical issues of scale up from laboratory to
20 manufacturing scale which had to be overcome."

21 To pause, doctor, and ask some questions, if I may,
22 about the meeting on 23 December 1985, you were present
23 at this meeting. Is that correct?

24 A. That's correct.

25 Q. Do you have a recollection of the meeting?

1 A. In general terms, yes.

2 Q. What is that general collection? What was discussed?

3 A. It was to discuss a paper which Dr Foster had put
4 together, which basically outlined two possible
5 strategies for how we could progress with our
6 development of a virus-safe Factor VIII product. Option
7 one was that at that time relatively unproven high
8 purity route, which Dr McIntosh had been working on,
9 which I'm sure he will tell you about in the next day or
10 two, and the second was to go for a product that was
11 closer to the 8Y process and which was similar to the
12 Factor IX product that we had already started issuing.

13 So there were pros and cons for each option. We had
14 a fairly lengthy and detailed discussion and eventually
15 it was our proposal from that meeting that going for the
16 terminal dry heat treatment route was the one that we
17 should put our R&D resources into because obviously our
18 R&D resources were not infinite.

19 Q. Thank you.

20 Dr Foster told us that, I think, those present were
21 himself, yourself, Dr Perry, Dr McIntosh and that
22 Dr Foster's view going into the meeting was that PFC
23 should continue to prioritise the high purity NYU
24 product while exploring alternatives, whereas
25 Dr McIntosh's view was that the terminal dry heating

1 should be prioritised and that Dr Foster, I think, came
2 round to Dr McIntosh's view. Which camp were you in?

3 A. Dry heat treatment.

4 Q. Why?

5 A. Because we had had great success with it in developing
6 the initial NY product in 1984, that involved fewer
7 technical developments, particularly in terms of
8 transferring processes from R&D to manufacturing.
9 I thought that was an appropriate issue. And there is
10 actually one quite clear pharmaceutical benefit of dry
11 heat treatment, which is that, because it's done to the
12 final sealed product, there is absolutely no possibility
13 of recontamination of the product once the process has
14 been completed. I thought that was a very compelling
15 argument.

16 Q. Contamination of the product by anything, not just
17 a virus but by anything?

18 A. That's correct.

19 Q. To what extent, if at all, was 8Y a factor in these
20 discussions and in particular the fact that 8Y had been
21 routinely manufactured and issued in England from
22 about September/October 1985?

23 A. It was a significant part of the deliberation. The fact
24 that we knew that such a product not only had been
25 manufactured but had been well tolerated made going down

1 that route less of a gamble, if you like, than it might
2 have been otherwise.

3 Q. Thank you.

4 The outcome was that those present agreed that
5 priority should be given to terminal dry heat treatment.
6 Was that a decision for PFC to take alone or do you
7 consider that it required approval or authorisation from
8 outwith PFC?

9 A. Oh, clearly we were part of an overall SNBTS process.
10 We were not entitled, I don't think, to make that
11 decision on our own. We had to take cognisance not only
12 of the opinion of Professor Cash and the medical
13 colleagues on a suitability of such a product but also
14 ultimately with the haemophilia directors, who would be
15 asked to trial such a product. So, no, we were not
16 empowered to make that decision alone.

17 Q. So who would ultimately sign off on that decision?

18 A. Professor Cash ultimately, I think would be the adviser
19 who would say whether or not our proposal was the one
20 that we should be backing.

21 Q. Thank you. You used the word "adviser" --

22 Professor Cash would be the adviser. By that do you
23 mean he was the ultimate decision maker?

24 A. Yes, as the head of SNBTS at the time.

25 Q. Yes, and we can ask him about that this afternoon.

1 Thank you.

2 Over the page, please. Page 4. We then asked two
3 questions, (c):

4 "What changes in the manufacturing processes were
5 made ..."

6 And then (d) we asked questions about the original
7 timescale and if it was not met, why and how. I have
8 gone over these matters with Dr Foster. So I think,
9 Dr Cuthbertson, I'll simply take your answers as read
10 and not go over them in any more detail.

11 In question 4 we asked:

12 "Did PFC's work on the development of a high purity
13 Factor VIII concentrate (NYU) in collaboration with
14 Professor Johnson result in any delay in the
15 introduction of Z8?"

16 Again, doctor, who would be in the best position to
17 answer that question?

18 A. I think in the order of the question, Dr McIntosh is
19 clearly the most able to answer that, and I'm sure
20 Dr Foster was able to give you some erudite opinions on
21 this yesterday, since they were the two individuals that
22 had far and away the most dealings with
23 Professor Johnson.

24 Q. Yes. We see certainly your opinion is that you don't
25 consider that the work on NYU resulted in any delay in

1 the introduction of Z8?

2 A. No, when we had made the decision we were going to go
3 for development of Z8 product, then the NYU process went
4 on the backburner. I think yesterday Dr Foster in his
5 testimony mentioned that there was in fact a problem, if
6 that's the right word, with the availability of
7 Factor VIII assays.

8 Q. Yes.

9 A. Because we only had so much capacity. So even if our
10 development colleagues wished to develop the NYU
11 process, then they would have got very second-rate
12 service from the testing lab that I managed, because
13 everything was giving priority to either routine
14 manufacture or to the development of the Z8 process.

15 Q. Okay. Question 5 -- I will take to you some documents
16 because we haven't explored this in detail yet -- we
17 asked:

18 "Did any difficulties in commencing clinical trials
19 of Z8, because of concerns over compensation/indemnity,
20 result in any delay in the introduction of Z8?"

21 I should say the documents I will take you to will
22 concern the question of the trials carried out rather
23 than the question of compensation, which I will leave
24 over for Professor Cash and Professor Ludlam. But in
25 your answer to 5, you say:

1 "There is absolutely no doubt that these concerns
2 delayed the initiation of the clinical trial of Z8.
3 Product was released for use in the trial in December of
4 1986, but the trial did not commence until March 1987.
5 This was principally due to concerns over indemnity in
6 the event of adverse reactions to the trial product.
7 These were legitimate concerns and nowadays no clinical
8 trial would be allowed to begin if such indemnity
9 arrangements were not in place."

10 Could I start, please, doctor, by taking you to
11 a passage in Dr Foster's statement, which is page 8 of
12 [\[PEN0171556\]](#). At page 8, please, if we can have that,
13 in the second last bullet point on the page Dr Foster
14 told us that:

15 "I had assumed that material prepared at pilot-scale
16 would be used for the clinical determination of efficacy
17 and tolerability, as this had been the approach taken
18 previously with pasteurised Factor VIII (ZHT). This
19 approach was not followed with Z8 and material was not
20 released for clinical evaluation until after full-scale
21 production had been established. I was not involved in
22 this decision as this was the responsibility of the PFC
23 quality manager."

24 What's your response to that, doctor?

25 A. Yes. I am afraid I can't recall the process issues and,

1 because I thought it might come up today, from
2 yesterday's transcript, I did see if I could do a little
3 research but unfortunately the relevant files are with
4 an external storage company.

5 There are two or three possibilities that come to
6 mind. I can offer them as possibilities, only because
7 I can't confirm them but could perhaps provide that
8 information in retrospect, if that would be helpful.
9 The issue about pilot scale manufacture would have
10 depended on exactly who had carried out the process and
11 how well defined the process was in comparing what was
12 prepared at pilot-scale with what was then manufactured
13 at full-scale. In other words, there is not much point
14 in starting a trial with material which was somewhat
15 different from the material you were going to use
16 routinely. So that's the first issue.

17 The second one is, I believe, but can't confirm,
18 that they might have been freeze-dried in an R&D freeze
19 dryer, which wasn't subject to the same GMP rigour as
20 the normal full scale manufacture, but I can't tell you
21 whether that's in fact the case or not.

22 Q. The other thought which occurred to me, doctor -- and
23 you may have read this from yesterday -- given the
24 changes which occurred in the process between the pilot
25 scale operation and full-scale production, in particular

1 the different freeze-drying step or parameters, is it
2 possible that even if a phase 1 trial had been
3 undertaken, using pilot scale product, given the changes
4 in process in full scale production, a fresh phase 1
5 trial may have been required?

6 A. I think that's what I was trying to allude to earlier
7 about there being changes to the process from those two
8 early pilot batches to the final batch that we issued
9 for clinical use. I think that's well possible.

10 Q. Put it this way: would you as quality manager at the
11 time have been happy to have released the batches made
12 from the full-scale process without fresh phase 1
13 trials?

14 A. I believe the answer to that is no, and I think that's
15 partly why I took the decision at the time.

16 Q. Doctor, if I may then look at a number of documents to
17 see what happened when in relation to the clinical
18 trial. Could we first, please, look at a letter,
19 [\[SNB0076241\]](#).

20 We can see this is a letter dated 13 November 1986
21 from Dr Cash to Dr Boulton, headed "Z8", and stating:

22 "You will be aware that PFC intend to begin routine
23 production, hopefully in the very near future, of a new
24 Factor VIII concentrate, which will be called Z8. This
25 product will be dry heat-treated at 75 degrees

1 centigrade for 72 hours. I would be most grateful if
2 you would liaise with Chris Ludlam, Charles Forbes and
3 Elizabeth Mayne with a view to obtaining t/2 and
4 percentage recovery data on this product. I believe in
5 the first instance we should aim at getting data from
6 a total of six patients. I understand this product will
7 be available for trial purposes soon and a specification
8 will be forwarded from PFC along with supplies of the
9 product."

10 I think we know that Professor Ludlam was based at
11 Edinburgh, Dr Forbes at Glasgow. I think Dr Mayne was
12 in Northern Ireland?

13 A. Belfast, that's correct.

14 Q. Belfast? The next document in the chain, please, is
15 [\[SNB0076268\]](#). This is a letter from yourself, doctor,
16 to Dr Boulton, dated 26 November 1986. In short
17 enclosing a copy of the draft specification for Z8.

18 The next letter, please, is [\[SNB0076270\]](#). This is
19 a letter from Dr Boulton to Dr Perry, dated
20 1 December 1986 and he acknowledges receipt of the
21 letters from Dr Cash and from yourself about the
22 specification of Z8. He had received a letter from
23 Dr Mayne saying that she will be very pleased to enter
24 into the trials as soon as the material is available.
25 He then says:

1 "I think it is best if I wait until the material is
2 actually in our cold room before I tell Dr Ludlam."

3 Do you know what the point of that was? Does it
4 matter?

5 A. I think it's just he wanted to be sure it was available
6 and the best way of making sure that it's available is
7 to have it. There had obviously been discussions
8 earlier in the year around supplies, when they would be
9 available. So I think he just basically didn't want to
10 do anything until it was available for him to start.

11 Q. Right. And Dr Perry is coming along, I think, tomorrow.
12 We can perhaps ask him about that as well.

13 Then:

14 "What is the best way of dealing with Dr Forbes?
15 The problem there is that, normally speaking, we would
16 go through Law BTS and John Davidson but I believe that
17 on this occasion it would be much better if I supplied
18 Charles direct with just a letter to Ruthven Mitchell
19 and John Davidson, saying that this has actually
20 happened."

21 What's that about?

22 A. The routine supply mechanism for Factor VIII to the West
23 of Scotland was through our centre at Law. So the
24 routine day to day contact between the BTS and the
25 treating clinicians was from the clinicians at Law

1 Hospital that worked for the Blood Transfusion Service.
2 So I think basically all that Dr Boulton was saying was
3 that since this was a request to enrol patients from
4 Glasgow into this relatively small trial, rather than go
5 through that mechanism, he went direct. So it's just
6 a bit of inter-medical particulars, I suppose.

7 Q. Then the next document, please, is [\[SGH0016672\]](#).
8 I think we have looked at this before. It's a note of
9 a clinical trial review meeting on 1 December 1986.
10 I think you were there, Dr Cuthbertson?

11 A. Yes.

12 Q. If we go to page 4, please, in item 9 we can see
13 Dr Perry reporting that:
14 "This product ..."
15 Being the Z8 heat-treated at 75 degrees for
16 72 hours:
17 "... was now available for half-life and recovery
18 studies in Edinburgh, Glasgow and Northern Ireland prior
19 to its introduction into routine use. Dr Boulton is
20 co-ordinating the study, the results of which will be
21 used for application for licence variation."

22 The next document is [\[PEN0171437\]](#). We have looked
23 briefly at this before, doctor, but I would like to ask
24 you some more questions about it, please. I think we
25 can see this is a batch issue sheet and we can see also

1 that someone has written in the top right-hand corner
2 "clinical trial, 75 degrees". Just going through the
3 various entries, we can see in the top right-hand corner
4 the batch number, 0310-60110. Does the numbering have
5 any meaning? Does it relate to dates or anything else?

6 A. Yes. The first two digits, the "03", are the product
7 code. The "10" means that it was manufactured
8 in October. The "6" means it was 1986. The "011" means
9 that it was the 11th batch that we had manufactured, and
10 the "0" means that it was a normal batch and hadn't been
11 subject to any unusual processes.

12 Q. Thank you. We see the expiry date, October 1988. Is
13 that essentially two years after the date of the month
14 of manufacture?

15 A. Yes, the month of manufacture was the date that it was
16 initially dispensed.

17 Q. I'm sorry?

18 A. It was the date it was dispensed into the vials. So the
19 expiry date was two years from that date.

20 Q. I see, dispensed into the vials. Then we see:
21 >Date placed at issue. 2 December 1986."
22 What does that mean?

23 A. That means that all the documentation relating to the
24 batch had been assembled, had been reviewed by a number
25 of people, ultimately by myself, and that the batch met

1 all of the relevant manufacturing parameters and that
2 all of the test results that had been performed on it
3 were within the release limits that were in the document
4 that I had previously provided to Dr Boulton. So I'm
5 basically certifying, by placing this at issue, that
6 it's fit for clinical use.

7 Q. I should have said, who completes the various entries in
8 this form?

9 A. Okay. The initial form is -- was generated by the
10 people who did the packaging. So at the same time as
11 they completed the packaging, they generated this -- the
12 form, so the bits that are in sort of black writing on
13 the top section would be by the senior inspection
14 person. That's lines 1, 3 and 4.

15 So basically at that time we knew that there was 878
16 vials that had been inspected and deemed fit for
17 release. The unit size of 20 mls was basically what it
18 was reconstituted as, and the biological value of 220iu
19 was the test assay value that came from the test results
20 that they had used to label the batch.

21 Obviously the line about "authorised for issue" is
22 signed by me and then the issue details with the dates
23 were by the dispatch department, as and when products
24 were issued, and then once the entire batch was issued,
25 this form was then returned to QA for archiving for

1 posterity.

