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

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

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

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

Et cetera.

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

Page 2. Dr Cash states:

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

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

Then we saw before the reference to:

"I do not regard the existing ..."

What Professor Cash called "furtive arrangements":

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

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

Common Services Agency, I think is the reference:

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

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

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

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

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

I'll stop there.

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

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

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

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

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

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

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

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

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

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

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

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

Q. Thank you.

Turning next, please, to page 13 in your statement

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

A. That's correct.

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

A. Very briefly.

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

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

know what was going on.

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

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

And he said:

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

We looked at that letter yesterday:

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

As you say:

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

In the next paragraph you say:

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

not included in the patent application for 8Y."

We discussed that yesterday.

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

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

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

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

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

Q. It could be fatal to the application?

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

Q. Was that a government patent lawyer?

A. No, that was a commercial patent lawyer.

Q. In private practice?

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

Q. I understand.

Question 9, please, doctor. We asked:

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

You responded that:

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

And that may in fact:

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

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

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

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

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

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

A. Okay.

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

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

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

THE CHAIRMAN: In a particular area?

MR MACKENZIE: Actually we have got the letter, I understand. Sorry, it's my wrong reference. It's [SGH0083036], I apologise.

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

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

Mr Macniven states:

"I'm writing about two unrelated aspects of the

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

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

In paragraph 2, Mr Macniven states:

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

Paragraph 3:

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

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

Et cetera.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

A. That's correct.

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

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

"Why was PFC able to make available for use clinical

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

At question (c) we asked:

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

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

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

Q. For all the reasons we discussed yesterday?

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

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

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

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

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

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

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

What do you mean by "produce"?

A. It should be "product".

Q. I'm easily confused:

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

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

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

Armour, a pharmaceutical company, Humate-P.

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

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

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

Q. Yes, I understand, thank you.

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

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

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

Q. Was that manufactured in America?

A. Yes, it would have been.

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

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

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

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

A. It was different but very similar.

Q. And manufactured in America?

A. It was manufactured in America.

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

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

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

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

That must be in America?

A. That's correct.

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

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

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

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

A. It is, indeed.

Q. Who are Melville Biologics?

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

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

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

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

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

A. No.

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

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

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

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

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

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

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

Q. Thank you.

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

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

You go on to say that:

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

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

as you then list in more detail.

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

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

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

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

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

A. Yes, that's correct.

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

Dr Foster, on a separate point, we can see a supplementary statement you provided. It's [PEN0171127].

This point arises from Professor Cash's statement.

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

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

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

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

So it didn't actually hold anything up.

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

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

Q. Dr Foster, that completes Factor VIII.

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

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

Under (c):

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

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

Does that accord with your understanding?

A. It does, yes.

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

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

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

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

Sir, I have no further questions.

THE CHAIRMAN: Mr Di Rollo.

MR DI ROLLO: Sir, Mr Mackenzie has been good enough to incorporate in his questions, the question that we wished to ask and I have no questions for Dr Foster.

MR ANDERSON: I have no questions.

MR JOHNSTON: I have no questions either.

THE CHAIRMAN: Is Dr Foster coming back?

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

THE CHAIRMAN: Dr Foster, I would like to say publicly thank you very much. You have applied a great deal of diligence to assisting us. We are all very grateful. Also very grateful for the way you have given your evidence, which we found very, very helpful.

A. Thank you very much.

MR MACKENZIE: Sir, the next witness is Dr Cuthbertson, who we asked to come at 10.30. So our timing is pretty spot-on today. But it may be helpful to have a 15 or 20 minutes' break.

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

MR MACKENZIE: I'm grateful.

(10.32 am)

(Short break)

(10.59 am)

DR BRUCE CUTHBERTSON (continued)

Questions by MR MACKENZIE

THE CHAIRMAN: Yes, Mr Mackenzie.

MR MACKENZIE: Thank you. Sir.

Good morning, Dr Cuthbertson.

A. Good morning.

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

A. That's correct.

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

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

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

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

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

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

Q. Thank you.

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

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

Q. Thank you.

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

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

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

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

Then each lot was tested for a range of biochemical

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

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

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

A. Yes.

Q. Thank you.

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

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

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

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

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

A. Yes.

Q. Thank you.

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

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

which is [PEN0171200]. At question 1 we asked:

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

Also, when was their awareness that the product was able to heated at 80 degrees centigrade for 72 hours? We have asked Dr Foster questions on this as well, doctor, but do you have a recollection of when you personally first became aware of these developments?

