Wednesday, 26 October 2011

(9.30 am)

DR PETER FOSTER (continued)

Questions by MR MACKENZIE

THE CHAIRMAN: Good morning.

Good morning Dr Foster.

A. Good morning.

THE CHAIRMAN: Yes, Mr Mackenzie.

MR MACKENZIE: Sir, thank you. We turn today to a new topic, topic C3, which is the implementation of heat treatment sufficient to inactivate Hepatitis C in blood products by the Protein Fractionation Centre in Scotland in 1987 and the technical background to such implementation, including the achievement of that objective by the National Blood Transfusion Service in England and Wales in 1985.

And, sir, this topic mainly deals with Factor VIII concentrate, in particular in the period 1985 to 1987, but we will also look a little at Factor IX concentrate during that period as well.

Sir, the first witness we have today is Dr Peter Foster.

Dr Foster, you, I think, were the head of the research and development department at PFC from 1974 until the closure of PFC in 2009. Is that correct?

A. That's correct.
Q. We don't have to go back to your CV but if anyone wants to look at that, I'll provide the reference. It's WIT0030389. So in particular Dr Foster, you would have been head of that research and development department during this period, 1985 to 1987?
A. That's correct.
Q. I would like to start, Dr Foster, by looking at a table to give an overview of this subject because we will be going into quite a lot of detail and some of the details are quite technical. So to prevent us drowning in a sea of detail, it may be helpful to start by looking at document [PEN0131309].

This, I think, doctor, is a briefing paper, which you prepared on behalf of the SNBTS in I think November 2010. Is that correct?
A. That is correct.
Q. Thank you. And in table 3 you have helpfully set out some key dates concerning the development of heat-treated coagulation factor concentrates, and we have also, I think, got some hard copies of this table to help any members of the public follow this. I think that can perhaps be distributed now.

Dr Foster, before looking at the product ZHT, I think before the development of heat-treated

coagulation factors, am I right in thinking that from about the 1970s, PFC produced an unheated, intermediate purity Factor VIII product called "NY"?

A. That's correct, yes.

Q. So that's the starting product, perhaps, the unheated NY product?

A. Certainly for this period that would be the case, yes.

Q. And then when we look at the table and we see the product ZHT, does that refer to zinc heat-treated?

A. It does, yes.

Q. I think I'm right in saying the ZHT product remained essentially a research project and this product was never issued for clinical use. Is that correct?

A. It was issued for clinical use on a trial basis but it never became a routine product.

Q. I understand, and we can see under the description for ZHT, that this was a factor concentrate of increased purity, heat-treated in solution. Does that mean pasteurisation?

A. It does, yes.

Q. Yes:

"In the presence of carbohydrate and amino acid stabilisers."

And we see the objective of this product was to inactivate the agents responsible for the transmission

of non-A non-B Hepatitis, with albumin pasteurisation as a benchmark. We can see certain dates then set out, which I'm not going to go to but essentially this project took place between 1981 and 1984, roughly?

A. That's correct.

Q. I'm grateful. Then if we look in fact over the page, we can see that 24 September 1984 was the date of the preparation of the last pilot batch of this product.

A. That's correct.

Q. I think we have heard earlier that work on ZHT was suspended in October 1984 to give priority to a new research and development project, namely a collaboration with Professor Johnston of New York University. Is that correct?

A. Yes, I think we saw the two projects as really being combined at some point, because the purpose of the work with Johnston was to make the pasteurisation process easier.

Q. I see. So the Professor Johnson collaboration was really a development of the ZHT project?

A. That was the principal objective at that time, yes.

Q. And I think the Professor Johnson project has been called the NYU project. Is that correct?

A. That's correct.

Q. Standing for "New York University".

A. That's true.
Q. So that's where we are at late 1984, and then the table helpfully sets out the initial heat treatment of the existing intermediate purity NY product at the end of 1984 and then in 1985. I'm not going to cover this in detail because we looked at this in your earlier evidence on topic B3 but in short, initially NY HT1 was dry heat-treated for two hours at 68 degrees and we can see that on 10 December 1984, that product was distributed for routine use. We can see that 13 September 1985 was the last issue of that product and 27 November 1985 it was recalled. Is that correct?
A. That's correct.
Q. And then product NY HT2. Again, it's the same intermediate purity Factor VIII concentrate but with a modified formulation. I think the sucrose was added as a stabiliser?
A. That's correct.
Q. That enabled dry heat treatment for 24 hours at 68 degrees and again, the objective of this, as in HT1, was in respect to inactivate HIV virus. Is that correct?
A. That's correct.
Q. And the NY HT2 product, we can see, was issued for routine use on 4 September 1985. 13 May 1987 was the

last issue of that product in Scotland. That product, I think, was not recalled for reasons we will come on to look at in due course. Is that correct?

A. That's correct.

Q. Thank you.

Then the next product in the table is a product which really does concern us today -- and we will take a little while looking at -- and it's product Z8. We can see a description. This was a Factor VIII concentrate of increased purity. Pausing there, doctor, am I right in thinking that Z8 was more pure than NY but not as pure as the NYU high purity product you sought to develop in collaboration with Professor Johnson?

A. Yes, the NYU product, we were looking for an increasing purification of the order of 100- to 200-fold; with the Z8 we are maybe talking about two to fivefold increasing purification.

Q. I'm grateful. Returning to the table, we can see that this was a Factor VIII concentrate of increased purity, modified formulation and new freeze-drying technique, and the objective was to increase dry heat treatment to 72 hours at 80 degrees centigrade to further increase the margin of safety with respect to HIV transmission and to possibly inactivate the agents responsible for NANBH transmission.

We will come back to look at this product in greater detail but again as an overview, we can see in the dates column that 21 November 1985 was the first experiment to design Factor VIII for dry heating at 80 degrees and then 23 June 1986 refers to pilot scale trial batch of Z8; 4 August 1986, the first production scale trial batch of Z8, and then December 1986, Z8 was available for clinical evaluation. 15 April 1987 was the first routine issue of Z8.

I hope that may be of some help when we come on to look at the detail in due course.

I should perhaps add to the table at this stage a product 8Y, which we know is an English product. I think this was a high purity Factor VIII concentrate, which was dry-heated at 80 degrees centigrade for 72 hours and was routinely issued from about September 1985. Is that right?

A. Yes, that's my understanding.

Q. And going back to the table, we then look at a Factor IX concentrate. This is HT DEFIX. And this is described as an established -- so this was actually the existing intermediate purity Factor VIII concentrate with a modified formulation, and it was dry heat-treated for 72 hours at 80 degrees centigrade. And again, the objective is stated as:

"To heat the modified product as severely as possible to provide a high margin of safety with respect to HIV transmission and to possibly inactivate the agent responsible for the transmission of NANBH."

I'm not going to go over the dates there, doctor, but in short this product became available for routine issue in August 1985 in Scotland. Is that correct?

A. It was August 1985, I think, certainly in Edinburgh -- but I think supplies to the whole of Scotland weren't available until October 1985.

Q. I see. I think around that same period, August, September, October 1985, in England a similar heat-treated Factor IX product was routinely issued at around that time as well?

A. Yes, the dates in England were virtually the same as the dates in Scotland because it was a joint project.

Q. I'm grateful, thank you.

THE CHAIRMAN: Can I interrupt just briefly?

Dr Foster, when one looks at the NY HT2 that went out for evaluation in Edinburgh and Glasgow in March 1985, how extensive was that evaluation exercise? Did it cover a wide range of patients or did it tend to be concentrated? In other words, were the quantities enough for the whole population or was it selective?

A. Could you just go over that question again?
THE CHAIRMAN: Yes. If we go back to NY HT2, we see that it went out for clinical evaluation in Edinburgh and Glasgow in March 1985. Is that right?
A. That's correct.
THE CHAIRMAN: And the question is how extensive an exercise of that kind would be. Would it cover most haemophilia patients or would it relate to a few only?
A. Okay. This would be a few only and it would be for half-life and recovery studies and tolerability. Very much what would be called a phase 1 study.
THE CHAIRMAN: So one shouldn't get the impression from this that HT2 was actually widely available in Glasgow and Edinburgh before the product was issued for routine use in September?
A. No, I think it wasn't issued routinely, simply -- this is -- you will have to discuss this with Dr Perry more than myself but my understanding is it's really an issue of having stocks of material available and building up stocks, so that you do have material available to deal with crises and treatment rather than having the cupboard bare all the time.
THE CHAIRMAN: That's fine, thank you very much.
MR MACKENZIE: Thank you.
Dr Foster, simply on the question of clinical

evaluation, my understanding -- and correct me if I am wrong -- is that one can perhaps look at this as a phase 1 evaluation and a phase 2 evaluation. A phase 1 evaluation being an initial evaluation of a product to look at half-life and tolerability studies. Is that correct?

A. Yes, it's really, does it actually work in dealing with haemophilia? Does it treat the condition? That's what you want to find out in the phase 1 study, and is the product tolerated reasonably by the patients. They don't have reactions to it.

Q. How many patients approximately might be involved in this sort of phase 1 study?

A. Again, I wasn't involved in these clinical trials but to the best of my knowledge, you are talking about three or four patients.

Q. Whereas one can perhaps describe a phase 2 clinical evaluation as being a much wider study, looking at whether a product is infective or not?

A. That's correct. The phase 2 is designed to determine whether the product is free from infection, and at this time, with non-A non-B Hepatitis, people who were working with surrogate markers of hepatitis, such as ALT tests, and I'm sure you have gone to this in some detail, that there were protocols devised for this and

it did require a relatively large number of patients and batches to be studied.

Q. And may take place over a much longer period of time?

A. It would take much longer, we are talking about years to do a study of that type.

Q. Presumably, just to follow that through a little, am I right in thinking that a product would require to go through a satisfactory phase 1 evaluation before it can be routinely issued?

A. That's correct, because in a sense, if you are -- even though you haven't proven that the product is free from infection, it's superior to the earlier products. So there is an obvious benefit in bringing that forward immediately and then over a number of years determining the true safety of the product.

Q. Yes. So once a product has been routinely issued, the phase 2 evaluation can really go on for many years?

A. That's correct, yes. I think you see that with all manufacturers, who do these kinds of studies. They last many years.

Q. I'm grateful, thank you, Dr Foster. I hope that was a helpful introduction, before now plunging into the detail.

What I would like to do, Dr Foster, is turn next to your statement, please, which is page 2 of [PEN0171556].

I'm not sure, doctor, if you have a hard copy with you. If you have, feel free to refer to it.

A. I don't have one, no.

Q. If you would like one, I'm sure we could print one-off.

A. No, I'm fine.

Q. I'm grateful.

What I would like to do, doctor, is to start by looking at events in England, and if we look 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, including severe heating of the product, and when and how did the SNBTS/PFC first become aware that those in England were able to dry heat Factor VIII and IX concentrates at 80 degrees centigrade for 72 hours.