2 Q. And "date placed at issue", where is the batch placed at
3 issue?

4 A. Once it had been approved for issue -- it was held in
5 a bonded area within our cold room and once it was
6 approved by issue, it was transferred into an unbonded
7 area of the cold room so that it was available to the
8 issuing staff to release. So up until that time, no one
9 would have been able to release it for use.

10 Q. So when it's stated:

11 "Date placed at issue, 2/12/86," that means the
12 product was placed at issue within PFC on that date?

13 A. Yes.

14 Q. Thank you.

15 Looking at the boxes, we can see the first box a
16 date of 22 December 1986, 20 units issued, receiving
17 centre, Dr Boulton at Edinburgh. So what has happened
18 then?

19 A. Our routine issue procedure was to issue them in units
20 of ten because they were packaged in tens. So that
21 basically means that two of those packets of ten were
22 sent from us to the Edinburgh Royal, which is obviously
23 was where the regional transfusion centre was, where it
24 would be held pending the initiation of the clinical
25 trial.

1 Q. Thank you.

2 Just looking down we can see on 24 December
3 a further 180 units were sent to Dr Boulton, and then
4 one down again on 25 May 1987, a further 678 units were
5 sent to EDI. Is the reference to "EDI" likely to be to
6 Dr Boulton or is it possible that would have been sent
7 directly to Professor Ludlam?

8 A. No, we didn't send Factor VIII directly to any treating
9 clinicians. The EDI reference is simply to our
10 regional transfusion centre at Lauriston Place, and the
11 difference between the annotations is simply that the
12 first 200 vials were issued specifically for the control
13 of Dr Boulton to carry out the half-life and recovery
14 study, and the 678 that were issued on 25 May were
15 issued for routine clinical use. So they would be
16 issued to Dr Ludlam but through the centre in
17 Lauriston Place.

18 Q. Thank you.

19 The final question I have, doctor, is this: we see
20 the number of units placed at issue are 878. Does that
21 help us in knowing whether these units were from the
22 pilot scale production or the full scale production, or
23 indeed a combination of both?

24 A. No, that was a single batch at full-scale.

25 Q. Thank you. We can put that document to one side, thank

1 you. Just to complete this, the next document in the
2 chain, please, is [\[SNB0076298\]](#). We can see this is
3 a letter dated 12 December 1986 from Dr -- or perhaps
4 Mr Crawford, I'm not sure, in Glasgow to Dr Perry in
5 relation to the clinical trial of Z8. He states:

6 "Ruthven has passed me a copy of your letter of
7 9 December. I'm well aware of the reasons why you found
8 it necessary to issue the product directly and not via
9 John Davidson's laboratory. However, I remain convinced
10 that the previous problems were not caused by John's
11 staff ..."

12 Et cetera. So what appears to have happened is that
13 a batch of Z8 was sent directly to Dr Forbes, perhaps,
14 rather than going through Law Hospital. Is that
15 correct?

16 A. I'm not sure that's my interpretation of this letter.

17 Q. What's your interpretation?

18 A. I'm not sure I know because from our records, although
19 we had originally planned a trial which would be in
20 three centres, what we ended up doing was it was only
21 carried out in the Edinburgh centre, and I'm not aware
22 that we actually sent any Z8 to Glasgow direct. So
23 I suspect that this is a letter that's basically saying
24 that there had been some previous problem with issue of
25 the NY product and that somehow or another we had gone

1 directly to the treating clinicians and not through --
2 John Davidson's lab was the haematology lab in
3 Glasgow Royal Infirmary. It looks like there have been
4 some issues about how that supply chain had worked.
5 I can't really make any more sense of this than that, I
6 am afraid, because, as far as I'm aware, we did not
7 supply any of the Z8 to Glasgow to carry out the trial.

8 Q. Okay.

9 A. The first issues, as you saw from the issue sheet, were
10 to Dr Boulton.

11 Q. Yes.

12 A. And the trial was all carried out with that particular
13 batch.

14 Q. I think there is a suggestion -- we will hear from
15 Dr Perry tomorrow -- it is a possibility and perhaps no
16 more than that, that Dr Boulton may have sent the
17 product directly to Dr Forbes?

18 A. That's possible.

19 Q. That's possible?

20 A. That is possible.

21 Q. We will continue, though, with the documents. The next
22 one, please, is [\[SNB0094073\]](#).

23 A. Actually I don't think it is possible from the dates
24 because this letter was written on 9 December.

25 Q. Yes.

1 A. And Dr Boulton didn't receive any product until
2 20 December.

3 Q. 22 December.

4 A. So I'm a bit mystified, I am afraid.

5 Q. I can see that. And indeed, that ties in with this,
6 I think, a memo from Dr Perry to yourself, dated
7 22 December 1986, subject:

8 "Z8 for clinical trial. In preparation for the
9 multcentred trial of this product, I would be grateful
10 if you could now send 200 vials of the selected batch to
11 Dr Boulton who will subsequently distribute it to
12 participating centres. It should be marked for his
13 attention and carrying clinical trial labels."

14 Certainly the date of that ties in with Dr Boulton
15 receiving initially 20 units on 22 December and then
16 a further 180 on 24 December.

17 The next document, please, is [\[SNF0013022\]](#). This is
18 a letter dated 13 January 1987 from Dr Cash to
19 Dr Ludlam, stating:

20 "We will keep you posted on the development of
21 events. Right now, assuming SHHD deliver the necessary
22 assurances ... [to do with compensation and indemnity]
23 ... we will keep your team in reserve to test the
24 80 degrees/72 hours material which will very soon be
25 with us. In the meantime Charles Forbes has agreed to

1 look at the 75 degrees/72 hours product."

2 Then the next document is [\[PEN0171470\]](#). This is
3 another batch issue sheet. We see in the top right-hand
4 corner someone has written "80 degrees", and we can see:

5 "Date placed at order" in the top right-hand corner,
6 11 February 1987. We can then, if we look at the boxes,
7 see that on 11 February 1987, 50 units were issued to
8 Edinburgh. Then the date of 22 May 1987, 368 units were
9 issued to Glasgow and certainly, doctor, from the batch
10 issue sheets provided to the Inquiry, that appears to be
11 the first record of Z8 units being issued to Glasgow.
12 Does that tie in with your recollection of what happened
13 at the time?

14 A. Yes, Dr Boulton certainly received the material for
15 clinical trial use. I assume the 50 vials were also
16 included in the clinical trial.

17 Q. Although --

18 A. "Available to be included in the clinical trial" might
19 be a more precise way of putting it.

20 Q. Presumably the issue to Glasgow of 368 units on
21 22 May 1987 was for clinical use, given the volume of
22 units issued?

23 A. Indeed.

24 Q. Yes. So there may still be a bit of a mystery -- we may
25 have to try and clear up perhaps with others -- as to

1 whether Dr Boulton directly sent any vials to Dr Forbes
2 for a phase 1 study.

3 A. We can check from the records of the half-life recovery
4 study where the patients were located. I just -- my
5 recollection is that it was in Edinburgh but it's
6 conceivable that some of them were in Glasgow.

7 Q. Is --

8 A. But I don't think so.

9 Q. Would it have been reported back to you if any part of
10 the phase 1 study had been carried out in Glasgow or
11 Northern Ireland?

12 A. Yes.

13 Q. Is that, therefore, something you would be able to check
14 from your records?

15 A. Yes.

16 Q. Could I ask you to do that, please?

17 A. Indeed.

18 Q. We would be grateful, thank you.

19 The next document, please, is [\[PEN0172205\]](#). This is
20 a letter dated 30 March 1987 from Dr Perry to Dr Lowe,
21 headed "Clinical Trial of Z8":

22 "I understand that you have now infused this
23 material into patients and that these infusions were
24 uneventful. We would be most grateful if you could
25 provide me with a summary of this trial so that I am in

1 a position to release this new product for general use.
2 This is now a matter of some urgency since stocks of the
3 existing product are now almost exhausted."

4 That letter does suggest that Glasgow did undertake
5 a phase 1 trial, albeit, if that did occur, it may not
6 have been perhaps until the same time as the Edinburgh
7 trial, March 1987?

8 A. Yes that seems to be the case.

9 Q. I don't think we can add any more to that at this stage.

10 The next document, please, [\[SNB0065609\]](#). This is
11 now Dr Howe from Edinburgh writing on 31 March 1987 to
12 Dr Perry enclosing the latest data on the phase 1 trial
13 at Edinburgh of Z8, relating to three patients. So
14 certainly by March 1987 Edinburgh had commenced the
15 phase 1 trial of Z8.

16 A. Yes.

17 Q. And then the next document, please, is [\[PEN0171451\]](#).

18 This is, for completeness, another batch issue record we
19 have. This is noted 75 degrees and the expiry
20 date, November 1988, suggests that this was perhaps the
21 75 degrees product, at least distributed into vial
22 in November 1986?

23 A. That's correct.

24 Q. We can see that 830 units are issued to Glasgow on
25 15 April 1987. Does that again suggest that's for

1 clinical use?

2 A. Yes.

3 Q. Thank you. Then, please, [\[SNB0076605\]](#).

4 On page 2, this is a letter dated 3 June 1987 from
5 Dr Boulton to Dr Perry and we only have to look at the
6 title and the first sentence and we see that this
7 relates to phase 1 trial of Z8. Then the second
8 paragraph:

9 "During March and April of this year, six men with
10 severe haemophilia were infused with 2,000 units of this
11 material, batch number 60270."

12 Then further details are given. So that again, I
13 think, confirms that at least in Edinburgh the phase 1
14 trial was carried out in March and April 1987.

15 A. Yes.

16 Q. Thank you. I went over that, Dr Cuthbertson, really to
17 set out for the Inquiry record our understanding of the
18 phase 1 trial. Does that essentially accord with your
19 understanding, subject to the query about whether, and
20 if so when, Glasgow participated in the phase 1 trial of
21 Z8?

22 A. All I can say is that I have checked the licence and
23 it's the data from Dr Boulton that we included in our
24 licence application in 1989.

25 Q. By "Dr Boulton", you mean the Edinburgh trial?

1 A. Yes, and Dr Boulton and Dr Howe's work was what we
2 reported in our licence application. I will check up on
3 the reference to possible work in Glasgow.

4 Q. I'm grateful.

5 Then finally on the question of the introduction of
6 Z8, could I, please, take you to a statement by
7 Dr Perry, which is [\[PEN0172201\]](#). The bottom of the
8 page, please. This is Dr Perry's understanding of
9 events. Yes, Dr Perry, we see his response:

10 "I can confirm that 200 vials of Z8 were sent to
11 Dr Boulton on 22 and 24 December."

12 We saw that was vouched by the batch issue sheet.
13 And Dr Perry states:

14 "I have been unable to locate any evidence or
15 information concerning its onward distribution to other
16 centres and my recollection is that this particular
17 batch of product was used only for clinical trials in
18 Edinburgh."

19 I think that accords with your recollection but you
20 helpfully will check that for us:

21 "However, there is evidence that Z8 for clinical
22 trial had been sent to Dr Forbes in Glasgow earlier
23 in December 1986."

24 We looked at that letter:

25 "Although I have been unable to determine if this

1 was sent via Edinburgh or directly from PFC."

2 I think you would query, actually, whether that
3 interpretation of the December letter is correct.

4 A. Yes, but I'll go through the files and I will find that
5 out.

6 Q. Rather than take up further time on this point, doctor,
7 we will await your response in due course on that.

8 Can we put that statement to one side, please?

9 Then, please, return to your statement at page 5. At
10 page 5, top of the page, question 6, we asked the same
11 question we had asked Dr Foster and other witnesses,
12 namely whether:

13 "Any wider management, organisational or other
14 issues resulted in any delay in the introduction of Z8
15 ..."

16 I think your answer in short to that is no, you --

17 A. That's the gist of what I have said, yes.

18 Q. What's that?

19 A. That is the gist of what I have said.

20 Q. Yes. You explain that:

21 "My recollection is that all elements of PFC ..."

22 By "elements", presumably you mean all personnel?

23 A. Yes, all parts of it.

24 Q. "... were fully committed to manufacture of Z8 in as
25 rapid a period as possible."

1 Your personal view is that the product was actually
2 brought to fruition in a remarkably short period of time
3 and an HCV-safe product was developed very quickly by
4 industry standards."

5 You stress:

6 "This product was available for treatment of
7 Scottish patients before any comparable product was
8 available from any of the commercial manufacturers who
9 supplied into the Scottish market, despite the fact that
10 these manufacturers had access to significantly greater
11 financial resources."

12 Et cetera. Question 7. We moved on to the question
13 of the relationship in dealings between the
14 fractionators north and south of the border. In
15 particular, whether any difficulties, if there were any,
16 between the directors of the respective fractionation
17 plants adversely affected the development of the heat
18 treatment programme in Scotland and in particular Z8.
19 I think your answer again in short to that is no, isn't
20 it?

21 A. Yes.

22 Q. Yes. And you do go on to say that:

23 "There was always good communication between SNBTS
24 and colleagues at BPL ... and PFL ... at the technical
25 and scientific level. This level of communication

1 remained in place throughout the period when such
2 developments were being undertaken. This is illustrated
3 by a high level of collaboration over the development of
4 a severe heat-treated product for the treatment of
5 Haemophilia B".

6 The Factor IX product. Et cetera.

7 You also at the bottom of the page refer to
8 extensive collaboration around the in vitro evaluation
9 of the degree of virus inactivation resultant from
10 various heat treatment/time combinations, et cetera. In
11 the early days such facilities weren't available at BPL?

12 A. Yes, that's correct.

13 Q. You do go over the page at the top of page 6. You say:

14 "Although relationships at director level were a bit
15 frosty, this did not prevent collaboration between
16 professionals in these organisations and there was
17 frequent communication between senior staff in the QA,
18 manufacturing and R&D departments of both organisations
19 to the mutual benefit of both. In conclusion, I do not
20 believe that there were any significant delays due to
21 any lack of collaboration between PFC and BPL."

22 Dr Cuthbertson, the reference to relationships at
23 director level -- and I think we mean Dr Lane and
24 Dr Watt -- being a bit frosty, Dr Foster suggested this
25 morning that there may have been a difference of opinion

1 between them about, for example, PFC fractionating
2 plasma from England and perhaps which centre should
3 fractionate for which country. Does that ring true or
4 ...?

5 A. Absolutely, I think when PFC was first conceived in
6 1974, it was intended that it would fractionate plasma
7 from Scotland and the north of England and successive
8 directors of BPL thought that was a bad idea. So on
9 that premise there was always a kind of frosty
10 relationship and Mr Watt and Dr Lane were definitely not
11 particularly soul mates, and fortunately, when Dr Perry
12 came to office, things improved a bit but not hugely at
13 director level.

14 Q. In your statement, when you say, "although relationships
15 at director level were a bit frosty", just for the
16 avoidance of doubt, what do you mean "at director
17 level", which individuals?