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

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

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

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

A. I am afraid not.

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

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

resulted in a product which did not transmit NANBH."

Can I ask, in a way, a precursor to that question: were you made aware in 1985 and perhaps early 1986 of the preliminary clinical data which was becoming available in respect of 8Y's use?

A. Yes, I'm sure that as soon as that was available, that was made known to all the PFC senior managers.

Q. How would you become aware of that preliminary clinical data, do you remember?

A. Almost certainly from conversations with Dr Foster, who was basically the principal conduit of such information, and Dr Perry possibly also.

Q. Did you yourself have dealings with the fractionators down south?

A. Oh, yes, I mean, I think, as I have said in the previous evidence, we had regular dealings with Dr Smith, who would pop into PFC from time to time, and although the meetings were principally with Dr Foster and Dr McIntosh, other senior managers would regularly meet with them and share information.

Q. Thank you.

A. As things progressed, we got into closer and closer formal collaboration.

Q. Thank you. Then your written response to question 2. You state:

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

You then say:

"The letter from Dr Smith ... "

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

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

A. Hm-mm.

Q. You say that:

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

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

A. Absolutely, yes.

Q. Absolutely yes?

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

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

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

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

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

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

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

You explain:

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

You say:

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

Then in the next paragraph --

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

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

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

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

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

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

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

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

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

A. Yes.

THE CHAIRMAN: Thank you.

MR MACKENZIE: Thank you, sir.

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

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

And we asked:

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

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

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

characteristics, in particular potency and solubility."

And that:

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

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

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

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

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

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

been manufactured in the main plant?

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

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

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

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

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

You explain:

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

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

for clinical use from December 1986."

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

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

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

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

Which was produced:

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

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

A. That's correct.

Q. Do you have a recollection of the meeting?

A. In general terms, yes.
Q. What is that general collection? What was discussed?
A. It was to discuss a paper which Dr Foster had put together, which basically outlined two possible strategies for how we could progress with our development of a virus-safe Factor VIII product. Option one was that at that time relatively unproven high purity route, which Dr McIntosh had been working on, which I'm sure he will tell you about in the next day or two, and the second was to go for a product that was closer to the 8Y process and which was similar to the Factor IX product that we had already started issuing.

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

Q. Thank you.

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

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

A. Dry heat treatment.

Q. Why?

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

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

A. That's correct.

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

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

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

Q. Thank you.

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

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

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

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

Q. Thank you. You used the word "adviser" -- Professor Cash would be the adviser. By that do you mean he was the ultimate decision maker?

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

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

Thank you.

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

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

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

In question 4 we asked:

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

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

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

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

the introduction of Z8?

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

Q. Yes.

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

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

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

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

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

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

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

What's your response to that, doctor?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

A. Belfast, that's correct.

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

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

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

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

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

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

Then:

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

What's that about?

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

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

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

A. Yes.

Q. If we go to page 4, please, in item 9 we can see Dr Perry reporting that:

"This product ..."

Being the Z8 heat-treated at 75 degrees for 72 hours:

"... was now available for half-life and recovery studies in Edinburgh, Glasgow and Northern Ireland prior to its introduction into routine use. Dr Boulton is co-ordinating the study, the results of which will be used for application for licence variation."

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

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

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

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

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

Q. I'm sorry?

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

Q. I see, dispensed into the vials. Then we see:

"Date placed at issue. 2 December 1986."

What does that mean?

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

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

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

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

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

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

posterity.

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

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

Q. So when it's stated:

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

A. Yes.

Q. Thank you.

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

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

Q. Thank you.

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

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

Q. Thank you.

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

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

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

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

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

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

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

Q. What's your interpretation?

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

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

Q. Okay.

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

Q. Yes.

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

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

A. That's possible.

Q. That's possible?

A. That is possible.

Q. We will continue, though, with the documents. The next one, please, is [SNB0094073].

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

Q. Yes.

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

Q. 22 December.

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

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

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

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

The next document, please, is [SNF0013022]. This is a letter dated 13 January 1987 from Dr Cash to Dr Ludlam, stating:

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

look at the 75 degrees/72 hours product."

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

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

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

Q. Although --

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

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

A. Indeed.

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

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

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

Q. Is --

A. But I don't think so.

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

A. Yes.

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

A. Yes.

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

A. Indeed.

Q. We would be grateful, thank you.

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

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

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

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

A. Yes that seems to be the case.

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

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

A. Yes.

Q. And then the next document, please, is [PEN0171451]. This is, for completeness, another batch issue record we have. This is noted 75 degrees and the expiry date, November 1988, suggests that this was perhaps the 75 degrees product, at least distributed into vial in November 1986?