Then your response. You firstly distinguish between the Protein Fractionation Laboratory in England and the Blood Products Laboratory in England.

A. It was actually the Plasma Fractionation Laboratory.

Q. I'm sorry. Yes, Plasma Fractionation Laboratory. I'm grateful. I think that was based at Oxford?

A. That's correct.

Q. And the BPL was based at Elstree?

A. That's correct.

Q. Was there a historical reason for having two plants?

A. Well, the Oxford facility really, I think, grew out of

the treatment of haemophilia in Oxford, which is one of the places in the world where this first began, and the Plasma Fractionation Laboratory was really almost part of the Churchill Hospital, which is where the haemophilia centre was based in Oxford.

So really it has historical roots back to the 1950s, where this type of treatment was first being devised in England, whereas BPL, they were concerned more with the large volume fractions, such as albumin and antibody preparations, and it was only later on that the two kind of began to have synergy and work together, and I can't today go into the detailed history of all of that but you could perhaps ask Dr Smith about that. He might be more familiar with the early history than I am.

But in this period, PFL had become essentially the development area for coagulation factors for BPL. That's where all the R&D was being done and early, small-scale manufacture was taking place at PFL, and it was only subsequently that each product, such as Factor VIII manufacture, were transferred to Elstree after the process had been devised at PFL.

Q. In terms of geography, were both PFL and BPL based around Oxford?

A. Elstree is in North London, which is maybe 40 miles away from the Oxford facility.

Q. I see. You set out on page 1 the difference you have just explained, and at the end of the paragraph on page 1 you say:

"Manufacture at PFC in Edinburgh was much closer to that of BPL in its scale, breadth of operation and in its organisation."

So that's all by way of, I think, preamble, Dr Foster. You then say that you cannot say for certain when you first became aware of BPL/PFL's research and development work on 8Y, including severe heating of the product, but you try to indicate what you knew, et cetera.

Over the page, please. You explain that you first became aware in May 1984 that a disclosure had been made at PFL which was to form the basis of the Factor VIII development that later became known as "8Y". You refer to a letter you received from Dr Smith. This is dated 22 May 1984. Could we go to that, please? It's reference [SNB0074402]. We can see Dr Smith in the first paragraph says:

"Can I remind you of a few questions that couldn't be answered a fortnight ago concerning the Factor VIII heated in solution."

Does that suggest, doctor, that there had been some prior communication on heating --

A. Yes, we had an ongoing dialogue at this time and Dr Smith was very interested in the work that we were doing on pasteurisation, which was the ZHT development that we looked at a few minutes ago, and he was asking me more questions about that and we had given him all the information that we had but he had some further questions.

Q. Thank you. Then he says:

"Can you tell me what source of heparin was used and if it was Pularin, where you currently get supplies."

If we can go down the page, please:

"As I mentioned on the phone, we have stumbled (literally) on an intriguing alternative to zinc. I'm trying to get a Crown record entered this week and will let you know immediately I have confirmation of this."

The reference to zinc, can you explain that briefly, please?

A. Yes. In the process that we have talked about a minute ago called ZHT, we used zinc as an agent to precipitate fibrinogen to give us an increased purification, but we didn't only have zinc present, I had also added some heparin, and I was aware from work done in Canada a few years earlier that heparin could precipitate some of these proteins. I had studied the effect of heparin but I had -- I had only studied it up to the level of 10

units per ml, and the reason for that is that after that level the heparin interferes with the Factor VIII assay, and this led to difficulties with this work in Canada where the results had become very misleading because the heparin was interfering with the Factor VIII assay.

So I hadn't gone into that area. I had restricted my studies to up to 10 units per ml. And I had found that there was an effect but there was no difference between one unit per ml and 10 units per ml. So I was using one unit per ml. I didn't want to add more than was necessary. However, in giving Dr Smith this recipe with the zinc and the heparin at one unit per ml, somehow a mistake had been made in Oxford, which Dr Smith described as having stumbled, literally, where more heparin was added than had been specified. And I didn't know at the time exactly how much but now I think it was probably about 100 units they had added rather than one unit, and that gave them a higher degree of precipitation, unexpectedly, and that was what Dr Smith was alluding to in this correspondence.

Q. And when you say a "higher degree of precipitation", does that mean a more pure product --

A. It means a higher degree of purification would eventually be the case.

Q. And you also mention heparin interfering with the

Factor VIII assay. Can you just explain what you mean by the "Factor VIII assay" and where that fits in, please?

A. Yes, obviously to understand what's happening here, you have to monitor what's happening to the Factor VIII and to do that there were tests constructed which tried to simulate, in a sense, the treatment of haemophilia. You would have a solution that was absent from Factor VIII. You would simulate the clotting process and then establish the effectiveness of the material you were adding back to see how much Factor VIII was there. And there were really two types of assay used at this time to measure the Factor VIII activity. One is known as the one-stage assay and one was known as the two-stage assay, and I think there has been evidence on this earlier in these proceedings.

By far and away the standard assay around the world was the one-stage assay, and that was what we used routinely, but the two-stage assay had actually been devised at Oxford and that was what they tended to use as their routine assay. And for reasons that I'm not an expert on, the two-stage assay was less interfered with by heparin than the one stage assay, and it was because of this that Dr Smith had managed to determine that this Canadian work that was done earlier was giving the wrong

results because he was able to analyse the material with the two-stage assay and to say, "Look, you are getting wrong results here," and that was why in Oxford, when they were using this higher level of heparin, they were able to make sense of that because they were working with a different assay system that was almost unique to them and which wasn't commonplace elsewhere. It was the two-stage assay rather than the one-stage assay.

Q. I see. When you received this letter, Dr Foster, did you understand at that time that the increased heparin could result in a purer product? Was that a deduction or a conclusion you made on receipt of this letter or was that something that only became clearer later?

A. That became clearer later. When I had this letter I knew little more than it states here, that Jim had discovered what he says: an alternative to zinc. And we obviously had a telephone conversation and I have no memory of that. I only have this letter to try to remind me what took place but I'm fairly clear that I didn't at that time appreciate that this was -- involved heparin and that there would be higher degree of purification.

Q. So you weren't clear at that stage why he was asking the second sentence, the source of the heparin?

A. No, I haven't --

Q. I understand?
A. -- put one and one together there to get two, I am afraid.
THE CHAIRMAN: I don't think I'm quite following everything that's happening here.
You had given Dr Smith the recipe as you put it, including zinc and heparin.
A. That's correct.
THE CHAIRMAN: And what he says here is that he stumbled on an intriguing alternative to zinc. Now, I see that there is a scale difference between one to ten units of heparin and 100. I don't see where the substitution comes in so far. Was he leaving zinc out?
A. Yes, exactly. What he eventually decided to do was to leave out the zinc and just work with heparin.
THE CHAIRMAN: So we have a number of things really coming together in this letter. One is the substitution of a much larger volume of heparin to precipitate out the fibrinogen itself --
A. Yes, it was fibrinogen and fibronectin --
THE CHAIRMAN: -- but also leaving zinc out.
A. Fibrinogen and fibronectin are the two proteins concerned, yes.
THE CHAIRMAN: Is there anyone you know who can give us an easy and understandable explanation as to why the

one-stage and two-stage processes, assays, were different and why one was effective and the other not?

A. Dr Smith might be able to help you with that.

MR MACKENZIE: We will store that one for Dr Smith.

Dr Foster you replied to this letter on 24 May 1984. That's [SNB0074403]. In paragraph 1 you give details of the source of heparin. I don't think we have to look at anything else in that letter. Could we then return, please, to your statement? We are still on page 2. It's now subparagraph (iv). You say:

"I believe that I learned more about this research over the subsequent months. For example, during discussions with Dr Smith and Mrs Winkelman, when they visited PFC on 24 to 26 June 1984 to observe the preparation of pasteurised Factor VIII (ZHT), but also via my colleague Dr Ronald McIntosh who was in regular contact with Mrs Winkelman, who had made the original discovery at PFL."

The visit, doctor, on 24 to 26 June 1984, I think we have only recently asked if you had any records on that and I think your reply was that you have a diary entry of the visit but no other records apart from, I think, a letter from Dr Smith, sent afterwards, enclosing photographs he had taken during his visit. Is that right?

A. That's correct.
Q. I take it the letter and the photographs don't in themselves tell us very much, other than recording what was happening at PFC at the time in terms of the ZHT process?
A. It records that and it also demonstrates the continued interest of BPL in the pasteurisation process.
Q. Yes. And I think you had agreed to let us have the letter and photographs in due course?
A. Of course, yes.
Q. Thank you. We can put that into court book once we have that. Thank you.

The next paragraph you say:

"I was aware by late November 1984 that the PFL were having some success in applying severe heat treatment to both Factor VIII (8Y) and Factor IX concentrates."

You say:

"In a letter [you] received from Dr Smith on 5 December 1984, Dr Smith recorded the outcome of meetings that he had held with SNBTS staff, including [yourself], on 29 to 30 November 1984."

I think. Dr Foster we had asked you -- at least we had asked the SNBTS -- whether there were any records of the meetings, 29 to 30 November 1984. I think the answer was no. Can you explain, doctor, just stepping

back a little, there seems to have been -- we will come on to see -- quite regular visits by the English fractionators and developers up to PFC. Can you describe the nature of these visits in term of their formality, informality, record-keeping, lack of record-keeping?

A. Well, they were a mixture of meetings. In most cases they were largely informal. There were some meetings where minutes were taken but to a large extent they were informal, and of course, Dr Smith is Scottish and comes from Edinburgh and he visited Edinburgh quite often. So it was convenient for him to pop in and have a chat.

So that was really the purpose of the exercise. I'm sure I took notes at the time but they would have been maybe in a notebook that no longer exists. So as I say, there were some instances where we had minutes taken of meetings but there were not that many, but there is some correspondence and I think following these meetings Dr Smith did write to us with maybe quite a detailed letter to lay out his understanding of the discussions that we had had.

Q. I think we can go to that letter. It's dated 4 December 1984. It's [PEN0121794]. I think this letter is headed "Dog infusions of Factor IX concentrate." We can perhaps scan through it. Am

I right in thinking everything in this letter refers to heating Factor IX and there is nothing referred to in the letter about heating Factor VIII?

A. That's correct, yes. The main objective of his visit at this time was to plan this study for -- the safety study of Factor IX concentrates using dogs, which we were doing jointly.

Q. Yes. We are back to page 2 of your statement, half way down:

"Dr Smith recorded that PFL were aiming to heat-treat their Factor IX concentrate at 80 degrees for 72 hours."