18 A. I mean between Dr Lane and Mr Watt and then subsequently
19 Dr Perry.

20 Q. Yes.

21 A. There was one constant in that, so I think you can
22 perhaps deduce why they were a bit frosty.

23 Q. Moving on, please, to question 8. We asked various
24 questions relating to the Central Blood Laboratories
25 Authority central committee on research and development

1 in blood transfusion, which first met on 21 June 1983.
2 Were you aware, doctor, of the existence of this
3 committee at the time?
4 A. No.
5 Q. When were you first aware of its existence?
6 A. When I got the papers with this witness statement.
7 Q. Yes. So have you had a chance to look at any of the
8 minutes or any extracts of the minutes of this
9 committee?
10 A. Oh, yes, I read all the documents that were sent with
11 the witness request.
12 Q. Question (a), the true status of the committee, I think
13 I will go over that with Professor Cash but we can see
14 what you have said. Essentially, I think you say that
15 it was an English committee. You say:
16 "It was not a national committee at all but a fairly
17 parochial body."
18 Presumably by "parochial" you mean English?
19 A. Yes, specifically -- I mean, CBLA was the body that was
20 set up to manage BPL, and I presume this committee was
21 to reassure CBLA that the BPL research portfolio was
22 a sound investment.
23 Q. Remaining strictly neutral, in Scotland we tend to hear
24 the word "parochial" in the context of Scottish but it's
25 interesting to see it being used as reference to an

1 English body.

2 PROFESSOR JAMES: Just a bigger parish.

3 A. It's just Scottish paranoia, I suppose, but the fact
4 that the Blood Transfusion Service in England was called
5 the National Blood Transfusion Service has always
6 irritated us.

7 THE CHAIRMAN: Not uniquely in your field.

8 MR MACKENZIE: Then we did go on to ask in question (b)
9 about PFC representation on the committee, or rather the
10 lack of it, and you do say that, in the third sentence
11 of your answer:

12 "In reading the minutes of this committee, it seemed
13 to be more of an overarching review body, rather than
14 initiating specific research. I believe that the
15 contact between experts in SNBTS and PFL/BPL was more
16 valuable in exchanging the relevant technical detail
17 than would have been participation in this particular
18 committee."

19 I think Dr Foster put it this morning that he
20 received information first hand from those involved,
21 rather than second or third hand via a committee, and he
22 thought that was better for obvious reasons.

23 A. I would agree with him.

24 Q. Over the page, please, at page 7. In answer to question
25 (c), in the last two sentences, you say:

1 "This type of forum could never be a mechanism for
2 exchange of the actual technical details which lead to
3 advances in research. I do not believe that the absence
4 of such a body had any impact on the rate of development
5 of the Z8 programme."

6 Question 9, we asked:

7 "Were more formal links between PFC and BPL/PFL
8 desirable?"

9 We can see your answer. You say that:

10 "Placing these on a more formal basis would have
11 been beneficial in ensuring that each party knew
12 formally of the work of the other party. However, in
13 the context of the Inquiry, there is no doubt that this
14 type of formal link would have had limited impact on the
15 development of severe heat-treated Factor VIII (either
16 8Y or Z8). As far as I know, no such formal links were
17 ever established."

18 You go on to look at confidentiality agreements and
19 how they may inhibit the exchange of information for
20 obvious reasons.

21 Question 10, we asked why PFC was able to
22 manufacture severe heated Factor IX before Factor VIII
23 and Dr Foster has provided a answer to that, in short
24 because it was easier. I don't think I have to go
25 through your answer. I will take that as read. Thank

1 you.

2 I think there is one final matter, doctor, I would
3 like to raise with you and it's a point raised by
4 Professor Cash in his statement. So could we, please,
5 go to that? It's [\[PEN0171085\]](#). It's at page 4 of the
6 statement, please.

7 In question 6 we had asked Professor Cash the same
8 question we have asked everybody else:

9 "Did any wider management ... or other issues result
10 in any delay in the introduction of Z8 ..."

11 Then Professor Cash has said:

12 "As regards the request for other potential issues,
13 I would advise that consideration is given to the
14 difficulties which arose in the development of in vitro
15 virus inactivation validation studies at PFC and how
16 these might have contributed to any delay."

17 The references supplied by Professor Cash relate to
18 HIV validation studies. I think in short an issue arose
19 at the very end of 1985 and continued through 1986,
20 possibly 1987/1988, whereby SHHD were reluctant for PFC
21 to carry out these validation studies at PFC, using HIV.
22 I think there may have been a concern about
23 cross-contamination, or at least a perception of that.
24 And Professor Cash has raised as an issue whether SHHD's
25 difficulties or concerns, rather, in that regard

1 affected the development or introduction of Z8.

2 I appreciate, doctor, I only raised this point with
3 you shortly before you gave evidence but I think you
4 said you were happy to reply to it.

5 A. Yes.

6 Q. Can I ask you to give your opinion on this point,
7 please?

8 A. As I think I said in my previous witness statement, the
9 whole thrust of the development of Factor VIII processes
10 were around us being able to do model work with viruses
11 and we selected models that mimicked certain properties
12 of the viruses of interest.

13 We did want to start doing work with HIV, which
14 obviously required us to (a), develop the techniques to
15 do the culturing and then do the work. And we developed
16 our relationship with an eminent virologist,
17 Professor Weiss in London, and we did the initial
18 experiments in a high security laboratory at the
19 bacteriology laboratories in Edinburgh. But to enable
20 us to actually do any work on HIV, we actually had to do
21 freeze-drying and we couldn't do that at these external
22 facilities. To enable us to do that, we needed to spend
23 some money to develop our virus containment area and
24 that was where the interaction with SHHD came from.

25 It took a while because I think initially they

1 thought we were planning to do these experiments
2 actually in the production area and there was much
3 disingenuousness on both sides probably, until we
4 resolved that issue.

5 We did eventually get some HIV data in 1987,
6 I think, but the purpose of it wasn't really to decide
7 whether or not Z8 was fit for release, it was simply to
8 verify in retrospect that our heat treatment programmes
9 in general had the desired effect of inactivating HIV.
10 We were very confident, after we had introduced dry heat
11 treatment, that -- and from the fact that we were
12 getting good clinical evidence, that patients who had
13 had individual batches which had included HIV positive
14 units, before the testing was initiated, had not become
15 infected. So we were very confident that Z8 at
16 80 degrees would inactivate HIV.

17 So I don't think in any shape or form this debate
18 with the SHHD delayed the overall programme. It was
19 a bit of a distraction. It was a bit irritating but in
20 terms of how long it took us to get from A to B, I don't
21 think it had any impact.

22 Q. Thank you. I have no further questions, thank you,
23 Dr Cuthbertson.

24 THE CHAIRMAN: Mr Di Rollo?

25 Questions by MR DI ROLLO

1 MR DI ROLLO: Dr Cuthbertson, can I ask you just about
2 phase 1 and phase 2 trials? With NY, the previous
3 product to Z8, there presumably was a phase 1 trial?
4 A. Indeed.
5 Q. Was there a phase 2 trial?
6 A. Not as such, no.
7 Q. With Z8 there was a phase 1 trial?
8 A. Yes.
9 Q. And obviously there was a phase 2 trial and anticipated
10 that there was going to be a phase 2 trial for that in
11 advance. Is that right?
12 A. There was a phase 2 trial, although, as a formally
13 documented trial, it wasn't initiated until 1988.
14 Q. You said there wasn't a phase 2 trial in respect of the
15 NY product.
16 A. No, there was just ongoing monitoring, in effect, of the
17 efficacy of the product, but it wasn't a formally
18 constituted trial.
19 Q. But it was anticipated that a formally constituted trial
20 would take place with Z8?
21 A. Correct.
22 Q. Can you explain why there is a difference then between
23 the two?
24 A. I think the purpose of the phase 1 trial with NY, and
25 indeed with Z8, was to demonstrate that the product had

1 appropriate in vivo characteristics, that you achieved
2 in non-bleeding haemophiliacs adequate levels of
3 Factor VIII and that the half-life of the product was
4 comparable with what they had experienced previously.

5 The purpose of the phase 2 clinical trials that were
6 established around coagulation factors, they were
7 specifically designed to see whether non-A non-B
8 Hepatitis was inactivated, and I don't think with our NY
9 product we had any notion that it would inactivate
10 entirely non-A non-B Hepatitis from the data that was
11 already available.

12 Q. And with Z8?

13 A. We expected that product to be capable of inactivating
14 non-A non-B Hepatitis, or Hepatitis C, as it became. So
15 we did develop a phase 2 protocol, which took some time
16 to negotiate with the relevant haemophilia directors,
17 who were going to have to perform it, partly around the
18 availability of so-called previously untreated patients,
19 who are, as I'm sure you are aware, relatively rare.

20 Q. In terms of compensation arrangements, there is
21 obviously an issue in the material here and before us
22 about concerns about compensation arrangements and
23 whether that did or did not have a bearing on any delay
24 that may or may not have occurred.

25 Can I just ask you: were similar concerns about

1 compensation arrangements expressed in respect of the NY
2 product?

3 A. Not that I'm aware of it.

4 Q. Right. But there were concerns expressed in relation to
5 the Z8 product?

6 A. Yes.

7 Q. Can you explain why that might have been? Why does
8 compensation rear its ugly head, as it were, in relation
9 to Z8 but not in relation to NY? Do you have any
10 insight into that?

11 A. I think you would have to refer that question to
12 Professor Ludlam, who was the person who specifically
13 raised the issue initially, I believe.

14 Q. Although he raised the issue, I think it would be
15 reasonable to think that others may have shared, once he
16 had raised the issue, a concern.

17 A. Absolutely.

18 Q. Right. Did you have any concern yourself at that point?

19 A. I think I was just a simple QA manager, rather than
20 being involved in issues of patient indemnity. I think
21 it's something that we, because we were involved in
22 a number of clinical trials thereafter, became aware of
23 as an issue that had to be addressed in every trial.
24 But I think prior to that it hadn't really crossed our
25 minds, I don't think.

1 Q. But do you have anything to offer by way of an insight
2 as to why this concern should be expressed at this
3 stage, the Z8 stage, not having been raised in quite the
4 same way before?

5 A. No, I don't think I do.

6 Q. All right. Sir, I have no further questions.

7 THE CHAIRMAN: Mr Anderson?

8 MR ANDERSON: I have no questions, thank you.

9 THE CHAIRMAN: Mr Johnston?

10 MR JOHNSTON: I have no questions, thank you.

11 THE CHAIRMAN: Anything you want to follow on?

12 MR MACKENZIE: Nothing further, sir, thank you.

13 Sir, the next witness is Professor Cash, who was due
14 to come at two. We have asked him to come at 1.45. So
15 I wonder if it would be appropriate to rise early and
16 start a bit earlier.

17 THE CHAIRMAN: I think that might be acceptable.

18 Is Dr Cuthbertson coming back?

19 MR MACKENZIE: I don't think so -- possibly.

20 THE CHAIRMAN: Well, subject to defeasance by your later
21 appearance, can I thank you for your contribution to the
22 Inquiry. You have been a great help.

23 A. Thank you.

24 (12.24 pm)

25 (The short adjournment)

1 (1.45 pm)

2 PROFESSOR JOHN CASH (continued)

3 Questions by MR MACKENZIE

4 THE CHAIRMAN: Yes, Mr Mackenzie.

5 MR MACKENZIE: Thank you, sir.

6 Professor Cash, thank you for coming in a little bit
7 earlier. Good afternoon.

8 A. Good afternoon.

9 Q. The topic we are considering today is our topic looking
10 at in short product Z8, which I'm sure you are familiar
11 with?

12 A. Yes.

13 Q. Professor, you have helpfully provided a statement
14 I would like to go to. It's [\[PEN0171085\]](#). Essentially,
15 we had a fairly standard set of questions we asked all
16 of the witnesses. If we scroll down a little on the
17 first page, we can see in the paragraph commencing:

18 "Witnesses should be advised ..."

19 This is our request to you for a statement -- in the
20 last sentence we did say that:

21 "Professor Cash should, of course, feel free to
22 defer to the PFC witnesses in respect of any technical
23 issues that he considers are more appropriately dealt
24 with by those witnesses."

25 On to page 2, please. That simply sets out the

1 topic and other matters, and then on to page 3, please,
2 and then the first of our standard questions was asked
3 about when and how the SNBTS/PFC first became aware of
4 the work down south on 8Y. Could I ask, professor, do
5 you recall when you personally first became aware of the
6 work down south on 8Y?

7 A. I don't honestly -- I really -- to be absolutely honest,
8 no. There was so much chit chat going on. We were all
9 pretty close up the road there. I don't remember
10 a sudden ...

11 Q. Thank you. Then the second standard question we asked
12 was: When did it seem likely from the clinical use of
13 8Y, that it was a product that did not transmit NANBH?

14 I think perhaps the other question I would like to
15 ask you in this regard is that 8Y was, I think, issued
16 for the phase 1 trials in approximately spring/early
17 summer 1985 in England and I think it was routinely
18 issued in England from BPL in
19 about September/October 1985. So in the second half of
20 1985 there was, I think, preliminary clinical data
21 resulting from the use of 8Y and the question in short
22 is: do you recall whether you received that preliminary
23 clinical data in any way in 1985 or in early 1986?

24 A. I don't, to be absolutely honest, no. I don't have any
25 records. Having read Peter Foster's wonderful document

1 so many times, I think I know but I honestly -- I have
2 no personal recollection.

3 Q. Okay. Then question 3. This relates to
4 in October 1985, when PFC discovered that their existing
5 intermediate purity Factor VIII product withstood
6 heating at 80 degrees centigrade, we asked firstly why
7 such heating of the existing product was not introduced
8 immediately, and you recall there were a number of
9 formidable technical challenges to be addressed, most
10 notably freeze-drying and Dr Foster has explained that
11 to us.

12 A. That's my recollection, yes.

13 Q. But then you also say that there was also time required
14 for preliminary clinical studies with regard to product
15 tolerability and efficacy. We have referred to that as
16 the phase 1 study. Would that be correct?

17 A. Yes, that's correct, sir.

18 Q. Then you go on to say:

19 "In this regard, I recall that I found that
20 operating outside the comfort of the Medicines Act 1968
21 gave rise to enhanced caution with regard to my
22 involvement in developing new products and thus may have
23 contributed in some measure to any delay."

24 Professor, it's the use of the words "in this
25 regard". I wondered what that related to. So when you

1 say that you found that "operating outside the comfort
2 of the Medicines Act" gave rise to enhanced caution,
3 does that relate simply to the undertaking of the
4 phase 1 studies or does it go beyond that?