A. That's correct.

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

clinical use?

A. Yes.

Q. Thank you. Then, please, [SNB0076605].

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

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

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

A. Yes.

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

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

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

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

Q. I'm grateful.

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

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

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

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

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

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

We looked at that letter:

"Although I have been unable to determine if this

was sent via Edinburgh or directly from PFC."

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

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

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

Can we put that statement to one side, please? Then, please, return to your statement at page 5. At page 5, top of the page, question 6, we asked the same question we had asked Dr Foster and other witnesses, namely whether:

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

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

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

Q. What's that?

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

Q. Yes. You explain that:

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

By "elements", presumably you mean all personnel?

A. Yes, all parts of it.

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

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

You stress:

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

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

A. Yes.

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

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

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

The Factor IX product. Et cetera.

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

A. Yes, that's correct.

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

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

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

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

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

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

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

Q. Yes.

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

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

in blood transfusion, which first met on 21 June 1983. Were you aware, doctor, of the existence of this committee at the time?

A. No.

Q. When were you first aware of its existence?

A. When I got the papers with this witness statement.

Q. Yes. So have you had a chance to look at any of the minutes or any extracts of the minutes of this committee?

A. Oh, yes, I read all the documents that were sent with the witness request.

Q. Question (a), the true status of the committee, I think I will go over that with Professor Cash but we can see what you have said. Essentially, I think you say that it was an English committee. You say:

"It was not a national committee at all but a fairly parochial body."

Presumably by "parochial" you mean English?

A. Yes, specifically -- I mean, CBLA was the body that was set up to manage BPL, and I presume this committee was to reassure CBLA that the BPL research portfolio was a sound investment.

Q. Remaining strictly neutral, in Scotland we tend to hear the word "parochial" in the context of Scottish but it's interesting to see it being used as reference to an

English body.

PROFESSOR JAMES: Just a bigger parish.

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

THE CHAIRMAN: Not uniquely in your field.

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

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

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

A. I would agree with him.

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

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

Question 9, we asked:

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

We can see your answer. You say that:

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

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

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

you.

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

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

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

Then Professor Cash has said:

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

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

affected the development or introduction of Z8.

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

A. Yes.

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

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

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

It took a while because I think initially they

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

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

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

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

THE CHAIRMAN: Mr Di Rollo?

Questions by MR DI ROLLO

MR DI ROLLO: Dr Cuthbertson, can I ask you just about phase 1 and phase 2 trials? With NY, the previous product to Z8, there presumably was a phase 1 trial?

A. Indeed.

Q. Was there a phase 2 trial?

A. Not as such, no.

Q. With Z8 there was a phase 1 trial?

A. Yes.

Q. And obviously there was a phase 2 trial and anticipated that there was going to be a phase 2 trial for that in advance. Is that right?

A. There was a phase 2 trial, although, as a formally documented trial, it wasn't initiated until 1988.

Q. You said there wasn't a phase 2 trial in respect of the NY product.

A. No, there was just ongoing monitoring, in effect, of the efficacy of the product, but it wasn't a formally constituted trial.

Q. But it was anticipated that a formally constituted trial would take place with Z8?

A. Correct.

Q. Can you explain why there is a difference then between the two?

A. I think the purpose of the phase 1 trial with NY, and indeed with Z8, was to demonstrate that the product had

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

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

Q. And with Z8?

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

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

Can I just ask you: were similar concerns about

compensation arrangements expressed in respect of the NY product?

A. Not that I'm aware of it.

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

A. Yes.

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

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

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

A. Absolutely.

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

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

Q. But do you have anything to offer by way of an insight as to why this concern should be expressed at this stage, the Z8 stage, not having been raised in quite the same way before?
A. No, I don't think I do.
Q. All right. Sir, I have no further questions.
THE CHAIRMAN: Mr Anderson?
MR ANDERSON: I have no questions, thank you.
THE CHAIRMAN: Mr Johnston?
MR JOHNSTON: I have no questions, thank you.
THE CHAIRMAN: Anything you want to follow on?
MR MACKENZIE: Nothing further, sir, thank you.
Sir, the next witness is Professor Cash, who was due to come at two. We have asked him to come at 1.45. So I wonder if it would be appropriate to rise early and start a bit earlier.
THE CHAIRMAN: I think that might be acceptable.
Is Dr Cuthbertson coming back?
MR MACKENZIE: I don't think so -- possibly.
THE CHAIRMAN: Well, subject to defeasance by your later appearance, can I thank you for your contribution to the Inquiry. You have been a great help.
A. Thank you.
(12.24 pm)
(The short adjournment)

(1.45 pm)

PROFESSOR JOHN CASH (continued)

Questions by MR MACKENZIE

THE CHAIRMAN: Yes, Mr Mackenzie.