And that you were intending to explore this with Factor VIII (DEFIX) from the PFC, which you did. You say you remember that when you had this meeting with Dr Smith, he explained that he had chosen to heat PFL Factor IX at 80 degrees for 72 hours in order to be consistent with the heat treatment conditions that he believed 8Y might be able to withstand. And you were also aware at that time that the ability of 8Y to withstand heating at 80 degrees for 72 hours was believed by Dr Smith and Mrs Winkelman to be due to the higher degree of purification of Factor VIII that was obtained by the 8Y process.

That last sentence, is that something that they

discussed with you, their understanding, their belief, as to why 8Y was able to withstand severe heating?

A. It's very difficult to remember that long ago exactly what was said, but certainly my memory is that that was the understanding as to why the product could withstand heating to that severe degree, which was really quite exceptional.

Q. And that was an understanding of Dr Smith and Mrs Winkelman and also yourself and those at PFC or ...?

A. Yes, I'm sure that is what everyone thought at the time.

Q. And in the next paragraph in your statement you say that you believe that by late November 1984, you were generally aware of the procedures used in the preparation of 8Y, most probably from informal discussions between Dr McIntosh and Mrs Winkelman, which Dr McIntosh had communicated to you.

Can you just explain to us, Dr Foster, where Dr McIntosh and Mrs Winkelman, and yourself and Dr Smith, fitted in in respect of the structures or hierarchies of the respective fractionation plants.

A. Yes, as you said at the beginning I was head of the R&D department at PFC and Dr McIntosh was a senior scientist in my department who reported to me and from 1984 had been assigned to work on Factor VIII developments, and in particular the NYU project, the high purity

Factor VIII project was his principal area of work.

In Oxford Mrs Winkelman had a similar role, where she reported to Dr Smith and she was primarily involved in the discovery that led to the development of 8Y, and it is actually her name on the 8Y patent alone. So she was seen as the inventor of that particular patented material, and because Dr McIntosh was really heavily involved in purification of Factor VIII with this NYU project, Mrs Winkelman was heavily involved with the 8Y project. The two were communicating and that was something that both Dr Smith and myself encouraged, and so I was really leaving this primarily to Dr McIntosh to chat with Mrs Winkelman to exchange information.

Q. Thank you.

I am going to come to the patent shortly and to ask questions relating to whether it inhibited, in any way, the exchange of information, but just to complete the sequence, I think the next item we should look at is a letter dated 7 January 1985. This is [SNB0074732].

It's a letter, if we go to the bottom of the page, please, and then over the page, from Professor Cash. If we can go back to page 1, please, we can see it's a letter to Dr Perry, and Professor Cash says:

"Dear Bob, at the recent meeting at BPL, I had the opportunity of meeting with the BPL team (after the

meeting with the haemophilia directors). The following points emerged which will be of interest to you and your team ... "

Then under "heat-treated Factor VIII", letter (b) it's stated:

"BPL plan to trial (in the next 3 to 4 months) their heat-treated product. Their initial product was dry at 60 degrees celsius for three days but they now plan to have 70 degrees celsius (dry) for one day. I had the impression that some of these batches can't stand these temperatures."

To pause at (b), is that perhaps a reference to the intermediate purity BPL product?

A. Yes, paragraph (b) is very much about the established BPL product that was the equivalent of our NY product, and they are examining heat treatment of that in the same way that we had introduced this very quickly in December 1984. At the same period, based on the same knowledge of the disparity in activating HIV, they were also looking at heat-treating their existing product. But in the event they didn't take that approach and they moved instead, after a period of time, to introducing 8Y.

Q. Thank you.

Paragraph (c):

"They don't plan to consider wet heat unless dry is shown to be inadequate."

Then (d):

"They appear to be well advanced in the production of a very high purity product."

Is that 8Y?

A. Yes, that would be 8Y.

Q. "They are not involved with the Alan Johnson techniques. Their method will be patented in due course and SNBTS will have free (Crown) access at that time."

Can we just go over the page, please? There is nothing further we have to look at there. Did you receive a copy of that letter, Dr Foster? Can you remember?

A. I think if you look down, I think my name was there.

Q. I see. Is that on page 1 or ...? Back to page 1 perhaps. We can see under the stamp on the bottom right-hand corner. I see.

So your name appearing there means that you received it, particularly the tick beside your name?

A. Yes, the writing is actually Bob Perry's writing, the tick is mine. It shows that I received this letter.

Q. Does a tick signify your receipt of it?

A. It does, yes.

Q. I'm grateful.

Is what is set out in that letter consistent with your understanding at the time from your various contacts with Dr Smith and others?

A. In terms of item (b) that we talked about, I didn't have that amount of detail about what BPL were doing with their existing product but I did know, in terms of paragraph (b), that they at Oxford were working on this higher purity product which became known as 8Y.

Q. I'm grateful.

I think the next item we should look at is a memo from Dr Smith to yourself dated 14 February 1985, and that is [PEN0171369].

Dr Foster, take a minute or two to look at this memo. What I'm unclear about is whether this relates to the English intermediate purity Factor VIII or whether it relates to the high purity 8Y.

A. It relates to neither. It relates to another project that was underway at Oxford -- in fact it was BPL here -- which was another method for achieving a very high degree of purification, and "AH" stands for aminohexyl chromatography, and it's a type of chromatographic purification which BPL were exploring, which in some ways had similarities to Dr Johnson's approach. So they were also investigating that kind of possibility.

Q. I see. And did this product ever proceed to routine issue?
A. No, I don't think so.
Q. I see. So it's not really relevant in looking at the development of 8Y?
A. No.
Q. Other than it's perhaps of interest to see at the top of the letter, the top of the memo, the contents of this document are "Confidential to the addressees and those who need to know". And various individuals, including yourself, are named. I suspect you won't know but do you know whether a patent application was filed for this development?
A. I don't know.
Q. No. I think we can just put that memo to one side in that case. Could we then look at [PEN0171372]? This, Dr Foster, is a copy from your diary, and on 19 February 1985 we see the word "Jim". I think that's a reference to Jim Smith?
A. I think it is, yes.
Q. The only reason I have brought this up, doctor, I think, is that at the very end of the briefing paper is quite a detailed chronology and I think there is reference there to you having met Dr Smith on this date. I think we had asked were there any records of that meeting, and

you explained you had a copy of your diary, but no other records, I think. Do you have any recollection of that meeting?

A. I am afraid not, no.

Q. No. Can you hazard a guess or an informed speculation as to the sort of the things you may have discussed?

A. Yes, I think the area we were -- at this point in time we were primarily -- and I was primarily concerned with introducing heat treatment of Factor IX, because we already had heat-treated Factor VIII in place to deal with HIV but we hadn't achieved that yet with Factor IX. We were doing this jointly with Oxford, and it was working out how to progress the safety study in dogs and we were working out a schedule to do that to try to get this through as quickly as possible, and I think that's what we were talking about here primarily.

Q. So the primary focus of this meeting would have been heating Factor IX, albeit it may have provided an opportunity for informal discussion of Factor VIII?

A. As you can imagine, that was the situation. We would have a primary objective but we would be chatting and talking about whatever else was of common interest.

Q. I'm grateful.

I think, if we then, please, return to your statement at page 3, we will come on to the actual

patent application of 8Y now. On the top of page 3 you say:

"The patent application for 8Y had been filed on 5 March 1985."

You explain that in the application:

" ... the resultant Factor VIII concentrate (8Y) was described as suitable for heat treatment, either by pasteurisation at 60 degrees centigrade for 10 hours or dry heat treatment at 70 degrees centigrade for 24 hours."

You go on:

"It is most probable that the suitability of 8Y to withstand dry heat treatment at 80 degrees centigrade for 72 hours was added 12 months later, as further information can be added to a patent application within the first 12 months of an application being filed, but is normally done at the 12-month point."

Could we look at the patent please? It's [SNF0011091].

We can see on the top left that the inventor is L Winkelman, that we heard about earlier, from PFL and the short title is "Separation of Factor VIII". Can we perhaps go to the bottom right-hand corner of the page? We can see the date is 5 March 1985. Can we go back to the resume, please? I'll just read the resume:

"This invention relates to a method of purifying the protein antihaemophilic Factor VIII from the blood plasma fraction cryoprecipitate by adding at least 0.15mg [heparin] ... "

I think that word should be "heparin"?

A. It should.

Q. "... per ml of the fraction to precipitate out the unwanted proteins of fibrinogen and fibronectin. After separating out the precipitant, the supernatant may be pasteurised to inactivate any viruses present, and then may be further concentrated by a series of known steps to produce freeze-dried Factor VIII concentrate."

Et cetera. The short title, "Separation of Factor VIII", is that essentially a reference to purification of the Factor VIII?

A. Yes, that would be what was meant by that.

Q. So the focus there is really on purification?

A. It is, yes.

Q. And perhaps interestingly, in the resume we saw the reference to the supernatant may be pasteurised. So again, at least from the resume, there appears to be a focus on pasteurisation, ie wet heating, rather than dry heating. Is that fair?

A. That's correct.

Q. And if we then go, please, to page 5 of this document, we can see what is said about heating. About half way down, we can see the sentence:

"Pasteurisation is an especially important step because it inactivates potentially harmful viruses which are transmissible by blood, (eg hepatitis viruses), and which are carried over into plasma fraction, such as cryoprecipitate. A typical pasteurisation step consists of heat treatment in solution at 60 degrees centigrade for 10 hours."

So an initial reference to pasteurisation. Can we then go down to the last paragraph on this page:

"Two other known methods of preparing heat-treated concentrates of Factor VIII, with the intention of inactivating blood-borne viruses, have been found to be most successful after efficient removal of fibrinogen and fibronectin by precipitation with heparin.

"(a) Factor VIII is precipitated from the heparin-containing supernatant by addition of high concentrations of glycine and sodium chloride, and the precipitate redissolved in a small volume of buffer solution. After desalting by gel filtration, the solution is sterilised, freeze-dried and heated in its final container to temperatures of at least 70 degrees centigrade for at least 24 hours, with little or no loss

of Factor VIII activity or solubility."

Option (a), Dr Foster, I have just read out, is that a reference to dry heating?

A. It is, yes.

Q. Is that essentially the process or the step which was followed for 8Y, as it turned out, in due course?

A. It is, yes.

Q. Albeit, I think, the 8Y, certainly come its issue in September/October 1985, had been heated or was being dry-heated at 80 degrees or 72 hours?

A. That's correct.

Q. But looking at least at this patent, that higher degree of heating appears to have been a later development?

A. It was a later addition to the document.

Q. Yes.

A. But I think before, when this document was submitted, they were already, obviously, having some success with that approach.

Q. I see. Option (b) I won't read out but I think that's a reference to another form of pasteurisation or wet heating?

A. That's correct.

Q. So that's the patent and we can put that to one side.

THE CHAIRMAN: Does this effectively reflect the importance attached to purification in the process in the minds of

Winkelman and others at that time?