5 A. No, no more than that. I think that "in this regard" --
6 the implication of the question is there is some delay
7 in getting to where we wanted to be and if that's
8 accepted, then I may -- I'm simply saying I may
9 personally have made a contribution because I was
10 leading a team that I was really a little concerned --
11 and I have said this before on other occasions -- that
12 outside the comfort of the Medicines Act, it was very
13 unclear to me as to the legal position that we were in
14 in terms of following the Medicines Act, in terms of
15 product licences, manufacturing licences and so on. But
16 I wouldn't wish to exaggerate that. I'm simply saying
17 that if there was some delay, I may personally have
18 contributed to it in a very small way.

19 Q. Because of your concern about the --

20 A. Yes, and I may have been asking people to dot the Is and
21 cross Ts perhaps, looking back, unnecessarily.

22 Q. So it's really a general comment or observation rather
23 than relating to anything specifically?

24 A. Absolutely.

25 Q. I see. The following questions on the page, I think you

1 then, and quite understandably, defer to your PFC
2 colleagues. So I won't ask about that but I would,
3 please, professor, like to ask about one meeting, which
4 we heard about, and in particular on 23 December 1985 we
5 heard there was a meeting at PFC.

6 I think this was Christmas Eve or two days before
7 Christmas, between Drs Perry, Foster, Cuthbertson and
8 McIntosh, where there was discussion about what should
9 PFC do in terms of product development, and in
10 particular Dr Foster wanted to continue to prioritise
11 R&D work in developing a high purity NYU product, but
12 I think we heard that Dr McIntosh wanted to prioritise
13 an 80-degree dry-heated product. And in the event, the
14 outcome of the meeting was that all four at the meeting
15 agreed that priority in the R&D work should be given to
16 developing an 80-degree dry-heated product?

17 What I'm interested in, professor, is what
18 involvement, if any, you had after 23 December?

19 A. Again, I can't recall but I'm pretty certain that
20 Bob Perry would have been in my office and reporting on
21 that meeting and I'm absolutely sure that I would have
22 agreed with the outcome of that meeting. I have no
23 knowledge of second guessing our expert team.

24 Q. I think the terminology used by the PFC witnesses thus
25 far is that PFC recommended that course of action but

1 they couldn't decide on that course alone; rather, the
2 recommendation would have to go to you as being
3 responsible for the wider SNBTS --

4 A. That's a fair comment.

5 Q. So you were the ultimate decision maker --

6 A. Yes, very much so, yes.

7 Q. I understand.

8 A. Thank you.

9 Q. Could I perhaps look at one document in this regard,
10 please? It's [\[SNB0015454\]](#). Now, I think these are
11 notes you prepared in February 1986 for one of these
12 regular meetings between the haemophilia and SNBTS
13 directors, coming up in March 1986.

14 Could we go to page 6, please? Down the page,
15 please, under subparagraph 5, "High Purity Product".

16 A. Yes.

17 Q. You refer for details to Dr Perry's report. Then:

18 "Colleagues would wish to know that difficulties
19 have arisen with regards to the heat treatment of this
20 high purity product. As a consequence, it is
21 anticipated that there will be some delay in it reaching
22 phase 1 studies. Accordingly, a decision has been taken
23 to introduce an interim solution."

24 This is a reference to what became Z8 but when we
25 see the words "a decision has been taken", should we

1 take this as a reference not just to the meeting on
2 23 December 1985 at PFC, but also Dr Perry having come
3 to you --

4 A. Absolutely.

5 Q. -- and you having agreed with that?

6 A. Absolutely. I ultimately must take responsibility.

7 Q. I understand. And albeit it may be there is no formal
8 record of that meeting or discussion between Dr Perry
9 and you or of your decision, you are clear that would
10 have taken place?

11 A. Yes, I can't dodge that, I am afraid.

12 Q. I'm not seeking to suggest you would, Professor Cash,
13 I'm simply trying to clarify the factual chain of
14 events.

15 A. I understand.

16 Q. And particularly in the absence of a record for us to
17 see, it's harder to pin down what happened but I fully
18 understand your evidence. Thank you.

19 Over the page, please in the statement. Our
20 standard question 4. You defer to your PFC colleagues.
21 So I won't ask you any more on that.

22 Question 5 relates to the matter of compensation and
23 we haven't covered that in any detail yet in this topic,
24 so I think shortly I should take you through a number of
25 documents to show the factual position. But we asked

1 whether any difficulties in commencing clinical trials
2 of Z8, because of concerns over compensation or
3 indemnity, resulted in any delay in the introduction of
4 Z8. You respond to that:

5 "I recall the issue of compensation/indemnity was
6 first raised in the autumn of 1986 and not resolved
7 until late February 1987. It follows that this may have
8 been a material cause of delay but I would judge by no
9 more than three months."

10 What I would like to do now, professor, if I may,
11 partly for the record of the Inquiry, is to go through
12 in chronological order all of the documents we have
13 relating to this issue of compensation. The first batch
14 of documents are really dated between 1983 and 1985 and
15 I propose to go through them reasonably quickly but then
16 to slow down once we get to 1986 and Z8 comes on the
17 scene, if I may.

18 So could I simply go through this list of documents
19 with you, professor? The first one is [\[SNB0015188\]](#). We
20 can see from the top these are minutes of the meeting
21 between the SNBTS and haemophilia directors of
22 14 November 1983, and if we can go to pages 2 and 3, in
23 short we will see that Professor Ludlam first raising
24 the question of compensation for clinical trials.

25 A. Any other business.

1 Q. Yes, thank you. At the bottom of the page. Then over
2 the page at page 3, we can see that you, professor,
3 agreed to raise the matter with the CSA, who could take
4 legal advice and liaise with SHHD. I should perhaps,
5 professor, try and summarise matters. It seems from the
6 documents we are about to look at that in short
7 Professor Ludlam first raised the matter
8 in November 1983 and you, I think, were sympathetic to
9 his concern and you, I think, did seek to progress
10 matters through the Common Services Agency, who in turn
11 would have to go to the SHHD, but for whatever reason --
12 and we will hear from SHHD witnesses next week -- the
13 issue of compensation remained unresolved as at the
14 autumn of 1986. I think that's a neutral way to present
15 the picture.

16 A. Absolutely right.

17 Q. Thank you. Just to continue the chain of documents, the
18 next document is [\[SNB0015252\]](#) and the last page, please.
19 This is a meeting of 2 February 1984 of the SNBTS and
20 haemophilia directors, and again in the last page we can
21 see Dr Ludlam expressing his concern and it being agreed
22 that Dr McClelland would prepare a paper on this subject
23 for submission in the first instance to the BTS
24 subcommittee of the CSA.

25 Could we please go to [\[SNF0013013\]](#)? This is

1 Dr McClelland's paper of 20 August 1984. I'm not going
2 to go into the details, professor, other than in short,
3 I think, there is a consistent line from those within
4 the SNBTS that they are sympathetic to
5 Professor Ludlam's concerns.

6 The next document, please, is [\[SNF0010241\]](#). Again,
7 these are the minutes of the meeting between the
8 haemophilia and SNBTS directors on 7 March 1985. Could
9 we, please, go to page 5? Paragraph 8, "Compensation
10 and Clinical Trials:

11 "It was generally agreed that the current situation
12 was unsatisfactory. Dr Cash explained the difficulties
13 that the SNBTS had perceived in attempting to resolve
14 the problems through the CSA. Dr Ludlam requested that
15 some action should be taken urgently. It was agreed
16 that the SNBTS would submit a paper to the CSA with
17 a view to discussion at the next BTS subcommittee
18 meeting, and Dr McIntyre undertook to raise the matter
19 within the department."

20 Perhaps we should go over the page for completeness.
21 Yes, there is nothing then on the next page. No.

22 The next document, please, is [\[SGH0031964\]](#). This
23 brings us up to 11 March 1985, a letter from yourself,
24 professor, to Mr Mutch, the secretary of the
25 Common Services Agency, and again in short you are

1 sympathetic to the request for compensation for patients
2 in clinical trials. Is that correct?

3 A. Yes, absolutely.

4 Q. Thank you. The next letter, please, [\[SNB0057320\]](#).

5 19 March 1985, a letter from Dr Ludlam to Dr Boulton.

6 In the second paragraph Dr Ludlam commenting that:

7 "Although I raised the question of compensation for
8 individuals who suffer materially as a result of testing
9 new products at St Andrew's House some time ago, there
10 has been little progress."

11 So a continuing concern on Dr Ludlam's part about
12 undertaking phase 1 trials in the absence of
13 compensation arrangements.

14 Then, please, the next letter is [\[SGH0031967\]](#) from
15 yourself, professor to, Dr Ludlam, dated 22 March 1985.
16 We can see in the first paragraph, you say:

17 "As you know, I have every sympathy with the issue
18 you have raised and hold identical views as yourself and
19 the need for proper compensation arrangements."

20 The next paragraph:

21 "During the meeting on 7 March, I detected for the
22 first time that the climate may now be changing."

23 You dispatched a letter, which we saw, I think, to
24 the CSA and this has already been lodged in SHHD for
25 their urgent consideration.

1 In the final paragraph:

2 "I write, therefore, to request that in the light of
3 the extremely difficult position the SNBTS is now in and
4 the evidence that the compensation issue is being
5 tackled, you reconsider your position and agree to
6 proceed with the requested clinical studies as soon as
7 possible and without referring the matter to the ethics
8 committee."

9 Et cetera.

10 Professor, can you remember which product this
11 letter related to? Let's see, if it's as at March 1985,
12 it certainly wasn't Z8; it wasn't on the scene. It may
13 have been an NYU product perhaps?

14 A. Yes, I think it was. Peter would be a better judge.
15 The fundamental problem we had was, as I think I have
16 been reminded of in this paragraph in front of me, is
17 that we had virtually stopped the production of the 682R
18 stuff because we had been alerted from New York that
19 this might not be good enough for HIV, and had switched
20 to -- I think it's New York -- the higher temperature
21 and were building up stocks of this but had not
22 clinically trialed it and Chris, bless him, said, "I'm
23 not going to include it in a trial, as you know, until
24 the compensation is sorted out." And we were running
25 into a disastrous situation in which there would be no

1 trials and no product. We had run out of product, the
2 old stuff, and all we had on the shelf was stuff that
3 had not been properly trialed. If we reached that
4 situation, then we would be into a situation where we
5 would be telling our clinical mates to buy stuff and
6 that was something that really made us very anxious from
7 the point of view of safety.

8 Q. Yes.

9 A. Peter will tell you -- I have got somewhere written here
10 the second product which was heated, I think, for --
11 I can't remember now. But it was not the Z8 because
12 that's the big one. That's 80 degrees.

13 Q. Yes. I suppose the only point in the purpose of
14 referring to this letter in this topic is just to
15 illustrate the continuing concern by Dr Ludlam.

16 A. Absolutely. We felt he was justified but I think I have
17 said in another correspondence, hitting us at that time
18 with the no, we were in big potential difficulties.

19 Q. I think the issue --

20 A. Supply.

21 Q. I think that issue arises again actually in relation to
22 Z8 and we will come to that again, but the next
23 document, please --

24 THE CHAIRMAN: Before you leave it, I wonder if I could ask
25 a question.

1 Professor Cash, there seems to be some reluctance
2 reflected in the bottom paragraph on that page to refer
3 the issue to the ethics committee. Can you explain
4 that, please?

5 A. Sir, I'm not entirely convinced what ethics -- I know
6 what an ethics committee is but I'm not at all sure
7 which ethics committee this was. Was that the Lothian
8 Health Board ethics committee, to which Chris Ludlam
9 would pay his allegiance? But the SNBTS also had
10 an ethics committee in which at one time
11 Professor Ronald Girdwood was chairman.

12 THE CHAIRMAN: I know of that in relation to the SNBTA.

13 A. A, that's right, sir.

14 THE CHAIRMAN: But it is your letter.

15 A. Yes.

16 THE CHAIRMAN: And you are urging Professor Ludlam to get on
17 with the work without referring the matter to the ethics
18 committee. So what did you have in mind?

19 A. I think I was picking up --

20 THE CHAIRMAN: You are picking up his expression?

21 A. I was picking up his suggestion that, "If there was
22 appropriate compensation, I don't think I need to go to
23 the Lothian ethics committee," and I was picking up that
24 theme, I think.

25 THE CHAIRMAN: Why would one hesitate to go to the ethics

1 committee at this time?

2 A. I honestly -- I really don't know. Going to ethics
3 committees was not part of my job but for Chris Ludlam,
4 I think he would need to answer that, sir -- I can
5 surmise that he might have felt that, as he was
6 operating -- as we were operating outside the Medicines
7 Act, there may have been people on the ethics committee
8 of the Lothian Health Board that would have registered
9 some concern about that.

10 THE CHAIRMAN: I see. But as far as you are concerned,
11 that's speculation?

12 A. Absolutely, sir.

13 MR MACKENZIE: If it helps, sir, I think there was
14 a reference in the previous letter, the letter from
15 Dr Ludlam to the area ethics committee.

16 A. That -- the Lothian.

17 THE CHAIRMAN: Yes, that identifies which ethics committee,
18 it doesn't necessarily help us understand why.

19 A. No, absolutely.

20 MR MACKENZIE: Yes. I should perhaps say, sir, that I quite
21 see the point, but I suppose it raises an ethics point
22 perhaps, which may not be best dealt with in this topic.

23 THE CHAIRMAN: I don't mind, it it's just because it leaves
24 the letter without a proper explanation, as it stands,
25 but if you can get it picked up later, I'm content.

1 MR MACKENZIE: Thank you.

2 Then, professor, please, the next document is

3 [\[SGH0020455\]](#). We can see that these are the minutes of

4 the meeting of the Blood Transfusion Service

5 subcommittee of the Common Services Agency of

6 20 August 1986. Can we go, please, to page 2? About

7 half way down we can see "Compensation of Volunteers".

8 This is perhaps becoming important in relation to this

9 topic because August 1986 is about the time when Z8 is

10 being scaled up for production at PFC. We can see:

11 "Compensation of Volunteers. The subcommittee noted

12 that the national medical director had held a useful

13 dialogue with the legal adviser ..."

14 Would that be a legal adviser of the

15 Common Services Agency?

16 A. Yes, indeed.

17 Q. "... concerning arrangements --"

18 A. That would be CLO almost certainly.

19 Q. CLO, I understand:

20 "... concerning arrangements for the compensation of

21 volunteers and agreed that the general manager of the

22 CSA ..."

23 A. Yes, perhaps I should point out these volunteers are

24 blood donors.

25 Q. I see, yes, of course.

1 A. They are not patients.

2 Q. Yes:

3 "... and agreed that the general manager should now
4 pursue the bringing forward of firm proposals."