MR MACKENZIE: Thank you, sir.

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

A. Good afternoon.

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

A. Yes.

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

"Witnesses should be advised ..."

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

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

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

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

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

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

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

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

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

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

A. That's my recollection, yes.

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

A. Yes, that's correct, sir.

Q. Then you go on to say:

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

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

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

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

Q. Because of your concern about the --

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

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

A. Absolutely.

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

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

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

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

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

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

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

A. That's a fair comment.

Q. So you were the ultimate decision maker --

A. Yes, very much so, yes.

Q. I understand.

A. Thank you.

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

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

A. Yes.

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

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

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

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

A. Absolutely.

Q. -- and you having agreed with that?

A. Absolutely. I ultimately must take responsibility.

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

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

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

A. I understand.

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

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

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

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

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

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

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

A. Any other business.

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

A. Absolutely right.

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

Could we please go to [SNF0013013]? This is

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

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

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

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

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

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

A. Yes, absolutely.

Q. Thank you. The next letter, please, [SNB0057320]. 19 March 1985, a letter from Dr Ludlam to Dr Boulton. In the second paragraph Dr Ludlam commenting that:

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

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

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

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

The next paragraph:

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

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

In the final paragraph:

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

Et cetera.

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

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

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

Q. Yes.

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

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

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

Q. I think the issue --

A. Supply.

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

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

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

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

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

A. A, that's right, sir.

THE CHAIRMAN: But it is your letter.

A. Yes.

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

A. I think I was picking up --

THE CHAIRMAN: You are picking up his expression?

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

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

committee at this time?
A. I honestly -- I really don't know. Going to ethics committees was not part of my job but for Chris Ludlam, I think he would need to answer that, sir -- I can surmise that he might have felt that, as he was operating -- as we were operating outside the Medicines Act, there may have been people on the ethics committee of the Lothian Health Board that would have registered some concern about that.
THE CHAIRMAN: I see. But as far as you are concerned, that's speculation?
A. Absolutely, sir.
MR MACKENZIE: If it helps, sir, I think there was a reference in the previous letter, the letter from Dr Ludlam to the area ethics committee.
A. That -- the Lothian.
THE CHAIRMAN: Yes, that identifies which ethics committee, it doesn't necessarily help us understand why.
A. No, absolutely.
MR MACKENZIE: Yes. I should perhaps say, sir, that I quite see the point, but I suppose it raises an ethics point perhaps, which may not be best dealt with in this topic.
THE CHAIRMAN: I don't mind, it it's just because it leaves the letter without a proper explanation, as it stands, but if you can get it picked up later, I'm content.

MR MACKENZIE: Thank you.

Then, professor, please, the next document is [SGH0020455]. We can see that these are the minutes of the meeting of the Blood Transfusion Service subcommittee of the Common Services Agency of 20 August 1986. Can we go, please, to page 2? About half way down we can see "Compensation of Volunteers". This is perhaps becoming important in relation to this topic because August 1986 is about the time when Z8 is being scaled up for production at PFC. We can see:

"Compensation of Volunteers. The subcommittee noted that the national medical director had held a useful dialogue with the legal adviser ..."

Would that be a legal adviser of the Common Services Agency?

A. Yes, indeed.

Q. "... concerning arrangements --"

A. That would be CLO almost certainly.

Q. CLO, I understand:

"... concerning arrangements for the compensation of volunteers and agreed that the general manager of the CSA ..."

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

Q. I see, yes, of course.

A. They are not patients.

Q. Yes:

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

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

A. That's correct.

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

We can see in the main paragraph:

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

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

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

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

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

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

Q. It is again a timing point?

A. Absolutely.

Q. Which we may come on to shortly.

A. Absolutely. Continuity of supplies.

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

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

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

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

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

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

A. Exactly.

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

A. That's it.

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

to ramp up production of Z8?