A. I think it does, indeed, yes.

THE CHAIRMAN: Not only is that the inventive step but it really draws one's attention to what they thought was significant in the way they were approaching the preparation.

A. I think that's very much the case, yes.

THE CHAIRMAN: And that becomes very interesting for you later on.

A. It does.

THE CHAIRMAN: Yes.

MR MACKENZIE: Thank you.

Dr Foster, I don't suggest you will have seen this at the time but I'm setting out the English chronology so it may be helpful if I just put it up now, if I may. This is document [DHF0015326].

We can see, top left-hand corner "In Confidence", the top right-hand corner, "CBLA", which I think suggests it may have either come from or gone to the Central Blood Laboratories Authority in England, and we can see it's headed "Licensing Arrangements for Heat-treated Factor VIII and Factor IX". If we can go over the page, please, we can see the date of the document. We can see it's dated 19 March 1985. If we can go back to the first page, please. I take it,

doctor, you didn't see this document at the time.

A. No, I haven't seen this until relatively recently.

Q. Thank you. I appreciate that. It's simply, I think, that it gives a helpful picture of what was happening in England at this time, which is why I would like to read it, if I may. We can see "Factor VIII" at paragraph 1:

"Intermediate purity, code HL(H)."

The document states:

"This product is a stop gap pending satisfactory clinical information from the trials on product VIII-Y, the new high purity heat-treated Factor VIII. If the current programme remains unchanged, the last HL(H) product was produced at Elstree during the first week of March."

We can see that:

"One hundred vials of HL(H) concentrate have been issued to determine safety and efficacy in named patients."

Is that essentially the phase 1 clinical evaluation we discussed at the outset?

A. Yes.

Q. "The first reports of these infusions are being received, indicating the product is well tolerated ... a licence application ... will not be made."

Paragraph 2 "Factor VIII-Y". The document states:

"Factor VIII-Y has now been released to selected haemophilia centres for a trial to determine safety and clinical efficacy in named adult patients."

Again, the phase 1 evaluation. Is that right?

A. That's correct.

Q. "Following clinical information, the trial will be enlarged to determine whether heat treatment has inactivated non-A non-B Hepatitis virus and HTLV-III."

So that's then the phase 2 evaluation?

A. That's correct.

Q. "We would anticipate that information on the process efficacy of heat treatment for the inactivation of hepatitis viruses is not likely to be available for a year."

So this document is dated March 1985. They really suggest that it may not be until March 1986 that that information on inactivation of hepatitis viruses is likely to be available. Reading on:

"Following completion of the first part of the 8Y trial determining safety and efficacy ... an abridged licence application will be developed and it is expected that this will take place at the beginning of May 1985. General distribution of 8Y is likely to commence by June 1985 and it is hoped that a satisfactory response to the abridged licence application will have

been received by that time."

Doctor, I appreciate you haven't seen the document until now. Were you aware of the state of play, if I can put it that way, at this time in March 1985 in respect to where England were with their intermediate purity heated Factor VIII and their high purity, severe heated 8Y?

A. At that time, my understanding was that they hadn't taken a final decision and that they were looking still at the option of possibly heating and releasing the heat treatment of their existing product in the way that we have done, but they were also considering the possibility of 8Y, and I didn't at that time know what decisions they had taken.

Q. Thank you.

Could we return now to your statement, please, at page 3? In the second paragraph you explain that:

"Mrs Winkelman and her colleagues from PFL/BPL visited PFC on 27 March 1985 to discuss the heat treatment of coagulation factor concentrates and I remember asking her about the strategy for the introduction of heat treated Factor VIII at BPL. She indicated to me that a final decision had yet to be taken between dry heating the established BPL Factor VIII ... "

If that the intermediate purity product?

A. That's correct.

Q. "... at 70 degrees centigrade for 24 hours or attempting to implement 8Y with dry heating at 80 degrees centigrade for 72 hours."

You say you were aware:

"... at this meeting that the 8Y process had been performed successfully at PFL but you regarded its satisfactory transfer to BPL and acceptable clinical performance of batches of 8Y prepared at BPL as being important milestones in determining the success of the project."

Can you perhaps just explain a little what you mean by "its satisfactory transfer to BPL and acceptable clinical performance of batches prepare at BPL"?

A. Yes, as I mentioned at the beginning, PFL was a relative small facility. It prepared relatively small volume batches of product. So it was really a developmental unit. The real test of a product is whether it can withstand manufacturing at full-scale, at large-scale, and that test would only happen when the procedure was transferred to BPL and you actually ran a number of batches to see if actually you got the same performance. Did you get a product that could be heated? Did you get an acceptable yield? Did you get that routinely? You

wouldn't get that information until you went into large-scale manufacture and you only get that at BPL. That would be the situation at PFC. We saw ourselves as being closer in scale of operation to BPL.

Q. You refer to the visit by Mrs Winkelman and colleagues on 27 March 1985. Again I think there are no contemporaneous notes or records of that meeting. We did ask.

A. No, that's correct. As I said, I might have made some notes but they no longer exist.

Q. Again, what is likely to have been the main focus of discussion at that meeting?

A. Well, there was Mrs Winkelman and I think also Dr Feldman was with her, and Mrs Winkelman focused very much on Factor VIII and Dr Feldman focused on Factor IX. So we would have covered both products in the discussions.

Q. I'm grateful.

A. Certainly Mrs Winkelman's presence shows that there was a lot of discussion about Factor VIII.

Q. I understand. Could we then, please, look at the next item, which is [SNB0075071]? This is a letter dated 17 April 1985 from P A Feldman, a project scientist at PFL, to yourself. I think this in fact confirms what you said, doctor, because Dr Feldman says:

"On behalf of Lowell, Greg and me, belated thanks for your time in discussing Factor VIII/Factor IX and for showing us around PFC the other week. I hope my eyes were not too obviously an envious green while seeing the benefits of a purpose-built laboratory, especially considering the expansion of the place since my visit seven years ago."

Reference to the dog trials on heated Factor IX. What does Dr Feldman mean by his reference to his "eyes not too obviously an envious green"? What's that about?

A. We had constructed an extension to PFC in the early 1980s, which included a relatively large pilot plant facility -- that's what we called a pilot plant facility -- for large-scale research, and at Oxford they didn't have anything as modern as that. It was a very old facility. So I think he was envious that we had this new laboratory and he was working in this very 1950s, rather ancient, facility.

Q. I understand. Then, returning to the patent, could we look, please, at [SNB0075065]? We will see this is a letter from Dr Smith to yourself dated 11 April 1985:

"Dear Peter,

"I enclose at last a copy of our 8Y patent specification. We have spoken briefly about what we aim to do with the product and how it has been scaled up

but, of course, you will be welcome to full details of its performance if you would like to visit us on a Tuesday."

And reference to Factor IX. Was this the first time you saw the patent, Dr Foster?

A. It would have been, yes.

Q. Can you remember, when you read the patent -- I assume you read it with interest.

A. Yes, of course.

Q. Did it contain anything new, any surprises to you, or what?

A. Well, there was new information. There were details that I hadn't had before. I had known from the communications between Dr McIntosh and Mrs Winkelman of the general nature of the process, that it involved a high amount of heparin and they were getting a high degree of precipitation and they had decided to leave out the zinc. So I had a general, reasonably good, idea of what the process was. But the patent gave us more detail in terms of exactly what the quantities were and the steps in order and how they were performed.

But, in terms of being of great interest to us, I must point out at this time we were heavily working on the purification process with Dr Johnson, which offered a much greater degree of purification than was being

obtained by this process, and the fact that it used the heparin that I said earlier was very awkward for us because of the assay systems, it wasn't particularly attractive to us to investigate the 8Y process at that time.

Q. And did receipt of the patent cause you to alter your research and development work in any way?

A. No, it didn't.

Q. This is a hypothetical question: if you had received the patent earlier -- I don't know, some time in the second half of 1984 -- is it likely that you would have altered your research and development work in any way?

A. No, it wouldn't.

Q. Can you explain briefly why that would have been?

A. Because, as I have said a couple of times, this high use of heparin wasn't something that was compatible with our operation, so it wasn't attractive. The other steps in the process, mostly had actually been taken from our work in the ZHT process. So we were already familiar with them and we had done a fair amount of work ourselves. So there was not a great deal of new technical knowledge here for us. We were at that time targeting a much higher degree of purification because that's what I wanted: to make the pasteurisation process much easier to operate at a large-scale.

Q. It's an oversimplification on my part, I'm sure, but the use of heparin in 8Y was a negative factor for you?
A. Yes.
Q. But on top of that you had what you thought was a more promising or better process, ie the NYU project?
A. At that time -- I mean, the objective was to have a product that was safe from non-A non-B Hepatitis, and at that time pasteurisation was the front runner in terms of the knowledge that existed, in terms of what might be safe, and in order to make that process work in our production operation, I wanted to increase the degree of purification so that I could reduce the volume of pasteurisation by maybe 50- or 100-fold, and the Johnson process would allow me to do and that's why we gave priority to that at that time.
Q. Yes.
THE CHAIRMAN: Dr Foster, I appreciate that you have said that you can't give an over-technical answer to the question of the difference between the one-stage and the two-stage assay. What was it, however, about the assay process that made it inflexible? One might think it's just a test. Why not just drop the single stage assay you were using and substitute another? Was it built into the process in some significant way?
A. It was built in in the sense that you have to monitor

the process at every step to see what's happening to the Factor VIII and to know what you have got. And obviously you do that during -- in research you depend entirely on that, and in the manufacturing process there are many samples taken to monitor what's happening to the Factor VIII and whether you have achieved the amount that you need, and you have to know that to be able to put the right amount in the vial at the end of the process. So the assay is absolutely critical and if there is some interference with that and it's giving you misleading results, you are ending up with something that's incorrect in the final vial.

THE CHAIRMAN: But in effect, you couldn't simply substitute the English, two-stage assay, for your single assay?

A. Both of these assays are highly specialised, skilled techniques and the two-stage assay was much more complicated than the one-stage assay, and it needed people who had, I think, considerable experience and knowledge of this type of approach to carry it out reproducibly, correctly. From my point of view, we could have attempted that at PFC but it would have been a diversion. We would have spent months, possibly years, trying to integrate this new assay, when we could have been spending the time developing a safe product.

THE CHAIRMAN: It's important for us to get a measure of the

difficulty, since superficially one might think, "Well, it's engineering after all, substituting one process for another".

A. The second aspect of this two-stage assay is that it was much more laborious and therefore you got less for your money, if you like. So it would actually have slowed us down even if we had managed to do it immediately. It would have actually slowed us down because we would have got fewer opportunities to do assays, and I think you come upon later on, assays being a limiting factor, the number of assays you can perform.

THE CHAIRMAN: Yes, thank you.