5 I think I should correctly say these are volunteers
6 and we didn't dwell on it but in your letter of
7 11 March 1985 to Mr Mutch, you also dealt with the
8 compensation for volunteers in that letter. So
9 certainly that letter dealt with compensation as an
10 issue, both for donors of blood, who may have an adverse
11 reaction but also patients in clinical trials?

12 A. That's correct.

13 Q. I understand. We are now focusing in on Z8; can I next,
14 please, go to [\[SNB0076274\]](#), which is a letter from
15 Dr Boulton to yourself of 5 December 1986, and this is
16 headed "Z8 Patient Trials."

17 We can see in the main paragraph:

18 "I know that Crown immunity has been removed from
19 BPL and I assume, although I have not heard
20 specifically, that the same applies to PFC. Christopher
21 is concerned about the situation as far as indemnity to
22 patients who suffer as a result of being infused with
23 the trial material. I have a strong feeling that he
24 will be unwilling to agree to such trials unless there
25 is a specific commitment by the SHHD that any patients

1 who suffer adverse effects as a result of the infusion
2 will be given appropriate compensation."

3 I think this is really an accurate prediction by
4 Dr Boulton of what will be Dr Ludlam's position on
5 commencing clinical trials of Z8 without compensation
6 and indemnity arrangements in place. Is that correct?

7 A. That's right. Frank was very close to the clinical
8 interface.

9 Q. And presumably Dr Ludlam's position in that regard
10 shouldn't have come as a surprise to anyone given he had
11 repeatedly raised concerns about the question of
12 compensation really from late 1983?

13 A. No, I don't think we could have been surprised. We were
14 dismayed.

15 Q. It is again a timing point?

16 A. Absolutely.

17 Q. Which we may come on to shortly.

18 A. Absolutely. Continuity of supplies.

19 Q. Yes. Just to follow the sequence of documents, please,
20 [\[SNB0058711\]](#). This is Dr Ludlam writing to yourself,
21 professor, on 11 December 1986. Dr Ludlam says:

22 "I was pleased to learn recently from Frank Boulton
23 that 8Z is shortly to be available for clinical
24 assessment. I have obtained ethical approval to
25 undertake recovery and survival studies in

1 haemophiliacs. I am now awaiting an appropriate
2 commitment from either PFC, SHHD or DHSS concerning the
3 question of indemnity should any of the patients
4 materially suffer as a result of assessing the new
5 Factor VIII product. As you know, I raised this a long
6 time ago with SHHD and there has been no response.
7 I have consulted a number of colleagues at other
8 haemophilia centres and there is very great disquiet
9 about the present lack of formal arrangements."

10 Again, professor, what was your response to this
11 letter, in terms of once you received this, what was
12 your initial response?

13 A. I need to be sure a little more about the timing but on
14 the one hand I would have been very sympathetic and very
15 sorry about all this but I suspect with the timing,
16 beginning to panic that we might be running out of juice
17 and that would raise some very serious problems.

18 Q. So perhaps sympathetic, unsurprised but dismayed at the
19 timing?

20 A. Exactly.

21 Q. Yes. And the question, for the avoidance of doubt, of
22 the timing is that I think production had stopped --

23 A. That's it.

24 Q. -- in about June 1986, I think, of the
25 68 degrees/24-hour product and therefore you were hoping

1 to ramp up production of Z8?

2 A. There was lots of Z8 stored up as a stock to run in.

3 The important point, I'm sure -- I'm sure you are
4 aware of this. When we went into heat treatment first
5 of all, we pulled back all the stuff that was out there
6 and heated it. So we never lost a drop. When we had
7 already got heated and were now going to put in
8 a completely new product, we couldn't recycle it so we
9 were back on our uppers in terms of plasma supply and so
10 on. So this was something very new for us and was
11 a big, big deal actually.

12 Q. Yes, and for obvious reasons your concern was that the
13 supply of Factor VIII concentrate from PFC could run out
14 and --

15 A. Yes, we would have tonnes of it on our shelf but it had
16 not been trialed. So therefore, in terms of stuff that
17 could be used clinically and acceptably, we would have
18 none.

19 Q. I understand. Then, please, the next item is
20 [\[SGH0031919\]](#). This is a letter dated 30 December 1986
21 from yourself to Dr McIntyre. There is reference to you
22 having spoken by telephone with Dr McIntyre on that date
23 and you say:

24 "I would very much appreciate a formal response from
25 SHHD colleagues, which indicated that patients receiving

1 coagulation factor concentrates prepared at PFC, not as
2 an integral part of their treatment but for efficacy
3 trial purposes, would be subject, in the event of
4 a significant untoward reaction, to the same
5 consideration with regard to compensation as blood
6 donors who undergo immunisation/boosting for the
7 procurement of anti-RhD immune plasma."

8 At that stage, when you telephoned Dr McIntyre and
9 spoke to him on 30 December 1986, what was the response?
10 Was Dr McIntyre sympathetic to your request or what?

11 A. I can't honestly remember. To be honest I can't
12 remember and it's interesting that I feel duty-bound to
13 put it in writing.

14 Q. We can see you are also working between Christmas and
15 New Year as well?

16 A. Yes.

17 THE CHAIRMAN: It does look as if you have worked out a form
18 of language that limits the scope of any indemnity.

19 A. Yes, yes, indeed, sir, and I don't appreciate -- all the
20 rhesus negative mums in Scotland were looked after by
21 a group of 12 blood donors in Inverness. These are the
22 ones being boosted, so -- for anti-D. So we had a lot
23 of experience in that and we eventually got appropriate
24 potential compensation if troubles arose, which was
25 a real possibility. So there was a template there that

1 could have been transferred very quickly if our good
2 friends in the Scottish Office had decided to move. But
3 I'm sure we were raising something that was not just
4 Scotland; they were interfacing with their colleagues
5 south of the border. So it was a big issue.

6 Q. And also in your letter of 30 December, the compensation
7 arrangements were to be restricted to the phase 1 trial.
8 That was what was sought at that stage?

9 A. Initially, yes.

10 Q. Yes. Then, please, the next item is [\[SGH0031911\]](#). This
11 is the letter from Dr Ludlam to yourself of
12 5 January 1987. I think if we scroll down, simply
13 I think, Dr Ludlam reiterating his position that he
14 would require compensation before clinical trialing.

15 Then the next item, please, is [\[SGH0031980\]](#).

16 A letter dated 7 January 1987 from yourself to
17 Dr Ludlam. I think in short you say that while you
18 sympathise with Dr Ludlam's position, you do pose some
19 questions:

20 "Given written SHHD assurance that appropriate
21 compensation will be available to patients, relatives in
22 the context of clinical assessment of Z8 ... "

23 In short, would Dr Ludlam be prepared to commence
24 clinical trials and some other matters too.

25 Then I think you also sent that letter to the other

1 haemophilia directors in Scotland as well. We won't go
2 to it but the reference is [\[SGH0031908\]](#). Just for
3 a glimpse of what was happening in SHHD -- and as I say,
4 we will have SHHD witnesses next week -- could we,
5 please, go to [\[SGH0031912\]](#)?

6 We can see this is a minute or memo from, if we look
7 at the bottom, Dr Forrester. If we go back to the top,
8 please, it is to Mr Macniven and copied to others and
9 dated 7 January 1987. We can see it's to do with
10 compensation for volunteers to test Factor VIII and you
11 asked for an assessment of the risk to these volunteers:

12 "I attach a copy of a statement just received from
13 Dr Cash."

14 And various other points are made but we can see,
15 Dr Cash, your statement at [\[SGH0031913\]](#). I don't
16 propose going through this, professor, rather do you
17 remember preparing in at the time?

18 A. Not terribly, sir, but ... reading it brings back
19 memories.

20 Q. I think it's to help the SHHD come to an informed
21 decision about the risks of what they are agreeing to
22 compensate and indemnify perhaps, with a view to you
23 trying to get the compensation in place so trials can
24 commence.

25 Then, please, [\[SNF0013020\]](#). A letter dated

1 9 January 1987. It's from Dr Ludlam to yourself and in
2 short Dr Ludlam is replying in the affirmative to your
3 previous letter to him that given written SHHD assurance
4 about compensation, Dr Ludlam would be happy to proceed
5 with the clinical trials. I don't want to spend any
6 more time on that just now.

7 A. May I just add -- but he is putting something new, as
8 I recall, not only for the trials but he wants the
9 compensation to continue until a product licence is
10 obtained.

11 Q. I understand, yes, we can see that.

12 A. That can be a big difference, and during that period
13 they are on a named-patient basis and this is the impact
14 of the Crown immunity Medicines Act, and I think that
15 emerges clearly later.

16 Q. I understand, yes.

17 A. So there is a new request in this letter.

18 Q. Yes. The next item is [\[SNF0013022\]](#). A letter dated
19 13 January 1987 from yourself to Dr Ludlam saying:

20 "We will keep you posted on the development of
21 events. Right now, assuming SHHD deliver the necessary
22 assurances, we will keep your team in reserve to test
23 the 80 degrees/72 hours material, which will very soon
24 be with us. In the meantime, Charles Forbes has agreed
25 to look at the 75 degrees/72 hours product. All being

1 well, we should just slip past the rocks I felt some
2 days ago we were destined to founder on."

3 For the avoidance of doubt, what's the reference in
4 the last sentence to just slipping past the rocks?
5 What's that a reference to?

6 A. It was the supply, we have talked about it already.

7 Q. Supply would hopefully be able to continue because Z8
8 could hopefully be clinically evaluated and then issued
9 routinely?

10 A. Yes, but the issue routinely would have to be on
11 a named-patient basis. The whole issue of
12 compensation -- I'm sure you are about to take me into
13 it. For the continuation of compensation, right up
14 until product licence, is a new deal and we have slipped
15 past the first rock. There is another rock further
16 down.

17 Q. I understand. There are then three documents I'm not
18 going to go to but just provide the references, and
19 these are from other haemophilia directors in
20 Scotland. Firstly [\[SNB0058713\]](#) is a letter dated
21 13 January 1987 from the Aberdeen centre, in particular
22 Drs Bennett and Dawson, who essentially tell you that
23 they agree with Dr Ludlam's position, that they are not
24 prepared to commence clinical trials without
25 compensation.

1 Then the next document is [\[SNF0013024\]](#). Again,
2 I don't have to go to it but I think it's record of
3 a telephone note from Dr Hepplestone at Dundee of
4 15 January 1987, agreeing with Dr Ludlam's position.
5 Then finally [\[SNB0058712\]](#). It's a letter from Dr Hann
6 at Yorkhill Hospital in Glasgow to yourself, of
7 19 January 1987. Again, indicating he wouldn't agree to
8 Z8 being clinically trialed in children.

9 A. I think he asked "what's Z8?"

10 Q. He did indeed. The next letter I would like to go to,
11 please, is [\[SGH0031870\]](#). This is, I think, the good
12 news from the Scottish Home and Health Department. It's
13 a letter, we can see from the bottom, from Mr Murray?

14 A. Sandy, yes.

15 Q. Of 6 February 1987 to yourself, and he is referring to
16 your letter of 30 December 1986 to Dr McIntyre and in
17 the second paragraph:

18 "I can confirm that the department agrees that such
19 compensation arrangements for the clinical trials of
20 heat-treated Factor VIII and that such arrangements
21 include application of the ABPI guidelines ..."

22 Et cetera. But from this letter, the compensation
23 relates to the phase 1 trials? Thank you.

24 We don't, I think, have to go to the next document
25 but we should simply perhaps note that [\[SGF0012261\]](#) are

1 the minutes of the meeting of the SNBTS and haemophilia
2 directors on 9 February 1987, at which the meeting is
3 told by a representative from the SHHD of the
4 compensation agreement. I know there is a subsequent
5 dispute with Dr Ludlam as to whether --

6 A. John Forrester.

7 Q. Yes, as to whether the minutes accurately record what
8 was said but on any view, I think there was no dispute
9 that there was an understanding at this meeting that
10 compensation was at least being provided for phase 1.

11 Could we then, please, go to [\[SGH0031859\]](#)? A letter
12 dated 23 February 1987. If we go to the bottom, we will
13 see it's from Dr Ludlam and it's to Mr Murray of the
14 SHHD. And Dr Ludlam is raising the point in the second
15 paragraph that:

16 "There is some ambiguity in your letter as to what
17 constitutes a clinical trial. Presumably the department
18 is prepared to follow the ABPI guidelines between the
19 first test injection of heat-treated Factor VIII
20 concentrate being given and a full product licence being
21 obtained from the CSM. As the PFC and SNBTS are very
22 anxious that appropriate trials begin immediately,
23 I should be grateful for an early reply."

24 I'm going on come back soon, professor, to look at
25 the documents relating to what trials were actually

1 undertaken when but I think, in short, in March
2 and April phase 1 trials were undertaken in at least
3 Edinburgh. But simply to finally complete the
4 compensation chain of documents, if I may then go to
5 [\[SNF0013039\]](#). This is a letter, we can see at the
6 bottom, from Duncan Macniven of the SHHD to yourself,
7 Dr Cash, of 9 November 1987 where, in short, I think
8 there is extension of the compensation provisions and
9 Mr Macniven states in paragraph 2:

10 "Let me deal first with Factor VIII. In his letter
11 of 6 February, Mr Murray confirmed that approval had
12 been given to compensation arrangements at the
13 non-therapeutic stage -- that is, for patients receiving
14 heat-treated Factor VIII not as an integral part of
15 their treatment but for efficacy trial purposes. We
16 have reassessed the position in respect of the
17 therapeutic stage and now conclude that the compensation
18 arrangements for heat-treated Factor VIII may be applied
19 to therapeutic trials also."

20 Et cetera. So there is then, I think, an extension
21 of the compensation provisions to the therapeutic
22 trials. What would you understand that to mean?

23 A. Treatment.

24 Q. Treatment?

25 A. I don't think they are trials at all, they are

1 treatment. In other words -- I don't know whether
2 Duncan, whom I knew very well, would understand the
3 difference, but what we are now talking about -- we are
4 out of trial, it looks good, it's fine and we are
5 issuing now for the management of patients, and Duncan
6 is presumably, if he understands, talking about
7 therapeutic trials as that gap between that and the --
8 obtaining a product licence.

9 Q. Thank you.

10 A. Which is all that Chris Ludlam and his team wanted and
11 almost certainly, as I recall from the UK haemophilia
12 director meeting, DHSS refused to do it.

13 Q. Yes.

14 A. Which is very interesting. So this second step that the
15 Scottish Office made was, to be honest, very much
16 appreciated and very important to the continuing supply
17 but it was not a step that our colleagues south of the
18 border had.

19 Q. I understand. So, professor, that is the chain of
20 documents in relation to compensation. There is also
21 a separate set of documents relating to the actual
22 phase 1 clinical trials of Z8. Before I go to some of
23 those documents, what was your role, professor, as
24 a national medical director in phase 1 evaluation of Z8?