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

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

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

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

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

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

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

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

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

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

A. Yes.

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

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

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

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

A. Initially, yes.

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

Then the next item, please, is [SGH0031980]. A letter dated 7 January 1987 from yourself to Dr Ludlam. I think in short you say that while you sympathise with Dr Ludlam's position, you do pose some questions:

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

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

Then I think you also sent that letter to the other

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

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

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

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

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

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

Then, please, [SNF0013020]. A letter dated

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

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

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

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

Q. I understand, yes.

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

Q. Yes. The next item is [SNF0013022]. A letter dated 13 January 1987 from yourself to Dr Ludlam saying:

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

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

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

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

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

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

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

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

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

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

A. Sandy, yes.

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

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

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

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

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

A. John Forrester.

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

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

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

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

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

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

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

A. Treatment.

Q. Treatment?

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

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

Q. Thank you.

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

Q. Yes.

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

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

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

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

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

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

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

A. Oh, indeed.

Q. For reasons we have discussed.

A. Yes.

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

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

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

Q. I understand.

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

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

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

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

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

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

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

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

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

trials.

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

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

Q. Perhaps I could take you --

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

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

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

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

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

Do you understand the point Dr Perry is making there?

A. I think I do.

Q. Yes.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Q. Yes.

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

Q. Don't apologise.

A. That might have lasted 20 years.
Q. Please don't apologise. But I think, professor, the point being made by Dr Perry in his statement in the final paragraph is that in a way, regardless of when Z8 became available for use, if a patient had outstanding stocks of a batch of a previous product, then that would be extinguished before that patient started receiving Z8?
A. Yes, that would apply too.
Q. So certainly for patients who were not in receipt of blood products, then they would presumably receive Z8 as soon as Z8 was available, but for perhaps a patient with severe haemophilia, who had a stock of the NY 68 degrees/24-hour product, that would be used up first because of this system of batch dedication?
A. Yes, that is correct. We didn't, as we did prior to that, pull back and recall everything and start afresh.
Q. Yes.
A. We didn't have that luxury.
Q. Well, when you say you "didn't have that luxury", why was the old product not recalled when Z8 became available? Was it for safety reasons to do with batch dedication or was it because you didn't have sufficient stock of the new Z8 product?
A. I would have to assume it was the latter, sir.

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

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

Q. I understand.

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

on to say:

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

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

A. Chief pharmacist, Scottish Home and Health Department.

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

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

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

A. Oh, yes.

Q. Yes.
A. He was in Market Towers Department of Health, and he may have been his counterpart in England and Wales. It was the department from which Graham came originally.
Q. The letter is headed "Evaluation of HTLV-III inactivation in blood products from the PFC."

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

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

Et cetera:

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

The next paragraph:

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

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

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

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

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

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

Dr Perry provided a short statement, [PEN0171863]. Can we scroll down a little, please? His headline response is:

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

A slightly fuller response is then given. Also

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

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

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

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

Q. Please do.

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

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

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

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

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

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

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

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

A. Yes.

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

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

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

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

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

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

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

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

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

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

Q. I understand.

A. That's all.

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

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

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

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

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

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

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

A. I apologise. I'm repeating myself.

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

A. Yes.

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

A. That's right.

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

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

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

MR MACKENZIE: I think --

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

Q. Thank you.

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

Sir, that may be an appropriate time.

THE CHAIRMAN: Yes.

(3.08 pm)

(Short break)

(3.32 pm)

THE CHAIRMAN: Yes?

MR MACKENZIE: Thank you, sir.

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

Reading your response, you say:

"It has always been my belief that had the two

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

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

A. Yes.

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

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

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

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

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

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

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

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

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

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

A. It is. I should say --

Q. That's a wider point.

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

Q. Not literally, I think.

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

Q. It's a matter --

A. It was pretty obvious.
Q. It's a matter of common sense really, isn't it?
A. Yes.
Q. A small country to pool and share expertise, particularly when everyone is working on the same side for the National Health Service. Really, I think, it brings us back to this topic, professor: would it be fair to say that at an informal level, the fractionators north and south of the border were working with each other in terms of sharing ideas but at the more formal level, which I think was your concern, there could have been improvements made?
A. Well, could I add a rider there, that it's natural that this Inquiry has been dominated by Factor VIII and Factor IX. Even in 1975/79 these were not the big deals. In the 70s it was albumin and in the mid 80s it was IVIGG, and if you actually asked PFC -- and I asked Peter the other day -- he said he hadn't got a bit of paper with it on -- "Give me a list of all the products that you have in fact developed there," you will discover that Factor VIII and Factor IX are but two of many. If you ask, were the PFC and Blood Products Laboratory fellows with IVIGG, with the Antithrombin 3 and all the other products, buzzing like Jim and Peter were, the answer is no.