MR MACKENZIE: Dr Foster, going back to something you said in your evidence in respect of the NYU project, that you wanted to increase the degree of purification, so you could reduce the volume of pasteurisation. Why did you want to reduce the volume of pasteurisation?

A. The pasteurisation step involved adding very high concentrations of a carbohydrate, which was basically almost like making jam and doing that in very large volumes, maybe 100 or 200 litres, it took a long time to heat up and a long time to cool down. It was very difficult to process that in a pharmaceutical facility, where you are trying to keep everything clean and free from bacterial contamination, and to make that step

easier, if you could do that in a 1 litre or 2-litre volume, rather than a hundred litre volume, it would have been a much more technically simple process to carry out and that was the target I was aiming for. And by having the increased purity, you can concentrate the Factor VIII to a much smaller volume, so you can do the pasteurisation in a relatively small volume, instead of a relatively large volume.

Q. Yes. Having a smaller volume for pasteurisation, that was essentially to make manufacturing easier than thinking that would make the degree of inactivation better?

A. It would be both. It would make it much easier to perform the process routinely in production but also it means that you can control the heat, the amount of heat, that you are putting in and the time of heating much more accurately, instead of having a long heat-up phase and a long cool down phase, which would destroy Factor VIII. You were trying to avoid destroying Factor VIII so you wanted to have more precise conditions.

Q. Smaller volume would give one greater control over the heating process and heating parameters?

A. Exactly.

Q. I understand.

Could I move on, please, to a document [PEN0171374]. This is again a diary entry, doctor, for 26 April 1985. Again, the only reason I bring this up is because I think it's mentioned in your chronology and the briefing paper, and we asked if there were any records of this meeting. I think you said there weren't but we can see you produced your diary and Friday 26 April, Jim, again, Dr Smith, appears.

A. That's correct.

Q. Would this have been one of these sort of informal meetings you mentioned before?

A. It would be very much like that, yes.

Q. It may just be speculation but can you remember what you discussed or even take an informed guess at what you are likely to have discussed, given the context?

A. I think very much, as with the previous meeting, the main focus here would be Factor IX concentrate because the principal objective was to have a heat-treated Factor IX, which we still hadn't achieved, and that was the situation also with Oxford; they wanted, obviously, heated Factor IX as well. So my guess is that that would have occupied most of our time trying to progress that as quickly as possible, but we would have certainly talked about Factor VIII as well.

Q. Thank you.

Again, I'm going to look at one or two documents just to complete the picture with what was happening in England at this time. Could we, please, go to [DHF0019576]. This is an annual report from the Blood Products Laboratory and the PFL. If we go to the top of the page, please, we can see it's stated "Commercial in Confidence", and it's a report for the period for 1984. If we go to the bottom of that page, please, over on to the next page, this is from the director -- is this the director of BPL, do you think?

A. I guess that would be the case. Dr Lane.

Q. Dated April 1985. I should ask you, Dr Foster, did you receive these annual reports at the time from down south?

A. No, we have never received these annual reports.

Q. No, I think we can see in the middle of this page it's stated:

"The report is from the director of BPL/PFL to the CBLA and is confidential."

So there is perhaps no assumption that you would have seen it. Anyway, if we can go on to the next page, please, I think it is quite helpful in, I think, setting out what was happening in England. The next page again, please. I think one more page, please. Yes. Can we look at the third paragraph? It states:

"Heat treatment of Factor VIII has been achieved and implemented on schedule. The programme has coincided with the development of a new, high purity product, designated 8Y, which is capable of maintaining satisfactory yield from fresh-frozen plasma. The product is undergoing satisfactory clinical trial and production has been scaled-up successfully at BPL. No intermediate concentrate is now being made."

It's the reference, Dr Foster, to "production has been scaled-up successful at BPL". Is it a reasonable inference, do you think, that as at the date of this report, April 1985, production of 8Y had been fully scaled-up at BPL or is that an inference we shouldn't or should be cautious about making?

A. I'm not really in a position to answer that. All I know is from the records, that BPL started issuing product routinely in the middle of September and they didn't issue it before that. So exactly what stage they had reached when this document was written, I'm not able to comment on.

Q. I understand. We can ask Dr Smith perhaps on this. Thank you.

Again, to complete the chronology of what was happening in England, could we then, please, look at document [DHF0030476]? This is a document dated

24 July 1985 from the Blood Products Laboratory and we can see it's an information sheet. In short, I think, on 8Y. Do you remember, doctor, would you have seen this at the time?

A. I don't remember seeing this at the time, no.

Q. Yes. Have you seen this at some stage in this Inquiry?

A. I think I have seen it amongst some papers in the last couple of years but I can't be certain when.

Q. Thank you. I say again, my main purpose in referring to this is simply to complete the chronology of what was happening in England at the time and we can see, reading the information sheet, that:

"As reported in the information sheet (May 1985), a new Factor VIII concentrate (type 8Y) is now replacing the intermediate specific activity products HL(H) and 8CRVH. General issue will begin from September 1st 1985."

We can see:

"The product has been dry-heated at 80 degrees centigrade for 72 hours to reduce the risk of infection by viral agents, although further assurance is sought over freedom from risk of viral transmission."

We can then see:

"Safety and efficacy trials of the 8Y concentrate are already proceeding at several haemophilia centres.

As of 1 July 1985, eight patients receiving 14 infusions ... "

That again, perhaps, doctor, is consistent with what you told us at the outset, that phase 1 evaluation would involve.

A small number of patients. We can then see:

"Clinical trials at six haemophilia centres are in progress to gain evidence of reduction or elimination of viral transmission and several patients have safely passed the point at which first evidence of NANBH virus transmission would normally occur with unheated Factor VIII."

Down the page, please, the final paragraph states that:

"It's 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."

Over the page, please, we can see in terms of how the product is to be distributed to which patients; it's stated:

"Therefore, haemophilia centre directors are being asked to compile lists of their patients considered 'at

risk', and most centres have complied. It's 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. Haemophilia patients who are HTLV-III Ab negative and have no history of hepatitis are being identified as suitable persons to comply with the clinical trial requirements."

So that was issued at the time, doctor. I think I could now return to your statement, please, and if I can finish this one paragraph in your statement, I think that will be a suitable break. We will then go on to a different matter after the break.

Can we return to page 3 of your statement. Half way down, you say:

"I do not know precisely when I learned that PFL's 8Y process had transferred successfully to BPL."

I think that's something we can ask Dr Smith:

"A meeting was held at PFC on 27 August 1985 which was chaired by Dr Cash and attended by Dr Smith and Dr Snape (BPL head of quality) to review heat treatment of Factor IX concentrates."

So that meeting is about Factor IX:

" ... but it is probable that we were also advised

1 informally of progress with 8Y at BPL at this time.
2 However, as the first batches of 8Y prepared at BPL were
3 not issued until 19 September 1985, clinical experience
4 of 8Y manufactured routinely at BPL would not have been
5 available."
6 This meeting was about Factor IX, doctor, but you
7 say it is probable that you were also advised informally
8 of progress with 8Y at BPL. What I wonder, at your
9 meeting on 26 April with Dr Smith, is it equally
10 probable that you would have been advised informally of
11 progress with 8Y at BPL?
12 A. I think it probably is the case, yes.
13 Q. But to be fair, you are saying, when asked now, you do
14 not know precisely when you learned that --
15 A. No, I mean, it was a very long time ago and I can't
16 really remember the conversations that we had.
17 Q. I understand that.
18 Sir, that may be a helpful point to stop.
19 THE CHAIRMAN: We will have a break at that point.
20 (11.02 am)
21 (Short break)
22 (11.25 am)
23 MR MACKENZIE: Could I now turn to question 2 in your
24 statement, and that's at page 4. We can see we asked
25 the question:

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

I suppose at the outset we should perhaps recognise that it depends what one means by "likely". As lawyers we tend to use the word "likely" as meaning a balance of probabilities, ie something over 50 per cent. So a 51 per cent chance of something happening to a lawyer means "likely", but I think I'm right in saying that, for a scientist, the word "likely" may have a slightly different meaning, in that a scientist may seek something achieving scientific certainly, ie something closer to 100 per cent. Is that generally fair, that distinction?

A. I think in science we tend not to use words like "likely", and in trying to make a product safe, I think it's either safe or it's not safe. So you are then dealing with uncertainty. I think you have to look at the information that's available and make a judgment on whether that's promising or not and the degree of promise that's held out, and that's really how I would have looked at it.

Q. Yes.

THE CHAIRMAN: We can spend a lot of time having a wonderful debate about that answer you have just given. I'm not

sure that it would take us anywhere. Certainly lawyers tend to look at probability but, of course, they recognise that probability doesn't come with an absolute level of assurance, that probability varies depending on what you are looking at and what you want. But in the case of a safe product, I can see that your objective is to exclude all known or foreseeable risks associated with the product. I'm not sure how you ever get to absolute certainty that it's safe.

A. You build up confidence over a period of time.

THE CHAIRMAN: You are still using your best judgment on the basis of the information available.

A. You are, yes.

THE CHAIRMAN: So it is that level of confidence that is compatible with current knowledge but can't exclude risks that may yet emerge in the future.

A. Yes, very much the case.

THE CHAIRMAN: It's tempting to go on.

PROFESSOR JAMES: Could I just add one small thing? You would use tests of probability. So if you do a clinical trial, for example, you would use a test of probability -- there is a probability of less than 5 per cent that such an event would occur, or less than 1 per cent or less than 0.001 per cent, and at that juncture you might say, "Well, that's pretty well

certain". That's the way, actually, things develop, isn't it?

A. That's quite right, and not just clinical trials but also all the experimental data would be analysed that way.

PROFESSOR JAMES: So that's the degree of probability. It's not that it's probable as in a legal sense, but it's probable as in a statistical test of probabilities.

A. That's correct.

THE CHAIRMAN: As I say, we could go on.

I do remember Lord Justice General Emslie pointing out that probability varies and that some events are more probable than others. But I think that we get the measure, Dr Foster, of what the scientist has to do to carry out his duties to the public. Thank you.

MR MACKENZIE: Thank you.

What I would like to do, Dr Foster, you started your answer with an event in May 1986 but again this is our first opportunity to set out the English chronology of what happened. So could I perhaps start with an event which you may not have been aware of but I would like to bring up on the screen, please. It is 9 July 1985. We should bring it up. It's [PEN0161142].

These are the minutes of the sixth meeting of the Central Committee for Research and Development in Blood

Transfusion. We will hear more about this committee in due course and its exact status but I think, essentially, it seems to be an English committee. We do know, though, that Dr McClelland was a member of this committee and that there was also an SHHD representative as an observer. Dr Foster, were you aware of this committee as at July 1985?