25 A. I can't -- I can't remember. Were these the ones where

1 we went out to Heriot-Watt and infused -- because I was
2 actively involved in that. I can't remember. Or was
3 that Liberate? I have lost track completely.

4 Q. I'll come to the documents in a second, professor, it's
5 just that I'm not clear what, if any, role you
6 personally would have had in organising --

7 A. I think that's a very fair question and I would have to
8 reply I was never at all sure as to my role beyond
9 whenever Bob Perry and his team wanted advice, I was
10 very happy to the best of my ability. But in terms of
11 as a pharmaceutical company would have, they would have
12 a medical director with the appropriate qualifications,
13 which embodied clinical trial work, we didn't have that
14 set-up. It was all part of the Crown immunity game.

15 Q. In terms of Z8 and looking at events in late 1986/early
16 1987, you clearly would have been concerned to ensure
17 that a phase 1 evaluation of Z8 did take place as
18 quickly as possible?

19 A. Oh, indeed.

20 Q. For reasons we have discussed.

21 A. Yes.

22 Q. So even if you weren't involved in the details of
23 organising the phase 1 trial, you must have been
24 aware --

25 A. Yes, and engaged. But the point I was trying to make,

1 I'm fairly sure, in fact I'm absolutely sure, I had no
2 role of signing it off ultimately.

3 Q. I understand.

4 A. So when it came to a product licence, my signature would
5 be there as medical director of the clinical trial.

6 Q. Yes. There may have been a greater role for PFC and
7 perhaps Dr Ludlam --

8 A. Yes, but I also think Ludlam and Charlie Forbes and
9 these guys were very important.

10 Q. I'll come to one or two documents in relation to the
11 phase 1 trial, professor, but in short, the slight
12 puzzle that we have just now is that we know that
13 Edinburgh did undertake a phase 1 trial in March
14 and April 1987 but we are unclear whether Glasgow and
15 Northern Ireland participated in the phase 1 trial and,
16 if so, when.

17 A. I am afraid I can't help. Is Elizabeth Mayne still
18 alive?

19 Q. I confess we haven't sought to ask --

20 A. She was a charming lady, but I'm sure Elizabeth was the
21 director in Belfast.

22 Q. Dr Cuthbertson has kindly agreed to check his records
23 again, and it may be, depending on his reply, we may
24 have to make further investigations.

25 A. I'm fairly sure Bruce is the final releaser for clinical

1 trials.

2 Q. Professor, if I were to take you through any of the
3 documents from the time, do you think that would help
4 you and your recollection of whether Glasgow and
5 Northern Ireland were involved in phase 1 trials or do
6 you think --

7 A. I doubt it but I'm happy to have a shot.

8 Q. Perhaps I could take you --

9 A. I have read all the documents -- all the bumph that has
10 been very kindly provided by my colleagues. There were
11 no recollections that I could be certain about Belfast
12 or Glasgow. I can't imagine Charlie Forbes -- I can
13 imagine when I read, "We think we sent it but we didn't
14 get a report back," I could imagine that, but I can't
15 imagine that Charles Forbes' team were not involved.

16 Q. I think, professor, rather than take you through the
17 documents in detail and have to speculate, it may be
18 better to leave things with Dr Cuthbertson in the first
19 instance and if we can perhaps take a step by step
20 approach after that.

21 The next matter that I think is of interest,
22 professor, is the question of batch dedication and
23 I think matters are quite nicely put by Dr Perry in his
24 statement, which I'll bring up. It's [\[PEN0171219\]](#).
25 Could we, please, go to page 1224? Could we scroll down

1 the page, please? At the bottom of the page, Dr Perry
2 states, in the final paragraph:

3 "However, given the accumulation of [NY FVIII]
4 stocks by July 1986 (when it ceased to be manufactured)
5 and the agreement to phase in the new Z8 product through
6 the batch dedication system, the routine introduction of
7 Z8 was determined primarily by residual NY Factor VIII
8 stocks rather than the extended development and clinical
9 evaluation timescales."

10 Do you understand the point Dr Perry is making
11 there?

12 A. I think I do.

13 Q. Yes.

14 A. I like to claim I was responsible for the idea of batch
15 dedication.

16 Q. Just so we know, what is the purpose of batch
17 dedication?

18 A. If you were a haemophiliac in any part of the world
19 getting commercial material, for instance, that was
20 bought, you would get boxes of the stuff and you would
21 notice that, as the weeks went by you had different
22 batches and every batch, if it was commercial, would
23 maybe be 100,000 blood donors, plasma donors in it. If
24 you then took a bottle from another batch, you were
25 immediately being exposed to 200,000 and so on. If you

1 go back to Scotland -- Peter has the figures in terms of
2 our batch size, in terms of plasma -- the idea I came up
3 with was why don't we see -- because we were rich in
4 product, we could leave it and dedicate then, a single
5 batch to a patient, a patient, that would last them
6 a whole year or more, instead of being exposed -- and
7 even in Scottish terms -- to lots of different batches
8 every time, they would only be exposed to a fixed, much
9 smaller group of donors.

10 Now, what that did was wonderful for the patients
11 but for Bob Perry and his team it meant that he had
12 a lot of product lying out there in people's fridges
13 waiting to be used in a year's time, as it were. There
14 it was all lying out there and meanwhile, of this
15 particular product, his stocks were going down.

16 Chris Ludlam was playing Russian roulette in terms
17 of the change over to Z8 and Bob was saying, I think it
18 would be quite right, "Look, if we get to a situation
19 where we run into the problems of stocks" -- this is of
20 the older stuff, because Z8 has not been trialed -- "we
21 will have to in fact go back to the patients and pull
22 back some of those stocks lying out there that have been
23 in batch dedication." So the whole concept of batch
24 dedication would have fallen for that period of time.

25 Q. Just to pause there, am I right in thinking that the

1 logic of batch dedication was that it was an attempt to
2 minimise the number of donors a haemophilia patient was
3 exposed to, which in turn would limit the risk of
4 infection from blood products?

5 A. Yes, it was designed to limit, to diminish, the number
6 of different blood donors.

7 Q. Yes, and do you recall approximately when this system of
8 batch dedication was brought in?

9 A. I don't but it's well recorded and I'm sure Peter in his
10 giant documents -- well recorded.

11 Q. I think it's early 1985, I think, the first part of
12 1985.

13 The point is being made, professor, that the
14 allocation was of certain patients to a batch, rather
15 than a batch to certain patients. That individual
16 patients didn't get their own batch; rather, one batch
17 perhaps may be available for a number of patients?

18 A. Oh, yes, but what you are doing is you are
19 restricting -- you are restricting the number of batches
20 that a patient will be exposed to and every batch is X
21 thousand blood donors, plasma donors.

22 Q. Yes.

23 A. I apologise if I have given the impression that one
24 batch was always one patient.

25 Q. Don't apologise.

1 A. That might have lasted 20 years.

2 Q. Please don't apologise. But I think, professor, the
3 point being made by Dr Perry in his statement in the
4 final paragraph is that in a way, regardless of when Z8
5 became available for use, if a patient had outstanding
6 stocks of a batch of a previous product, then that would
7 be extinguished before that patient started receiving
8 Z8?

9 A. Yes, that would apply too.

10 Q. So certainly for patients who were not in receipt of
11 blood products, then they would presumably receive Z8 as
12 soon as Z8 was available, but for perhaps a patient with
13 severe haemophilia, who had a stock of the NY
14 68 degrees/24-hour product, that would be used up first
15 because of this system of batch dedication?

16 A. Yes, that is correct. We didn't, as we did prior to
17 that, pull back and recall everything and start afresh.

18 Q. Yes.

19 A. We didn't have that luxury.

20 Q. Well, when you say you "didn't have that luxury", why
21 was the old product not recalled when Z8 became
22 available? Was it for safety reasons to do with batch
23 dedication or was it because you didn't have sufficient
24 stock of the new Z8 product?

25 A. I would have to assume it was the latter, sir.

1 Q. I see.

2 A. I don't think, if I may say so, the whole area of plasma
3 supply has not featured very strongly thus far in this
4 Inquiry, and I can tell you, as an ex-regional
5 transfusion director, it was a nightmare. When
6 Peter Foster's team rightly were pinching 2,000 litres
7 to just do some experiments, you know, we were -- some
8 of us were terrified by the thought. When the
9 experiment -- "Oh, it hasn't worked" -- that was
10 2,500 litres of plasma that we had gathered for patient
11 care gone down the drain.

12 These were very tense times, they really were, and
13 Peter and his team were very patient with us getting
14 very jumpy about this, because if we didn't crack it, we
15 would have been purchasing commercial stuff.

16 Q. I understand.

17 Moving on, please, professor, back to your
18 statement, please, at page 4. In question 6 we asked
19 whether any wider management, organisational or other
20 issues, resulted in any delay in the introduction of Z8.
21 We had referred to a couple of documents in particular
22 in that regard, which I think related to later
23 modifications of the Z8 process. And you say you defer
24 to your PFC colleagues on the question of the interface
25 between R&D and the production department. You then go

1 on to say:

2 "As regards the request for other potential issues,
3 I would advise that consideration is given to the
4 difficulties which arose in the development of in vitro
5 virus inactivation validation studies at PFC and how
6 these might have contributed to any delay. These
7 developments were intended to provide pre-clinical data
8 on efficacy of different heat treatment programmes. The
9 delay in the introduction of this important development
10 arose following an intervention by SHHD".

11 Can we then, please, go to the last page of your
12 statement? You list certain references and you have
13 kindly provided documents 1 to 12, which relate to this
14 potential issue you raise. I'm not going to go to all
15 of the documents but I think one might give us a flavour
16 of this issue. Could we, please, go to [\[SNB0106183\]](#)?
17 This is a letter dated 6 February 1986. Could we go to
18 the bottom, please? It's from Graham Calder. Can you
19 remind us who he was, please?

20 A. Chief pharmacist, Scottish Home and Health Department.

21 Q. Thank you. At the top of the letter, please, it was to
22 Mr Brian Hartley. Who was he?

23 A. I am afraid I don't know, sir.

24 Q. He appears to have been in the Department of Health?

25 A. Oh, yes.

1 Q. Yes.

2 A. He was in Market Towers Department of Health, and he may
3 have been his counterpart in England and Wales. It was
4 the department from which Graham came originally.

5 Q. The letter is headed "Evaluation of HTLV-III
6 inactivation in blood products from the PFC."

7 It sets out that the director of SNBTS -- that would
8 have been you, professor:

9 "... has submitted to the secretary of the Scottish
10 Health Service Common Services Agency (CSA) ..."

11 Et cetera:

12 "... a proposal to validate the safety of PFC
13 products with respect to the transmission of the
14 HTLV-III viruses."

15 The next paragraph:

16 "While we appreciate that the safety of the products
17 require to be validated we are concerned about the
18 introduction of HTLV-III viruses into the PFC. The
19 intention is that the HTLV-III viruses would be
20 propagated, at least in the first instance, in
21 Professor Collee's level 3 containment laboratories at
22 the University of Edinburgh and thereafter conveyed to
23 the PFC where the spiking experiments would take place."

24 Essentially, the concern being raised, I think, by
25 Mr Calder is the possibility of cross-contamination of

1 such handling of the HTLV-III viruses undertaken at PFC,
2 and in particular whether that virus might get into the
3 manufacturing plant and also, I think, questions of
4 public perception as well. Does that give the general
5 flavour of this issue that arose?

6 A. Yes, I think that's right, sir, yes.

7 Q. Professor, I don't propose to get to the bottom of this
8 issue, other than to consider whether this issue
9 affected the development or the introduction of Z8,
10 because that's the more narrow topic that we are
11 concerned with in these hearings.

12 We did put the potential issue you had raised,
13 together with all of the supporting documents, to the
14 PFC witnesses. In short, they are quite clear that this
15 issue did not affect the development or introduction of
16 Z8, and perhaps I should just quickly go to their short
17 written responses on this.

18 Dr Perry provided a short statement, [\[PEN0171863\]](#).
19 Can we scroll down a little, please? His headline
20 response is:

21 "The developments referred to by Professor Cash
22 post-dated the introduction of Z8 and therefore did not
23 affect the timing of its introduction
24 in April/May 1987."

25 A slightly fuller response is then given. Also

1 Dr Foster, if we can please go to [\[PEN0171127\]](#). Again,
2 Dr Foster's view is that the issue did not in any way
3 delay or interfere with the introduction of Z8:

4 "Nor, to the best of my knowledge, with the clinical
5 use of Z8 at any time."

6 Et cetera. Again, Dr Cuthbertson, when he spoke
7 this morning, was of the same view that this issue
8 didn't delay the development or introduction of Z8. Are
9 you content, professor, to defer to the PFC witnesses on
10 this narrow question, at least, of whether this issue
11 affected the development or introduction of Z8?

12 A. Yes, I am but can I give a rider?

13 Q. Please do.

14 A. 30 years later, when it's all over and you can see where
15 you have been and what has happened, you can be very
16 confident that what didn't happen clearly didn't matter
17 in the end -- at the end game and I fully appreciate
18 that.

19 Furthermore, it's very interesting that if you ask
20 Peter -- and he has done it in his document, and Bruce
21 and Bob -- what made you suddenly that night say, "The
22 heating we are doing is not enough, we are going to have
23 to change," and the answer to that question is -- it's
24 in Peter's document -- it's a paper published by Alfred
25 Prince from the New York Blood Centre, in which there

1 was a major fractionation centre. And what Alfred
2 Prince demonstrated was that the range of model marker
3 viruses he was using, as Bruce Cuthbertson was using
4 right from 1982/1983 -- brilliant work was going on in
5 PFC -- they did not cover the particular AIDS that
6 Alfred Prince was using, the problem of HIV, and when he
7 put HIV into his validation studies, the heating didn't
8 kill it.

9 So I would say -- I would say the odds were on then
10 that the viruses that Bruce Cuthbertson, with
11 Duncan Pepper, my colleague, selected as their marker
12 viruses, looked as though they covered this fine. I'm
13 not at all sure whether in the context of Hepatitis C --
14 I really can't -- I haven't the knowledge what has
15 happened in this last ten years since I retired, but it
16 looks as though, looking back, the marker viruses that
17 they were using, which didn't include HIV, were okay.
18 They served us well.

19 I could tell you for somebody who is clinically
20 responsible for the releasing of product, this great
21 confidence that my mates now have in what happened,
22 I didn't share at the time. I was just not sure that
23 the marker viruses we were using -- and this was no
24 criticism. Please, I wasn't criticising my colleagues.
25 But I wasn't sure. And what I would have liked was HIV

1 in there so we could actually say -- or the Bruce would
2 say, "It has killed it dead," and I would have slept
3 better at night.