Q. But --
A. So this Factor VIII, the things that you are interested in, are really -- critically have been dependent on the chance -- what a chance! -- that Jim Smith fell out with John Watt, walked out in a huff of PFC and, thank goodness, landed in Oxford.
Q. Yes.
A. So, yes, there was lots going on but in this one region of products.
Q. In relation to the heat treatment of Factors VIII and IX?
A. Yes.
Q. Thank you. Then the next question, please, is question 8, and we raised the question of the CBLA central committee on research and development in blood transfusion, which first met on 21 June 1983. Just for the avoidance of doubt, professor, did you know about this committee at the time?
A. Yes, Harold Gunson told me about it, yes.
Q. I understand. We asked various questions about this particular committee and the first question we asked was:

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

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

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

Q. No. Yes.

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

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

You explain:

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

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

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

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

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

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

Then over the page of your statement, please, to

page 6, at the top of this page we had asked:

"Why was there no PFC representative on the committee?"

And whether that affected the development of Z8. Your response was:

"I do not know why there was no place for PFC on this committee. I assume it was for the same reason that the SHHD adviser in blood transfusion was also excluded."

To pause there, who was the SHHD adviser in blood transfusion?

A. Me.

Q. That was you, yes. Do you recall, was there any discussion at this time, back in early 1983, involving you about the composition of this committee?

A. No, I don't -- no. In short, no. But I know I wasn't on.

Q. In terms of what happened, were you essentially presented with a fait accompli as in, "This is the membership of the committee"?

A. It was CBLA's.

Q. This was their committee?

A. Their committee, yes.

Q. You say that:

"I never believed that this committee in any of its

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

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

A. As the MRC committee was.

Q. I understand. Truly a UK committee.

A. Yes.

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

A. I agree with you, yes.

Q. Thank you.

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

commercial brief of the CBLA, and your response was:

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

And one example of why you were uncomfortable was the if somebody had fallen under a bus -- the informality of the communications. I understand that point.

Then we asked question 9, whether more formal links between PFC and BPL/PFL were desirable and were such formal links eventually established. In the final page of your statement you state that:

"In my view, formal links were desirable because I believed they were in the public interest."

One can fully understand that as a matter of logic and common sense:

"However, there was sufficient evidence that they did not enjoy the support of ministers, despite the comments of directors Moore and Smithies."

I should perhaps pause just to look at this document, if we may. It's [SNB0060464].

This is, I think, a minute or a note from Drs

Smithies and Moore of the Department of Health and Social Security. The advisory committee on the National Blood Transfusion Service, central committee for research and development. I see in paragraph 1:

"Following the last meeting of this committee, proposals for a committee reporting structure from the central committee were agreed with the SHHD ... [and were also] agreed by the transfusion directors of England and Wales and by the CBLA."

In paragraph 2:

"The proposals were comprehensively rejected by Scottish transfusion directors ..."

For various reasons which are then set out. In paragraph 3:

"English ministers have previously indicated their wish to have a UK-based research committee and DHSS will therefore pursue the objective of a UK central committee at ministerial level."

I think the point you have made in your statement, professor, is that despite the sentiment expressed there, about the desire on the part of English ministers to have a UK-based research committee, I think your opinion is that -- is what?

A. Oh, my opinion was if that was really so, ministers would have stepped in to the MRC and said, "Under no

circumstances disband this excellent committee". That would be point 1. Beyond that, if you then ask the question, well, then what happened following Roger Moore and Alison Smithies's memo there; did ministers step in? Was I and my mates talked to by our colleagues in the Scottish Office? No. I mean, nothing happened until 1988. I think I have got it right. Harold Gunson writes to me again, and it seems as though we are into completely different -- and we say, "Let's try it," nothing happened again.

Q. Let's just then go back to your statement to complete that passage of evidence, if we may. We had finished off after the number 14. You go on to say:

"To the best of my knowledge, they were never established more formal UK research committee or in particular more formal links between PFC and BPL/BFL."

And you are not aware of records which demonstrate that this committee ever sponsored or commissioned any research. Is this a reference to the CBLA central committee on research and development in blood transfusion?

Then you go on to say that the same applied to the ill-fated NBTS research committee, promised in 1988. We should perhaps pause to look at that reference. That is [SNB0115050]. This is a report by Dr Gunson on behalf

of the national directorate of the NBTS in England and Wales, and the report is headed "National Blood Transfusion Service RTD committee."