A. No, I wasn't.

Q. When did you first become aware of its existence?

A. Probably when I saw these documents produced by the Department of Health on their website.

Q. As part of their freedom of information disclosure?

A. That's correct.

Q. I see. Looking at apologies, we can see that in fact at this meeting apologies for absence were received from Dr Forrester of the SHHD and Dr McClelland. So they weren't present. I should also say that in the top left-hand corner, again I see the words "In Confidence", but if we, please, could go to page 3, we see what is said about 8Y and in particular its safety.

About half way down, in the second paragraph, starting in the second last sentence of that paragraph, it states:

"The new concentrate (8Y) now being introduced in England and Wales has been dry-heated in the final vial

at 80 degrees for 72 hours."

The next paragraph:

"The concentrate is now in full-scale production at BPL ..."

Et cetera. The next paragraph:

"The immediate safety and efficacy of the 8Y concentrate have been demonstrated by clinical trial."

Then the next bit:

"Evidence for reduction or elimination of viral transmission is being sought after infusions in haemophiliacs who have been treated with concentrate, either for the first time or after a long interval, and who are thought to be susceptible to infection with Hepatitis B, NANBH and HTLV-III. This trial is at a critical stage, but several patients have already safety passed the point at which the first evidence of NANBH transmission would have been expected. An application is being prepared for a product licence 8Y, with only provisional evidence of reduced infectivity; this may be granted in November."

I appreciate, Dr Foster, you weren't aware of these minutes, indeed this committee, as at July 1985 but this question of the clinical evaluation of 8Y in particular, with the phase 1 and then the phase 2, were you aware of the clinical evaluation of 8Y in 1985 and, if so, when

and how?

A. I would say I was generally aware from my conversations with Dr Smith that these clinical evaluations had begun and I would -- although I did not have this information, I would have been taking the view that no news was good news. I would have expected that if there had been evidence of infection, that we would have heard of that and that in the absence of being told that, the results would be looking promising, but how many patients and how much data they had and the quality of the data would obviously have to be examined, to see how meaningful it was and we didn't obtain that for some -- over some months after this point.

Q. Again, a hypothetical question, if I may, doctor, if you had been sent a copy of these minutes and if you had seen this sentence:

"The trial is at a critical stage, that several patients have already safety passed the point at which the first evidence of NANBH transmission would have been expected."

If you had received that information, say, in late July 1985, is that likely to have caused you to alter your R&D work in any way?

A. It's really difficult to answer that. I think, as I said a minute ago, I was assuming no news is good

news; therefore, the patients in the study would still be free from hepatitis. What I would have been aware of is that the material being tested would have been manufactured at Oxford and these are relatively small pool products and this is not the full-scale routine manufacture you would get at BPL. So I would perhaps be more interested in seeing the results from products manufactured at BPL.

Q. I understand. If I may then put that to one side, please and turn to the next document, which is [PEN0161152]. These are the minutes of the next meeting of this committee on 19 December 1985. We can see that Dr McClelland was present and Dr Forrester of SHHD was in attendance. Could we, please, go to page 2, paragraph 14.3? There is a short update on heat-treated Factor VIII. It states:

"Dr Rizza reported upon further trials carried out with heat-treated Factor VIII, which he had now been using for approximately nine months. He confirmed that none of his patients, including children, had become clinically ill and therefore the immediate signs were encouraging."

Again, doctor, I take it that you didn't receive this minute at the time. Were you aware of the information I have just read out, at the time?

A. No, I wasn't aware of that. But what I would like to add is that prior to this, in August 1984, I had attended the congress of the International Society of Blood Transfusion, where data had been presented by the company Behring on their studies of safety they thought they had achieved with their pasteurised product, and they were severely criticised by the medical community, in particular Professor Mannucci, and that led to the development of a very strict protocol that people had to follow, and so I would be interested in knowing the extent to which that protocol had been followed in these studies.

Q. Is that a reference to the ISHT protocol?

A. That's correct.

Q. We will come on to that in due course.

Again, in looking at what is said in this minute, we don't, I suppose, know whether the product under evaluation was produced by PFL or by BPL.

A. What's the date of this meeting?

Q. This is December 1985.

A. Yes -- that's probably correct, you wouldn't know where the product had come from.

Q. Yes. Could we then, please, look at the next document, which is a PFC document. It's [SNB0015469]. Can we go to the last page of this document, please? We can see

this is a document by Dr Perry, dated 10 January 1986. Can we, please, then go back to the first page? We will see from its title it's a report for a meeting in March 1986 of the haemophilia and SNBTS directors, and if we could, please, then go to pages 4 and 5. We will come back to look at this document in a little more detail later, when we come to look at events in Scotland but sticking with England, could we see the paragraph just appearing at the bottom of this screen:

"Directors will be aware that the Blood Products Laboratory are currently issuing a Factor VIII product which had been heated at 80 degrees for 72 hours and preliminary clinical data indicates that this material is non-infective with respect to HTLV-III."

Were you aware of the preliminary clinical data on the evaluation of 8Y at that time, doctor?

A. No. No more than is stated here.

Q. This is page 4. Were you updated on the data emerging from the evaluation of 8Y or are you not somebody that data would go to? Would that go to somebody else in PFC or what?

A. The first data I was given was by Dr Smith in October 1986. Prior to that, all I had was verbal communications with Dr Smith and any feedback that Dr Perry may have got through his discussions with

Dr Smith and with perhaps Dr Lane and other people.
Q. As a generality, would PFC be interested in the accumulating data from the 8Y clinical trial?
A. Very interested and, as I said a moment ago, I would have taken the view that no news is good news. They were continuing with the trial and they were getting no negative results, no evidence of transmissions. So as the trial went on, it was getting more and more promising.
Q. How were you aware of that?
A. I'm making that assumption. I'm making the assumption that if they had had a transmission of hepatitis, then we would have been told that immediately. If we were not being told that, I'm assuming that the results are promising.
Q. Is it possible that Dr Smith, in any of your meetings or communications with him, would have verbally informed -- updated you of any emerging data from that trial?
A. I don't remember that, no, and I think if he had anything significant to say -- and something significant from my point of view would be a negative result, a transmission -- then he would have told me that and he didn't tell me that. So I presumed that the trials were proceeding with very encouraging results. But I did not have any details of that in writing to say how many

patients had been studied, et cetera, et cetera, until Dr Smith prepared a report for the UK haemophilia directors in October 1986.

Q. And Dr Perry has produced this report for this particular meeting of the haemophilia and SNBTS directors. Would you have had any involvement in the production of this report?

A. I don't remember being involved in the production of that report, no.

Q. Would it have been copied in to you at the time?

A. I was a member -- involved in this committee that the report was intended for and I probably would have been shown -- given a copy before the meeting, certainly, along with the agenda papers, but I don't remember if Dr Perry discussed it with me or not beforehand.

Q. If you had seen this report at the time and you had seen that sentence that:

"Preliminary clinical data indicates the material is non-infective with respect to HTLV-III, NANB and Hepatitis B."

What, if anything, would you have done --

A. No, because we had already taken the decision to develop our severe heat-treated product as quickly as possible before this was written.

Q. Sorry, I'll come back to that. I meant more, would you

have asked to see the data?

A. I was really leaving that to Dr Smith. I didn't want to pressurise him. He is a very careful, fastidious scientist and I wouldn't want to put him under undue pressure. So I would wait for him to come forward with the information when he judged it was appropriate.

Q. If you had read that sentence at that time, would that have been consistent or inconsistent with your understanding or feeling about the safety of 8Y?

A. It was consistent with my general knowledge, as I said. I was assuming that if they had had transmission, we would have been told and if we weren't told, then they were making good progress and they were not having transmissions. Therefore this was consistent with the view that I was taking at the time.

Q. Perhaps a cautious optimism or so far so good --

A. Yes, that's correct.

Q. Thank you.

I think the next document in looking at accumulating data of 8Y is a document, 17 March 1986, which is document [SNB0075664]. We can see this is a note of a meeting held at PFC. Various people from BPL and the SNBTS, including Dr Smith and yourself, Dr Foster. Various, I think, matters discussed. But if we could in particular go to page 3, please. Yes, in paragraph 5,

the note states:

"Dr Smith outlined clinical trial results of the 8Y Factor VIII product so far. While results cannot be considered conclusive at this stage, he indicated that no cases of virus infection have occurred (attributable to 8Y material) after 12 months experience of 8Y in virgin haemophiliacs."

Does that accord with your recollection of your knowledge at that time?

A. Yes, it does.

Q. Thank you, doctor. As I say, I want to follow the whole chronology of the accumulating evidence of the safety of 8Y, so if I may just complete that. We then return to your statement at page 4, where you refer to a presentation on 9 May 1986 in Australia. We have that document. It's [PEN0171264]. If we look at the first page, we can see the heading "Interim Results", and it's a presentation by Drs Smith, Winkelman and Feldman. In the abstract, we can see in the second paragraph:

"33 patients receiving Factor VIII concentrate (8Y) and Factor IX ... for the first time ..."

Were given regular liver function tests. And further details are given. Could we then look at the last page of this document, please? Under "Discussion" the authors state:

"We do not apologise for presenting cases with less than immaculate follow-up for two main reasons."

Which are then set out. Then the next paragraph the authors state:

"Let me again concede that this collection of data of variable quality does not carry the full authority of a formal prospective clinical trial. However, when all reservations have been made about imperfect follow-up to date, the weight of this varied evidence justifies our asking clinicians to put many more previously untreated patients into a more formal trial, using even more batches of product. Although these are only interim results on a limited number of batches, we think we are justified in thinking that the severe heating has been more effective in preventing transmission of NANBH than the milder heating accorded to the Hyland and Armour products in studies published last year. It is too early to know whether NANBH transmission has been eliminated by severe dry heating or whether we may see transmission by only a few batches, as has occurred with Alpha's Factor VIII concentrate heated in heptane."

I think I will let those words stand as they are, Dr Foster, rather than trying to put gloss on.

Going back to your statement, please, you say:

"On 9 October 1986, Dr Smith gave [you] a copy of

his interim report on the BPL surveillance study that had been prepared for a meeting of UKHCDO that was held in Edinburgh on 10 October 1986."

Was it the first occasion, doctor, that you saw written data on the 8Y evaluation?

A. I think that was the case, yes.

Q. You go on to say:

"Data were provided on 10 recipients of 8Y and six of 9A. If recipients of Factor IX are excluded because the risk of NANBH transmission by unheated Factor IX might not have been the same as with unheated Factor VIII, then the calculated rate of NANBH infection for 8Y was from 0 to 30 per cent. I'm not sure if this estimated rate of infection meets the definition of 'likely' to be free from transmission of NANBH or not."

Doctor, have you arrived at the 0 to 30 per cent from the rule of three. Is that what it's called?

A. That's correct.

Q. Are you content, doctor, if I go through that with Dr Cuthbertson or would you like to do that now?

A. I wouldn't like to do it now, no.

Q. It is set out in a Mannucci paper of 1999, which I will have a reference for later. I think it is a reasonably clear explanation of it and I think I will not take up time now but rather go for that later.