4 So I'm absolutely certain if they say there was no
5 delay, there was no delay. Looking back, however,
6 I still, you know, go over that period and say, "Gee,
7 weren't we, once again, very lucky".

8 Q. I think you are perhaps again emphasising the
9 uncertainty at the time.

10 A. Yes.

11 Q. And also just what a great risk HIV virus was and --

12 A. Absolutely, and some of us may have overreacted and if
13 that is so, I was probably one. But what my main
14 problem with this is, I was unable to get my mates in
15 the Scottish Office to engage in discussing this right
16 through, so that we could eventually all come together
17 and say X or Y. That was my main problem.

18 Looking back, it looks as though it didn't matter.
19 "Gee, that was lucky," and it reminds me of the guys who
20 had holes in their life jackets and when the boat
21 capsized just passing was a helicopter, and ten years
22 later, you say, "It didn't matter having these holes
23 in -- you know, you were all saved anyway". And that's
24 a fact.

25 Q. The other point which could be made, professor -- and

1 again, I'm looking at things through quite a narrow
2 perspective -- did this issue adversely affect the
3 development and introduction of Z8? I don't think any
4 of the contemporaneous documents relating to the
5 development or introduction of Z8 raise this as an
6 issue. Would that be right?

7 A. I'm not sure what you mean raising it as an issue.
8 I have raised it as an issue but if you look at
9 Peter Foster's outstanding document for this B --
10 whatever it is, C3 or whatever it is, I have got it all
11 marked. He shows a series of -- a table of events
12 taking place. On almost every page there is
13 Bruce Cuthbertson has done his inactivating. So they
14 were playing a significant role.

15 Bruce Cuthbertson and his inactivation validation
16 studies throughout the period from when he, Bruce, and
17 Duncan Pepper, decided this was worth setting up.
18 I should add, it all began with a visit from
19 David Aronson from the FDA in the States in 1982. But
20 if you look at Peter's thing and if you also look
21 at March, whatever it is, 16th, of Peter's table, BPL
22 people turn up because they want in on the act of using
23 Bruce's labs, and absolutely right.

24 Q. Professor, I may be looking at this too narrowly perhaps
25 but I think the point I sought to put to you was that

1 when one looks at the contemporaneous documents in
2 relation to the development of Z8, I don't think we see
3 in any of these documents concern expressed that PFC
4 were being held up by the SHHD in carrying out HIV in
5 vitro studies at PFC.

6 A. I think I have already declared that I have never
7 thought it delayed but it would be worth asking my
8 mates -- and you have done that and they say "no delay".
9 That gives me some comfort. Certainly no comfort as the
10 person responsible ultimately saying, "Let's go, let's
11 issue this stuff for clinical trial".

12 Q. I understand.

13 A. That's all.

14 Q. Sir, there is one final paragraph in this answer. We
15 could deal with it now. Equally it's a separate matter
16 and it could wait until after a short break, if that's
17 better?

18 THE CHAIRMAN: In your hands if you would rather --

19 MR MACKENZIE: I wonder if I may just finish this next
20 paragraph. I'm grateful.

21 Returning to your statement, please, professor, at
22 page 4, it's back to the question of plasma. I think,
23 you raised earlier:

24 "Finally, it is worth re-emphasising the complex
25 problems PFC had with regard to the plasma supply during

1 product development and implementing product changeover.
2 As I recall when the first heat-treated Factor VIII was
3 issued, the unheated material was returned to PFC,
4 heated and reissued. It followed that the net demand on
5 additional plasma sourcing of this transfer was
6 marginal. However, in a situation where product cannot
7 be recycled and there is no permitted facility to boost
8 a matching plasma intake to cover the gap, then the
9 logistics of introducing a new product such as Z8, which
10 was heated at 80 degrees for 72 hours, were much more
11 challenging."

12 What exactly, professor, is the point you are making
13 there, just for the avoidance of doubt?

14 A. I apologise. I'm repeating myself.

15 THE CHAIRMAN: Yes, I thought you had said this, professor.

16 A. Yes.

17 THE CHAIRMAN: That the problem where one could recall and
18 reheat is totally different from where you are building
19 up stocks of a product that has gone beyond the
20 treatment of the superseded product. You can't reheat
21 it back to NY.

22 A. That's right.

23 MR MACKENZIE: So really you are starting from scratch and
24 having to build up stocks of the new product.

25 A. Yes, and I should add -- and it may appear -- we failed

1 to get our colleagues in the Scottish Office to fund
2 a major plasmapheresis programme. Do I need to explain
3 that at all?

4 MR MACKENZIE: I think --

5 A. We couldn't boost our plasma intake artificially, which
6 plasmapheresis would have done. We were relying on our
7 ordinary blood collection on recovered plasma.

8 Q. Thank you.

9 I think we are perhaps straying outwith the topic if
10 we look at that separate issue but I do take your point.
11 Thank you.

12 Sir, that may be an appropriate time.

13 THE CHAIRMAN: Yes.

14 (3.08 pm)

15 (Short break)

16 (3.32 pm)

17 THE CHAIRMAN: Yes?

18 MR MACKENZIE: Thank you, sir.

19 Professor, could we please go back to your statement
20 and continue with the remaining questions. I think we
21 had reached question 7 at the bottom of page 4, where we
22 had moved on to ask about the dealings and contact
23 between the Scottish and English fractionation centres.

24 Reading your response, you say:

25 "It has always been my belief that had the two

1 organisations (BPL and PFC) been able to pool their
2 limited R&D resources, and perhaps some manufacturing
3 resources, it may have been made a significant
4 difference, throughout the 1980s, to the availability of
5 desirable plasma products in the UK. The most certain
6 example of this was IVIG. It is my understanding that
7 the availability of IVIG from BPL was some years after
8 PFC had a licensed product. It follows that in this
9 period IVIG was purchased at considerable cost to
10 regional health authority pharmacy budgets."

11 So is IVIG an example of a particular product where
12 perhaps the Scots could have helped the English
13 a little?

14 A. Yes.

15 Q. I suppose another area -- and this isn't an invitation
16 to go into this now, professor -- is that the question
17 of the Scots, perhaps fractionating plasma from parts of
18 England perhaps, in the 70s and early 80s, may be
19 another wider issue where closer collaboration may have
20 been desirable. But really, professor, for this topic
21 I think you will appreciate my particular interest is Z8
22 and really my question is this: did any difficulties
23 between the directors of the BPL and PFC adversely
24 affect the work at PFC on heat treatment of coagulation
25 factors, including in particular the development and

1 introduction of Z8? That's a question I have put to
2 certainly Drs Foster and Cuthbertson, who have said
3 that, as far as they were concerned, any difficulties
4 between the directors didn't affect their work.

5 Would you defer to them, at least in respect of the
6 heat treatment of coagulation factors, in particular Z8?

7 A. Yes, I would totally defer to them but if I may, I would
8 add a little rider and ask myself, I wonder whether the
9 Inquiry has wondered what would have happened then if
10 Jim Smith had dropped dead when he walked out of
11 John Watt's office and left the PFC, or he had gone off
12 to the University of Sydney, which was highly probable,
13 and wasn't down in PFL in Oxford to play this immensely
14 enriching role he played with Peter Foster and so on.
15 I have often, in the dark days, thanked my lucky stars
16 that none of this happened, that Jim was there and
17 things could play out in the way -- so if you
18 continue -- if you actually stay with Z8 and you ask the
19 question: did Jim Smith play a contribution to this, my
20 gut feeling is -- and I think Peter would agree -- yes,
21 in an important way. Did Peter play a role in giving
22 assistance to BPL? I'm sure the answer to that is yes.
23 So ...

24 So, you know, I have been sitting in that room and
25 thinking, you know, one of the great things about our

1 organisation -- we had some fantastic people, like
2 Peter, Bruce and so on, but I'll tell you what, we had
3 a lot of luck as well, and you can say you make your own
4 luck and that may be right but by jove, we were lucky
5 that Jim was down in Oxford and I'm sure he might say
6 that he was lucky that Peter and Ronald and the team
7 were up here. And in fact, we were just talking about
8 the virus validation studies. By October 1986
9 Bruce Cuthbertson's team had completed the virus
10 validation studies on 8Y. Brilliant stuff.

11 So -- I mean -- I have to say this, the fact that
12 Bob Perry was falling out with Richard Lane is total
13 nonsense. In the 70s there was a major problem,
14 I discovered, between Richard and John Watt, and as you
15 know, at previous hearings I tried very hard to get
16 that -- and I didn't, apart from two minor spats with
17 Richard, fall out -- I had very excellent relationships.

18 That doesn't deny the fact that at CSA, the
19 Department of Health level, major efforts were made by
20 some well meaning people to get these organisations
21 together at a supramanagement, strategic level; frankly
22 we failed. With the one exception, and that is when
23 DHSS decreed that BPL were to go up to Scotland to get
24 the virus inactivation validation studies done. That
25 was the only occasion. If you read Jim Smith's

1 documents, he refers to that as being the only occasion
2 it happened.

3 Q. Yes, professor, I think to be fair to you, one of the
4 constant themes that emerge from your tenure as national
5 medical director are the consistent attempts by you to
6 try and forge closer relationships, I think in many
7 different areas, between the Scottish and English
8 transfusion services. I think that's fair to say, isn't
9 it?

10 A. It is. I should say --

11 Q. That's a wider point.

12 A. -- it was imprinted by a visit to the States in 1969
13 that you have heard about before, in which I sat in
14 a room at Cutter Laboratories, a major fractionation
15 centre, a commercial organisation, and I sat in a room
16 talking all morning with a group of 25 Peter Fosters.

17 Q. Not literally, I think.

18 A. No, I mean, they were all post-docs and they were all
19 committed to this company, to coagulation factors. And
20 I mean, if we had had 25 Peter Fosters, we would have
21 been fractionating on the moon. You know, so there was
22 a critical shortage, I felt, when I compared our
23 competitors, of sheer -- R&D manpower, and one way was
24 to link up with our mates. So it wasn't a big new idea.

25 Q. It's a matter --

1 A. It was pretty obvious.

2 Q. It's a matter of common sense really, isn't it?

3 A. Yes.

4 Q. A small country to pool and share expertise,
5 particularly when everyone is working on the same side
6 for the National Health Service. Really, I think, it
7 brings us back to this topic, professor: would it be
8 fair to say that at an informal level, the fractionators
9 north and south of the border were working with each
10 other in terms of sharing ideas but at the more formal
11 level, which I think was your concern, there could have
12 been improvements made?

13 A. Well, could I add a rider there, that it's natural that
14 this Inquiry has been dominated by Factor VIII and
15 Factor IX. Even in 1975/79 these were not the big
16 deals. In the 70s it was albumin and in the mid 80s it
17 was IVIGG, and if you actually asked PFC -- and I asked
18 Peter the other day -- he said he hadn't got a bit of
19 paper with it on -- "Give me a list of all the products
20 that you have in fact developed there," you will
21 discover that Factor VIII and Factor IX are but two of
22 many. If you ask, were the PFC and Blood Products
23 Laboratory fellows with IVIGG, with the Antithrombin 3
24 and all the other products, buzzing like Jim and Peter
25 were, the answer is no.

1 Q. But --

2 A. So this Factor VIII, the things that you are interested
3 in, are really -- critically have been dependent on the
4 chance -- what a chance! -- that Jim Smith fell out with
5 John Watt, walked out in a huff of PFC and, thank
6 goodness, landed in Oxford.

7 Q. Yes.

8 A. So, yes, there was lots going on but in this one region
9 of products.

10 Q. In relation to the heat treatment of Factors VIII and
11 IX?

12 A. Yes.

13 Q. Thank you. Then the next question, please, is question
14 8, and we raised the question of the CBLA central
15 committee on research and development in blood
16 transfusion, which first met on 21 June 1983. Just for
17 the avoidance of doubt, professor, did you know about
18 this committee at the time?

19 A. Yes, Harold Gunson told me about it, yes.

20 Q. I understand. We asked various questions about this
21 particular committee and the first question we asked
22 was:

23 "Was the committee truly a UK committee or was its
24 role restricted to research and development in England
25 and Wales?"

1 I think your view in short is that it was not truly
2 a UK committee. It will be a matter ultimately for the
3 chairman perhaps but that does seem to be an obvious
4 conclusion, I think, to reach.

5 A. Yes, I don't think it was a research committee either.

6 Q. No. Yes.

7 Dealing firstly with was it a UK committee, you
8 refer to, I think, a letter received from Dr Gunson,
9 which leads you to believe it was never conceived as a
10 UK committee. I'll give the reference for that without
11 going to it. It's [\[SNB0024347\]](#). You say:

12 "Certainly there was no consultation by SHHD with
13 the SNBTS prior to its establishment and moreover I was
14 advised it was put together at the behest of DHSS in
15 response to the demise of the MRC blood transfusion
16 research committee."

17 You explain:

18 "The explanation given by the MRC for the demise of
19 this committee did not concur with the briefings
20 I received, which included the chairman of the committee
21 ..."

22 It may be helpful to go to that letter, if we can,
23 that's [\[SNB0025864\]](#). We can see, professor, that this
24 is a letter to yourself of 19 July 1982 from Helen Duke
25 of the MRC. She states that:

1 "As regards the MRC blood transfusion research
2 committee at the recent meeting, the systems board
3 considered the report of the blood transfusion research
4 committee and I am writing now to inform you of the
5 board's decision. The board received the report with
6 great interest but considered that, in the light of the
7 activities of bodies outside the MRC and the proposed
8 establishment of the British Society of Blood
9 Transfusion, the work of the committee was being
10 duplicated elsewhere. Accordingly, the board decided
11 that the committee had fulfilled its remit and should be
12 disbanded."

13 You clearly regarded that as a backward step and as
14 most unfortunate, not, I think, for reasons specific to
15 PFC or heat inactivation but from the point of view of
16 research and blood transfusion generally. Is that
17 correct?

18 A. Yes, but very relevant to PFC but not heat inactivation.
19 I won't bore you with the details. But I can do, if you
20 wish.

21 Q. I think, professor, we can note your concerns and
22 position in that regard but I don't think they directly
23 arise for the topic I'm looking at just now. But we do
24 note your position.

25 Then over the page of your statement, please, to

1 page 6, at the top of this page we had asked:
2 "Why was there no PFC representative on the
3 committee?"
4 And whether that affected the development of Z8.
5 Your response was:
6 "I do not know why there was no place for PFC on
7 this committee. I assume it was for the same reason
8 that the SHHD adviser in blood transfusion was also
9 excluded."
10 To pause there, who was the SHHD adviser in blood
11 transfusion?
12 A. Me.
13 Q. That was you, yes. Do you recall, was there any
14 discussion at this time, back in early 1983, involving
15 you about the composition of this committee?
16 A. No, I don't -- no. In short, no. But I know I wasn't
17 on.
18 Q. In terms of what happened, were you essentially
19 presented with a fait accompli as in, "This is the
20 membership of the committee"?
21 A. It was CBLA's.
22 Q. This was their committee?
23 A. Their committee, yes.
24 Q. You say that:
25 "I never believed that this committee in any of its

1 forms would bridge the wide gap between the SNBTS and
2 BPL/NBTS because, at least in the 1980s, a desire to
3 bridge this gap did not seem to enjoy the support of
4 either DHSS or SHHD."