What does the "RTD committee" stand for?

A. Regional transfusion director.

Q. We see paragraph 1:

"The national director of the NBTS was formed on 1 October 1988."

Could we go further down, please? Perhaps onto the next page. Professor, you had referred us to this document. Is there a particular passage in this document you wanted to take us to? If we can perhaps carry on scrolling down it.

A. I thought -- and we need to keep going -- that this was Harold -- which he sent to me saying, "Why don't we set up an NBTS research committee then?" This was soon after he took over in this directorate position in Manchester and I had assumed, when I pulled out this for you, that that was what it was partly all about. I don't see it at the moment.

Q. No.

A. We keep ...? Yes, 6.9:

"A research committee for the NBTS will be formed to coordinate research work in RTCs."

That's regional transfusion centres, and that's not

BPL/PFL.

Q. RTCs but in England and Wales?

A. NBTS means England and Wales.

Q. Yes.

A. And Harold at some point wrote to me and said, "Do you want to come in on this? You have already rejected the other thing. Do you want to come in?" And we come back -- we have got the papers somewhere, "Yes, let's give this a whirl," and nothing happened.

Q. Nothing happened. I understand. Returning to your statement, please, page 7. You say:

"Both these research committees ..."

By "these research committees", what do you refer to in your statement, professor, when you say:

"Both these research committees were in existence ..."

Which research committees?

A. The CBLA and then the NBTS.

Q. I understand:

"... were in existence at a time when the scientific challenges of the transmission of viruses by blood transfusion in the UK were formidable. As I recall, they made no contributions to this or anything else. I suggest that Dr McClelland would be a better judge of this."

So presumably, professor, in the absence of formally constituted UK committees considering the issues which arose and giving guidance, really those at the coalface had to get on and deal with things as they thought best?

A. Absolutely.

Q. And perhaps discuss things perhaps in a more informal way with each other? Thank you.

Then the last question, 10, is one in which you understandably defer to your PFC colleagues.

I have no further questions. Thank you, professor.

A. Thank you very much.

THE CHAIRMAN: Mr Di Rollo?

Questions by MR DI ROLLO

MR DI ROLLO: Professor Cash, I would like to ask you --

A. I can't hear.

Q. Sorry. I would like to ask you about the situation in relation to 8Y and Z8, contrasting Scotland and England. Could you have a look, please, at [DHF0030476]? This is an item that was distributed to haemophilia directors in England and Wales and we can see from this that general issues begin in respect of 8Y in England from the 1 September 1985, and it says:

"This high purity product ... to reduce the risk of infection by viral agents, although further assurance is sought over freedom from risk of viral transmissions."

Is what it says in the second paragraph. Then it goes on to say in the final paragraph on the first page:

"It is recognised that, until the new production unit at Elstree is completed, output of 8Y will meet about one third of current demand for concentrate and for this reason, attempts have been made to define those patients likely to benefit most from the security inherent in 8Y."

If we just go over the page, please:

"Therefore, haemophilia centre directors are being asked to compile lists of their patients considered 'at risk' and most centres have complied. It is the considered view at BPL that, where possible, liaison between the haemophilia services and the BTS should aim at directing Factor VIII-Y to these patients, using the existing framework of distribution and supply."

I think you were asked in your evidence about an awareness about the possible increased safety, if I can put it like that, that the 8Y might provide and you said you couldn't remember when you first became aware of that increased safety. Would you have been aware that this kind of direction was going out in England at this time?

A. I would think so, yes. I would think so.

Q. How would you become aware of that? Was that just

through the grapevine or would there be any more formal means of being told that?

A. It would be grapevine. It would not be formal. I would probably get it from Peter Foster. Might even get it from Chris Ludlam, but it wouldn't be formal.

Q. Right. I think if we go further on to [SNB0015469], this is another document that we have seen. If we go to paragraph 3.1. I think it's on page 4.

As I understand it, this is a report by Dr Perry, PFC, for SNBTS haemophilia directors meeting on 5 March 1986. The phrase that's used is:

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

Again, would you have been aware of that information at that time?

A. I don't know but if Bob says that we will be aware, I'll accept what Bob says. I can imagine my friend Bill Whitrow from Inverness would have said, "I have never heard of it", but, yes, I'll accept it as it's written.

Q. The situation then appears to be that there has been produced in England 8Y, which it does look as though

there is an increased margin of safety, and certain patients might benefit from that presumably, such as patients who have not previously been exposed to concentrates. You are nodding. Is that right?