A. I'm not a statistician, so I would prefer not to do that.

Q. We should look at the interim report. It's [SNF0011123]. We can see it's stated "Interim Report". If we go on to the next page, please, and on to page 3, please. Under "What Next?" we see:

"These data, showing no clinical or laboratory events attributable to transmission of the three main blood-borne viruses, may further encourage HCDs to use 8Y and 9A in previously untreated patients.

"The present data are inconclusive in that some gaps in follow-up allow a small chance of having missed a very transient ALT/AST elevation. Data are currently being more rigorously assessed by a statistician, but one simple treatment ('The Rule of Three') suggest that, within 95 per cent confidence limits, 21 negative cases are still compatible with an infectivity rate of 0 to 14 per cent. This is plainly better than the underlying rate of [over] 90 per cent for unheated concentrates, but at least 60 successive negative cases will be required to reduce this probability to 0 to 5 per cent. It is proposed that this pilot study be followed by a formal prospective clinical trial with a stricter protocol to establish with at least this degree of confidence whether severe dry heating has eliminated

transmission of blood-borne viruses."

Looking at what is said there, it perhaps illustrates the difficulty of it all depends what you mean by "likely", whether you express that in a word "likely" or whether you try and do some number crunching and express it in terms of numbers.

The next document, putting that to one side, is an updated version of this report, [SNF0011138]. We can see this is by Dr Colvin and colleagues but the report is assembled by Dr Smith, and it's dated 16 September 1987. At page 2, please, we see the first paragraph states:

"This updated analysis, covering approximately two years of study in several haemophilia centres, is stricter than the one presented to HCDs last year, in terms of admission criteria and assessment of compliance. Since some will still find these standards too lax, sufficient detail is given to allow further categories of patient to be excluded."

We can see "admission criteria". The numbers of patients:

"This analysis is restricted to three classes of patient ..."

Seven who received 8Y and had no previous exposure to any blood product. 12 who received 8Y and were

previously exposed only to single donor products and then ten patients receiving 9A.

In terms of 8Y, this analysis is based on 19 patients, only seven of whom have no previous exposure to any blood products. Then at page 4, please, a short conclusion on page 4. The conclusion states:

"It is not possible to determine the true incidence of transmission of NANBH by 8Y and 9A from this imperfect evidence but the apparent near zero incidence justifies the inclusion of a further series of patients in a more formally controlled prospective trial, to be coordinated by Dr Rizza and Dr Kernoff."

This is perhaps, an illustration, doctor, of what we discussed at the very outset, that the phase 2 clinical evaluation can really go on for a number of years.

A. Yes, and effectively what happened was that, having done this initial phase 2 evaluation, BPL did a second phase 2 evaluation, which was more definitive.

Q. Thank you. Then for the next document in this chain of events, we should, I think, look at [SNB00017768]. These are the minutes of a meeting of the UK haemophilia centre directors on 25 September 1987, at which Dr Smith's updated report was considered. If we could go, please, at page 7, in item 9 there is reference to Dr Smith's updated interim report. In item

10 it states:

"Proposed clinical trial of NHS Factor VIII and IX (8Y and 9A). Dr Kernoff said that the experience with 8Y and 9A, clearly indicated that they were more safe than previously available NHS and commercial concentrates as regards HIV and hepatitis transmission. However, it was undeniable that the evidence on safety was somewhat 'soft' in scientific terms. 'Hard' evidence, comparable with that available for certain new commercial products, could only be obtained from a rigorously performed virgin patient study, carried out in accordance with the protocol suggested by the ISTH. For this reason, a new study was to be mounted of the 8Y product in patients who had never previously been exposed to any blood or blood products."

That's consistent, with what you told us about a second phase 2 evaluation?

A. That's correct.

Q. Thank you.

Could I then, please, go to [LIT0010330]? We can see that this is a report in the Lancet of 8 October 1988 by the UKHCDO study group, led by Dr Colvin and others, of their evaluation. We can see from the summary that:

"32 patients with coagulation factor deficiencies

and likely to be susceptible to NANBH virus infection were treated with a total of 20 batches of a Factor VIII concentrate and 10 batches of a Factor IX concentrate."

A little on:

"Severe dry heating appears to have reduced the risk of NANBH transmission from about 90 per cent in untreated concentrates to a statistically determined rate of 0 to 9 per cent."

Could we then, please, look at page 3, please, the very last paragraph of the report:

"After this demonstration that dry heating at 80 degrees centigrade is highly effective in inactivating NANBH virus ... a second trial of 8Y and 9A, rigorously in line with ICTH criteria, has been started to quantify more precisely any residual risk."

So I think, doctor, then this paper, the Colvin paper, is reporting on the first phase 2 trial. Is that right?

A. That's correct.

Q. Thank you:

"In the absence of objective and specific tests for the virus or viruses transmitting NANBH, clinical trials cannot prove that transmission has been eliminated by an inactivation method."

Then the last sentence:

"Physicians should continue to prescribe as if all blood products still carry a diminishing but finite risk of transmitting blood-borne viruses, particularly the agents for NANBH."

I think we can finally look at the report of the second phase 2 trial, and that is the 1993 paper by Rizza et al, [SNB0045996], published in the British Journal of Haematology, the title is:

"Confirmation of Viral Safety of Dry-heated Factor VIII Concentrate 8Y, Prepared by BPL: A Report on Behalf of UK Haemophilia Centre Directors."

The summary states:

"27 Factor VIII deficient patients, who had previously not been treated with blood or blood products, were studied after infusion of a total of 24 batches of NHS Factor VIII (VIII-Y) concentrate produced by [BPL]. Follow-up was carried out according to guidelines laid down by the International Society on Thrombosis and Haemostasis. Serial estimations of amino transferase level, carried out over a 26 week period, revealed no elevation of these enzymes attributable to hepatitis. Studies of various virological markers found no evidence of infection with Hepatitis C, Hepatitis B or HIV following transfusion. This confirms a previous finding that severe dry heating of Factor VIII at

80 degrees centigrade for 72 hours seems to reduce the risk of transmitting Hepatitis C from approximately 90 per cent to a rate of 0 to 11 per cent."

Perhaps two observations, Dr Foster. Firstly, of course, by this time the Hepatitis C virus had been discovered. I think it was discovered in 1988, albeit there wasn't scientific publication of that until 1989. Hence in the summary, the reference is to Hepatitis C, rather than NANBH?

A. It goes beyond that. It means there is a test available, a direct test. So you can now get much more precise information than you could using surrogate tests, and it makes this kind of monitoring of patients much easier for everyone concerned.

Q. What it also perhaps interesting is the last sentence of the summary. The really very careful, precise and perhaps cautious language used, in that it's stated that:

"This confirms a previous finding that severe dry heating seems to reduce the risk of transmitting Hepatitis C from approximately 90 per cent to a rate of... "

What is set out. So even at this late stage, the language used perhaps is still somewhat precise and cautious.

A. I think people are being very careful not to perhaps make some definitive statement and then suddenly find that they have got egg on their face and they have got a patient infected. They have to be very, very careful.

Q. Just to complete the references for this chain but not going to the document, the ISHT protocols are set out in a 1988 paper by Mannucci and another, which is [SGF0011758] and I'll perhaps consider that with Dr Cuthbertson, I think.

So that completes that chain of documentation.

I should perhaps then just return to your statement, please, doctor, at page 4 to complete that. And page 4, half way down, (iii), you say:

"When the final report of the study was published in the Lancet on 8 October 1988 ..."

This is the Colvin reported we have just looked at:

"... it seemed to me that this was the first time that I considered it likely that the heating regime for 8Y resulted in a product which did not transmit NANBH. As to the best of my knowledge, this was the first publication of these data that had been peer-reviewed."

You also then go on to state that:

"Although this final report claimed that the risk of NANBH transmission was 0 to 9 per cent, there were a number of reservations about the study."

"Firstly it did not comply fully with the protocol that would be established by the ICTH, and secondly there was one potential case of NANBH transmission excluded from the analysis."

Over the page:

"Thirdly, the analysis combined recipients of Factor IX ... and Factor VIII."

You query whether it's:

" ... valid to combine patient data from two different products, in which the baseline, unheated risk of NANBH transmission may not have been the same."

I think we can see that point.

I think then, doctor, that then finishes question 2 and the position in England, and I think we can now move on to the position in Scotland, if we may.

To cover the position in Scotland, I think I would like to put your statement to one side, please, and instead go to the briefing paper which you have prepared for us previously. This is page 40 of [PEN0131309].

We should perhaps go back to page 32, which is .1340. We can see paragraph 4.4. This whole chapter concerns research and development of heat treatment by the SNBTS. We looked at the table previously. So we can skip that, please. We then go to page 34. You set out events from 1981 on. Again, I'm going to skip the

first few pages because they have been covered under the previous B3 topic.

Where I would like to start, please, is at page 40, which is point 1348. The second paragraph talks of scientific staff from the PFL/BPL visiting PFC at the end of March 1985. I think we covered that earlier this morning, but what I'm interested in, Dr Foster, is the next paragraph, beginning:

"A number of questions remained concerning the development of 8Y ..."

And you list them. I take it that the reference to "a number of questions remaining" will refer to as at March 1985.

A. That's correct, yes.

Q. What I'm interested in, doctor, is which, if any, of these questions remained as at perhaps September/October 1985, so once BPL were in full-scale production of 8Y and it was being routinely issued for clinical use. Can you just go through these questions, please, and tell us which would have remained as at that point, sort of September/October 1985?

A. I think, when BPL are issuing product from September 1985, then I would assume that they had established for themselves that the product was stable at that scale of operation. But in these types of

processes, some of these problems sometimes only emerge after a period of time. So you do -- today we talk about due diligence, and you would actually want to see data from a number of batches that have been produced consecutively before you conclude that it has been -- it meets all of the requirements that have been set.

So you would probably be looking for data from maybe half a dozen batches prepared at BPL, to establish whether these conditions had been met. And that would probably have been achieved, certainly by the beginning -- I would say round about October or late -- I don't want to be too specific about it. I can't be too specific but it would have been late 1985.

Q. So I think that's the first bullet point:

"Would the product be stable ... "

Just going through them one by one.

A. The second one really deals with this idea of this very severe heat treatment, and it's one thing to be able to do that with product prepared at Oxford but doing it at the larger scale routinely at BPL, there was a question of would all the batches survive that treatment, and I think, as we came to find out later, not all the batches did survive heat treatment. They did have continuing problems. So we were all at the bottom of a learning curve here and BPL were still learning at

this point in time. But they didn't manufacture enough material to be able to supply about a third of the requirement for England -- maybe 25 per cent at that time. But I think they also failed batches. So it wasn't entirely straightforward.