5 A number of points perhaps arise, professor.
6 Firstly, you were perhaps looking for truly joint UK
7 committees, rather than the SNBTS having an involvement
8 in an English CBLA committee. I understand that point.

9 A. As the MRC committee was.

10 Q. I understand. Truly a UK committee.

11 A. Yes.

12 Q. And also, when you talk about the wide gap between the
13 SNBTS and BPL/NBTS, I understand there may be wider or
14 more general issues, but again if you remember, my
15 narrower interest for this topic is in respect of work
16 on the heat treatment of coagulation factors and in
17 particular Z8, given the informal dealings between, in
18 particular, Drs Foster and Smith, it doesn't appear in
19 that narrower context there was a wide gap between the
20 two organisations?

21 A. I agree with you, yes.

22 Q. Thank you.

23 Then the next question we asked was the question of
24 what would have been the appropriate forum for
25 exchanging information and a question of a perceived

1 commercial brief of the CBLA, and your response was:

2 "Sadly, I would suggest that in the circumstances,
3 the best opportunity for exchange of information between
4 BPL and PFC with regard to the development of 8Y and Z8
5 lay with the personal liaisons between Dr Foster's team
6 and Dr Smith. Whilst uncomfortable with this position,
7 I was content for us to enjoy its rewards."

8 And one example of why you were uncomfortable was
9 the if somebody had fallen under a bus -- the
10 informality of the communications. I understand that
11 point.

12 Then we asked question 9, whether more formal links
13 between PFC and BPL/PFL were desirable and were such
14 formal links eventually established. In the final page
15 of your statement you state that:

16 "In my view, formal links were desirable because
17 I believed they were in the public interest."

18 One can fully understand that as a matter of logic
19 and common sense:

20 "However, there was sufficient evidence that they
21 did not enjoy the support of ministers, despite the
22 comments of directors Moore and Smithies."

23 I should perhaps pause just to look at this
24 document, if we may. It's [\[SNB0060464\]](#).

25 This is, I think, a minute or a note from Drs

1 Smithies and Moore of the Department of Health and
2 Social Security. The advisory committee on the National
3 Blood Transfusion Service, central committee for
4 research and development. I see in paragraph 1:

5 "Following the last meeting of this committee,
6 proposals for a committee reporting structure from the
7 central committee were agreed with the SHHD ... [and
8 were also] agreed by the transfusion directors of
9 England and Wales and by the CBLA."

10 In paragraph 2:

11 "The proposals were comprehensively rejected by
12 Scottish transfusion directors ..."

13 For various reasons which are then set out. In
14 paragraph 3:

15 "English ministers have previously indicated their
16 wish to have a UK-based research committee and DHSS will
17 therefore pursue the objective of a UK central committee
18 at ministerial level."

19 I think the point you have made in your statement,
20 professor, is that despite the sentiment expressed
21 there, about the desire on the part of English ministers
22 to have a UK-based research committee, I think your
23 opinion is that -- is what?

24 A. Oh, my opinion was if that was really so, ministers
25 would have stepped in to the MRC and said, "Under no

1 circumstances disband this excellent committee". That
2 would be point 1. Beyond that, if you then ask the
3 question, well, then what happened following Roger Moore
4 and Alison Smithies's memo there; did ministers step in?
5 Was I and my mates talked to by our colleagues in the
6 Scottish Office? No. I mean, nothing happened until
7 1988. I think I have got it right. Harold Gunson
8 writes to me again, and it seems as though we are into
9 completely different -- and we say, "Let's try it,"
10 nothing happened again.

11 Q. Let's just then go back to your statement to complete
12 that passage of evidence, if we may. We had finished
13 off after the number 14. You go on to say:

14 "To the best of my knowledge, they were never
15 established more formal UK research committee or in
16 particular more formal links between PFC and BPL/BFL."

17 And you are not aware of records which demonstrate
18 that this committee ever sponsored or commissioned any
19 research. Is this a reference to the CBLA central
20 committee on research and development in blood
21 transfusion?

22 Then you go on to say that the same applied to the
23 ill-fated NBTS research committee, promised in 1988. We
24 should perhaps pause to look at that reference. That is
25 [\[SNB0115050\]](#). This is a report by Dr Gunson on behalf

1 of the national directorate of the NBTS in England and
2 Wales, and the report is headed "National Blood
3 Transfusion Service RTD committee."

4 What does the "RTD committee" stand for?

5 A. Regional transfusion director.

6 Q. We see paragraph 1:

7 "The national director of the NBTS was formed on
8 1 October 1988."

9 Could we go further down, please? Perhaps onto the
10 next page. Professor, you had referred us to this
11 document. Is there a particular passage in this
12 document you wanted to take us to? If we can perhaps
13 carry on scrolling down it.

14 A. I thought -- and we need to keep going -- that this was
15 Harold -- which he sent to me saying, "Why don't we set
16 up an NBTS research committee then?" This was soon
17 after he took over in this directorate position in
18 Manchester and I had assumed, when I pulled out this for
19 you, that that was what it was partly all about. I
20 don't see it at the moment.

21 Q. No.

22 A. We keep ...? Yes, 6.9:

23 "A research committee for the NBTS will be formed to
24 coordinate research work in RTCs."

25 That's regional transfusion centres, and that's not

1 BPL/PFL.

2 Q. RTCs but in England and Wales?

3 A. NBTS means England and Wales.

4 Q. Yes.

5 A. And Harold at some point wrote to me and said, "Do you
6 want to come in on this? You have already rejected the
7 other thing. Do you want to come in?" And we come
8 back -- we have got the papers somewhere, "Yes, let's
9 give this a whirl," and nothing happened.

10 Q. Nothing happened. I understand. Returning to your
11 statement, please, page 7. You say:

12 "Both these research committees ..."

13 By "these research committees", what do you refer to
14 in your statement, professor, when you say:

15 "Both these research committees were in existence
16 ..."

17 Which research committees?

18 A. The CBLA and then the NBTS.

19 Q. I understand:

20 "... were in existence at a time when the scientific
21 challenges of the transmission of viruses by blood
22 transfusion in the UK were formidable. As I recall,
23 they made no contributions to this or anything else.
24 I suggest that Dr McClelland would be a better judge of
25 this."

1 So presumably, professor, in the absence of formally
2 constituted UK committees considering the issues which
3 arose and giving guidance, really those at the coalface
4 had to get on and deal with things as they thought best?

5 A. Absolutely.

6 Q. And perhaps discuss things perhaps in a more informal
7 way with each other? Thank you.

8 Then the last question, 10, is one in which you
9 understandably defer to your PFC colleagues.

10 I have no further questions. Thank you, professor.

11 A. Thank you very much.

12 THE CHAIRMAN: Mr Di Rollo?

13 Questions by MR DI ROLLO

14 MR DI ROLLO: Professor Cash, I would like to ask you --

15 A. I can't hear.

16 Q. Sorry. I would like to ask you about the situation in
17 relation to 8Y and Z8, contrasting Scotland and England.
18 Could you have a look, please, at [\[DHF0030476\]](#)? This is
19 an item that was distributed to haemophilia directors in
20 England and Wales and we can see from this that general
21 issues begin in respect of 8Y in England from the
22 1 September 1985, and it says:

23 "This high purity product ... to reduce the risk of
24 infection by viral agents, although further assurance is
25 sought over freedom from risk of viral transmissions."

1 Is what it says in the second paragraph. Then it
2 goes on to say in the final paragraph on the first page:

3 "It is recognised that, until the new production
4 unit at Elstree is completed, output of 8Y will meet
5 about one third of current demand for concentrate and
6 for this reason, attempts have been made to define those
7 patients likely to benefit most from the security
8 inherent in 8Y."

9 If we just go over the page, please:

10 "Therefore, haemophilia centre directors are being
11 asked to compile lists of their patients considered 'at
12 risk' and most centres have complied. It is the
13 considered view at BPL that, where possible, liaison
14 between the haemophilia services and the BTS should aim
15 at directing Factor VIII-Y to these patients, using the
16 existing framework of distribution and supply."

17 I think you were asked in your evidence about an
18 awareness about the possible increased safety, if I can
19 put it like that, that the 8Y might provide and you said
20 you couldn't remember when you first became aware of
21 that increased safety. Would you have been aware that
22 this kind of direction was going out in England at this
23 time?

24 A. I would think so, yes. I would think so.

25 Q. How would you become aware of that? Was that just

1 through the grapevine or would there be any more formal
2 means of being told that?

3 A. It would be grapevine. It would not be formal. I would
4 probably get it from Peter Foster. Might even get it
5 from Chris Ludlam, but it wouldn't be formal.

6 Q. Right. I think if we go further on to [\[SNB0015469\]](#),
7 this is another document that we have seen. If we go to
8 paragraph 3.1. I think it's on page 4.

9 As I understand it, this is a report by Dr Perry,
10 PFC, for SNBTS haemophilia directors meeting on
11 5 March 1986. The phrase that's used is:

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

18 Again, would you have been aware of that information
19 at that time?

20 A. I don't know but if Bob says that we will be aware, I'll
21 accept what Bob says. I can imagine my friend Bill
22 Whitrow from Inverness would have said, "I have never
23 heard of it", but, yes, I'll accept it as it's written.

24 Q. The situation then appears to be that there has been
25 produced in England 8Y, which it does look as though

1 there is an increased margin of safety, and certain
2 patients might benefit from that presumably, such as
3 patients who have not previously been exposed to
4 concentrates. You are nodding. Is that right?

5 A. Yes.

6 Q. Did anybody think at this time of obtaining some of this
7 material, 8Y, for the use of previously untreated
8 patients in Scotland, so that until the SNBTS programme
9 to provide the Z8 was complete, those patients could be
10 given that extra margin of safety?

11 A. I have no idea. Certainly, it's very unlikely I would
12 because -- but the clinicians, Chris Ludlam and Charlie
13 Forbes and so on would be perfectly at ease so to do,
14 but it's unlikely I would and for very good reason. For
15 every unit I took out of England, an English patient
16 would suffer. You know, I'm not in that game.

17 So I wouldn't instinctively have done it.

18 As I recall -- and to be honest, I never understood
19 this -- some 8Y did come up to Scotland for a short
20 period. You can rest assured that I wasn't directly --
21 from what I have said -- directly involved in initiating
22 this but no, I wouldn't -- the point that you have
23 stopped, I wouldn't be saying, "Let's have some of this
24 stuff up from England". I'm a great United Kingdom man
25 myself and the people down there were in dire trouble.

1 Q. You say they were in dire trouble but I think the
2 situation presumably, in one respect, would be similar
3 in that those that had been exposed to factor
4 concentrates wouldn't require that extra margin of
5 safety or it wouldn't be as acute to give them that
6 extra margin of safety, whereas they obviously are
7 looking at restricting the supply to those that it might
8 be useful to provide that extra margin of safety, and it
9 does appear, I think we know, that if it had been asked
10 for, it might have been provided, and you would have
11 been in a position to ask the English, would you not,
12 for that material?

13 A. Yes, I would, but you can be assured, I would first
14 consult with the clinical team, Chris Ludlam and Charlie
15 Forbes, as to whether they thought this was a good idea.
16 But yes, I would be in a position, but actually in
17 practice, so would Bob Perry and I have got a hunch that
18 the little bit of 8Y that we got up, Bob got up for
19 a particular purpose later on. Yes, I would, sure.

20 Q. Are you saying this didn't occur to you or it did occur
21 to you and you decided not to do it?

22 A. I said twice I cannot remember whether it did or it
23 didn't. You have asked me, would I -- I could have done
24 those things. The fact that I didn't may have been,
25 I have said, I can't recall, that I didn't wish to take

1 a safe product out of the hands of part of the
2 United Kingdom that was in very serious difficulties and
3 I wasn't to know -- I'm not sure many people know -- how
4 many of -- first, how many patients there were that
5 would fit into the high risk group that you rightly --
6 that needed this stuff, point 1. And I have, and I have
7 made it evident to this Inquiry before: I was always
8 concerned that the notion that, oh, once you have been
9 exposed, you can have it, it doesn't matter, I have
10 never been a great supporter of this, not for any
11 super-scientific reason, but I have always lurked behind
12 the possibility that second exposures and third
13 exposures to great big plugs of virus, even although you
14 have got antibody already, may not be very good for you.
15 And if you look at the paper by Peter Simmonds in the
16 Lancet of 1990, that actual issue has popped up.
17 Christopher Ludlam is a co-author.

18 Q. I think we can fully understand that. Clearly it
19 probably wouldn't be a good idea to expose someone more
20 than once, and certainly nobody could argue with the
21 situation that it would be less than ideal to provide
22 that material, but there is a distinction to be drawn,
23 is there not, between that situation and the patient who
24 has not been treated before, because --

25 A. A higher priority is -- we call them PUPs, absolutely

1 right.

2 Q. So it does appear that one thing that might have been
3 considered at least would have been to have made some
4 sort of approach to England to obtain some of that
5 material, until SNBTS had actually completed its
6 programme to produce material heated to the same
7 protocol.

8 A. It might, yes.

9 Q. The other matter I want to ask you about, professor, was
10 the issue of compensation and Mr Mackenzie, I think, has
11 explored this in some detail and I don't really want to
12 take up much time about this. One thing I would like to
13 ask you is if you could give us an insight into why it
14 was that heels were dug in in relation to Z8 but they
15 hadn't been dug in before, with NY. Obviously the issue
16 was raised with NY but presumably the phase 1 trials
17 went ahead without --

18 A. Pure speculation.

19 Q. It would be pure speculation?

20 A. It would, on my part, it really would, and I think on
21 this issue very improper.

22 Q. Right.

23 A. They were not my heels that were dug in.

24 Q. Somebody else's heels?

25 A. Yes.

1 Q. All right. I'll leave it at that.

2 THE CHAIRMAN: Mr Anderson.

3 MR ANDERSON: Thank you, sir, I have no questions.

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

5 THE CHAIRMAN: Thank you very much, Professor Cash. It
6 would appear that they are anxious to let you go this
7 evening, early.

8 A. Thank you, sir, very much.

9 MR MACKENZIE: Sir, tomorrow we have Dr Perry and
10 Professor Ludlam.

11 THE CHAIRMAN: Very well, until tomorrow morning, then.

12 (4.10 pm)

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

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