A. Yes.

Q. Did anybody think at this time of obtaining some of this material, 8Y, for the use of previously untreated patients in Scotland, so that until the SNBTS programme to provide the Z8 was complete, those patients could be given that extra margin of safety?

A. I have no idea. Certainly, it's very unlikely I would because -- but the clinicians, Chris Ludlam and Charlie Forbes and so on would be perfectly at ease so to do, but it's unlikely I would and for very good reason. For every unit I took out of England, an English patient would suffer. You know, I'm not in that game.

So I wouldn't instinctively have done it.

As I recall -- and to be honest, I never understood this -- some 8Y did come up to Scotland for a short period. You can rest assured that I wasn't directly -- from what I have said -- directly involved in initiating this but no, I wouldn't -- the point that you have stopped, I wouldn't be saying, "Let's have some of this stuff up from England". I'm a great United Kingdom man myself and the people down there were in dire trouble.

Q. You say they were in dire trouble but I think the situation presumably, in one respect, would be similar in that those that had been exposed to factor concentrates wouldn't require that extra margin of safety or it wouldn't be as acute to give them that extra margin of safety, whereas they obviously are looking at restricting the supply to those that it might be useful to provide that extra margin of safety, and it does appear, I think we know, that if it had been asked for, it might have been provided, and you would have been in a position to ask the English, would you not, for that material?

A. Yes, I would, but you can be assured, I would first consult with the clinical team, Chris Ludlam and Charlie Forbes, as to whether they thought this was a good idea. But yes, I would be in a position, but actually in practice, so would Bob Perry and I have got a hunch that the little bit of 8Y that we got up, Bob got up for a particular purpose later on. Yes, I would, sure.

Q. Are you saying this didn't occur to you or it did occur to you and you decided not to do it?

A. I said twice I cannot remember whether it did or it didn't. You have asked me, would I -- I could have done those things. The fact that I didn't may have been, I have said, I can't recall, that I didn't wish to take

a safe product out of the hands of part of the United Kingdom that was in very serious difficulties and I wasn't to know -- I'm not sure many people know -- how many of -- first, how many patients there were that would fit into the high risk group that you rightly -- that needed this stuff, point 1. And I have, and I have made it evident to this Inquiry before: I was always concerned that the notion that, oh, once you have been exposed, you can have it, it doesn't matter, I have never been a great supporter of this, not for any super-scientific reason, but I have always lurked behind the possibility that second exposures and third exposures to great big plugs of virus, even although you have got antibody already, may not be very good for you. And if you look at the paper by Peter Simmonds in the Lancet of 1990, that actual issue has popped up. Christopher Ludlam is a co-author.

Q. I think we can fully understand that. Clearly it probably wouldn't be a good idea to expose someone more than once, and certainly nobody could argue with the situation that it would be less than ideal to provide that material, but there is a distinction to be drawn, is there not, between that situation and the patient who has not been treated before, because --

A. A higher priority is -- we call them PUPs, absolutely

right.

Q. So it does appear that one thing that might have been considered at least would have been to have made some sort of approach to England to obtain some of that material, until SNBTS had actually completed its programme to produce material heated to the same protocol.

A. It might, yes.

Q. The other matter I want to ask you about, professor, was the issue of compensation and Mr Mackenzie, I think, has explored this in some detail and I don't really want to take up much time about this. One thing I would like to ask you is if you could give us an insight into why it was that heels were dug in in relation to Z8 but they hadn't been dug in before, with NY. Obviously the issue was raised with NY but presumably the phase 1 trials went ahead without --

A. Pure speculation.

Q. It would be pure speculation?

A. It would, on my part, it really would, and I think on this issue very improper.

Q. Right.

A. They were not my heels that were dug in.

Q. Somebody else's heels?

A. Yes.

Q. All right. I'll leave it at that.
THE CHAIRMAN: Mr Anderson.
MR ANDERSON: Thank you, sir, I have no questions.
MR JOHNSTON: I have no questions either, sir, thank you.
THE CHAIRMAN: Thank you very much, Professor Cash. It would appear that they are anxious to let you go this evening, early.
A. Thank you, sir, very much.
MR MACKENZIE: Sir, tomorrow we have Dr Perry and Professor Ludlam.
THE CHAIRMAN: Very well, until tomorrow morning, then.
(4.10 pm)
(The Inquiry adjourned until 9.30 am the following day)

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