Q. The third bullet point.

A. I think in terms of the pharmacokinetics and clinical efficacy and tolerability, I think that would have been established, again by October. Clearly they wouldn't have been issuing the product routinely if they hadn't established that by October.

Q. The next bullet point concerns whether heat treatment at such high temperature would create new antigens.

A. This is really not my area of expertise but I think Professor Ludlam said it would take -- I can't remember now -- a few weeks or a few months to establish whether this would happen or not. So I think he would want a few months' experience to see whether this was going to happen or not.

Q. The next one:

"What degree of virus inactivation would be obtained (given that no experiments had been performed using marker viruses)."

Far less the Hepatitis C virus.

A. That was obviously a major issue, and what we have just

been talking about is whether this has actually been effective in dealing with non-A non-B Hepatitis, and what many people were doing by this time was having what we called model viruses and marker viruses that you would study in the laboratory to establish the degree to which this process might or might not be effective and compare it to, say, the pasteurisation of albumin or the pasteurisation of Factor VIII as performed by Behringwerke, so get some kind of measure of how effective this process might be. BPL didn't have those facilities and they had no data at all like that. So really they had nothing to back up the process, other than the monitoring of the patients, which was taking a very long period of time.

Q. Does that perhaps tie in with the final bullet point:

"Would the dry heat treatment be effective in preventing the transmission of NANBH."

Was that still an outstanding question --

A. It was very much an outstanding question, yes.

Q. We have just looked at this series of documents, which perhaps illustrates that.

So finally, I think, we can leave England at this stage and properly turn to look at what was happening in Scotland, and you go on to say at the bottom of page 40 that:

"Given the degree of uncertainty associated with alternative options, the SNBTS continued its strategy aimed at producing a high purity concentrate suitable for pasteurisation, but to which either solvent detergent treatment or severe dry heat treatment could be applied instead, if they proved to be superior."

And the reference there is, I think, to the NYU project. Is that right?

A. That's correct.

Q. Just to remind us, doctor, are you able to summarise for us the main steps or progress that had been taken with the NYU project between roughy January 1980 and September/October 1985?

A. Certainly. We had actually begun practical work. Although we had discussions with Professor Johnson from 1983 onwards, we had started practical work at PFC in -- I think it was, August 1984, in which we were looking to take his development, his invention, if you like, and make that into a practical process that could be run in a manufacturing operation. And Dr McIntosh was leading this and we had made considerable progress in identifying appropriate reagents in conjunction with a company called Pharmacia, who were the world-leading company at that time for providing chromatographic reagents for the pharmaceutical industry. And we had --

some of their new materials they had produced seemed to be appropriate. But because these were new materials, quite a bit of work was required to work the system up, and that was what Dr McIntosh was working on and he was making really excellent progress.

So by this point in 1985, we certainly had a prospect that we could reasonably quickly have a much higher degree of purification, which, as I said earlier, was initially -- had the advantage that it would help us to develop the pasteurisation process. But if the pasteurisation process turned out not to be the best process, if other procedures came through, then it also was compatible with that. It would -- by having this increased purity, it was compatible with the notion from BPL that it was increased purity that allowed them to achieve heating at 80 degrees.

So if we had something that was even more pure, not only should that survive heating at 80, but we could go higher. We could heat at 90, 100, who knows; whatever might be needed to destroy this virus. It might be more heat resistant than heat treatment at 80 degrees.

So we were positioning ourselves here to have options, if you like, we were doing what we thought -- or what I judged was the best option, but we were leaving the options open so that we could change

direction to do whatever emerged as being better if that did happen. And of course, it was conceivable at this point in time that none of these methods would work. And there is one eminent author who produced a paper, who argued that non-A non-B Hepatitis was caused by a prion agent, and if that had turned out to be the case, none of these methods would have been effective.

Q. Can I put it this way -- again it may be an over-simplification -- that the success at BPL of severely heating 8Y perhaps gave you some reassurance that you were on the right lines with NYU, for the reasons you have just explained, that if a BPL high purity product could be severely heated, then it may be that an even purer product could be heated to such temperatures.

A. That's right, and that to my mind seemed to be at that point in time, the possibility that we could go beyond 80-degree heat treatment, if that was what was required, as an option.

Q. So in a way the success of the 8Y product didn't make you think, "Hang on, we are going down the wrong route". From what you have said, it suggests it gave you some reassurance that you were in fact going down the right route.

A. At this point in time, my judgment was that, in terms of

the data that were available, the better data came from the pasteurisation process in terms of safety to patients.

Q. I understand.

A. Therefore, that was the front runner. But we were positioning ourselves to change if we got new information that showed that perhaps dry heat treatment, for very severe conditions, was going to be a good option. And that, if we had to go beyond -- heat at 80 or go beyond 80, the higher purity product should be capable of doing that because it was much more highly purified than 8Y.

Q. I would like to go over to page 41 and just continue the Scottish chronology, if I may. At the top of page 41, you say:

"The SNBTS Factor VIII concentrate heated for 24 hours at 68 degrees was released for clinical trial on 14 March 1985."

I think this is the NY HT2 product referred to in the table we looked at earlier. Is that right?

A. Sorry, which page are we on?

Q. Sorry, the top of page 41, the first sentence.

A. Okay. Yes, that's correct.

Q. Yes. So that's NY HT2. I think we looked at that in B3. So I'm not going on ask you any questions about

what's on that page. We can see what it says for ourselves. I want to try and focus on Z8. Over the page to page 42, please. Then the second paragraph explains:

"SNBTS Factor VIII concentrate, heated for two hours at 68 degrees, continued to be released in Scotland until 13 September 1985. SNBTS Factor VIII concentrate heated for 24 hours at 68 degrees was issued routinely from 4 September 1985 ... "

The two hour concentrate was subsequently recalled. Then events which are more pertinent to this topic, in the next paragraph:

"By October 1985, the volume of high purity Factor VIII ..."

The NYU product?

A. That's correct.

Q. "... solution that could be prepared in the PFC research laboratory was sufficient to fill the number of vials needed to perform a trial of freeze-drying."

You say that:

"Surprisingly, the highly purified Factor VIII NYU was destroyed using the established freeze-drying conditions that were used by the SNBTS to dry Factor VIII concentrate (NY), leading PFC researchers to design a new cycle from first principles to freeze-dry

high purity Factor VIII."

Just for the avoidance of doubt, doctor, am I right in thinking it was the freeze-drying step which destroyed the NYU product rather than the separate and later heating step?

A. Yes, it was the freeze-drying only. There was nothing after the freeze-drying left to heat.

Q. Right. Moving on, a new freeze-drying cycle for the NYU product was designed. The next paragraph states:

"The high purity material tolerated this new freeze-drying cycle but, contrary to expectation, a sample of the ... intermediate purity Factor VIII concentrate (NY), which had been included as an experimental control, not only survived freeze-drying but also tolerated 80 degrees dry heat. By contrast, the samples of high purity Factor VIII failed to withstand 80 degrees dry heat."

So at this stage you are looking at the heating step. I think you have found that the NYU product did not tolerate that step but a sample of the intermediate purity NY Factor VIII did. Can you just tell us a little bit about the vial or sample of the intermediate purity product which did survive the heating?

A. Yes, this was an experiment performed by Dr McIntosh and

the amount -- the high purity Factor VIII that he was freeze-drying, because it was highly purified, was a very small volume and it was -- he was freeze-drying these small volumes, a few millilitres, and he chose to include in the experiment, as you have pointed out, some of the established Factor VIII as a control, and he took just a few millilitres of that as well.

So it wasn't a bottle of the standard product. It was just a sample from the standard product that he used. And this was the very surprising result that he obtained, and it was surprising to me because I had expected the high purity product to withstand dry heating at 80 and even to be able to withstand heating beyond 80, and of course it didn't.

By contrast, the product that we thought would be destroyed by 80-degree heating survived. So it was a double shock, if you like, to get this knowledge.

Q. And the sample from the existing Factor VIII concentrate, was that taken from concentrate which had been produced in the research laboratory or was it taken from a standard vial that was being issued to patients?

A. No, it would have been a standard vial from the production department, where Dr McIntosh would have taken a sample from that and then dissolved it and added a few mls into a small vial and used that as his

control.

Q. Was that product inserted as a control?

A. You would have to ask Dr McIntosh.

Q. We will.

A. That was his choice. I have to say, if I had done that experiment, I probably wouldn't have done that, but he did the experiment, not me.

Q. Put it this way, would that have been standard practice?

A. He says it's good science always to have a control, and that was the best control he could come up with.

Q. Do you think that was good science?

A. I think he is probably right, yes. I think he included albumin as a control as well in the experiment, not just the Factor VIII.

Q. You weren't surprised that he included that sample as a control?

A. He hadn't discussed it with me beforehand. So when he produced the results I hadn't expected it but when he explained it to me, it made sense.

Q. Yes, I think you said that albumin had also been included as a control?

A. I think that might have been -- I think there might have been a sample of albumin as a control as well. You need to check with Dr McIntosh.

Q. We will do that, thank you.

Going back to your statement, please, at page 42, you explain that:

"This observation implied that it was the nature of the freeze-drying process and not product purity that determined whether or not 80/70 dry heating could be tolerated by Factor VIII. Details of the freeze-drying procedure had not been given in the patent application of 8Y, so further information was sought from the PFL."

If we could look firstly, please, at [PEN0171376]. This, I think, doctor, is a memorandum from yourself to Dr McIntosh, dated 22 October 1985, concerning the heat treatment of Factor VIII. Why is the memorandum from you to Dr McIntosh, rather than the other way round, if he conducted the experiment?

A. I think he had given me his results and I had been reflecting on them and I had just written down my thoughts for him to think about.

Q. Am I right in thinking that there is no reference in this memo to the control we talked about, which successfully tolerated the heating?

A. There might not be. I haven't read this for 25 years.

Q. Take a couple of minutes to look at it, please.

A. My first surprise was that the higher purity product had not survived heat treatment and I was trying to think about that. I had expected it to survive the 80-degree

heat treatment. So why did it not? That's what I was thinking about. This is the day after the experiment, I think. That was my first -- the things I was thinking about.

Q. So your focus was on the NYU; why didn't it tolerate the severe heating?

A. Yes.

Q. That was presumably a bit of a puzzle and you have explained that. Can we then, please, look at [SNB0075355]? This is you then writing to Dr Smith. We will see in a second, 13 November 1985. Initially you give Dr Smith some recent PFC publications and then at the end of the letter you say:

"One question I have been meaning to ask you: what are the freeze-drying conditions for your new Factor VIII concentrate, especially during primary drying. We have some preliminary data that suggests that drying conditions may be particularly critical for the subsequent sensitivity of both protein and virus components to heating (not unexpected)."

The preliminary data you refer to in your letter, I assume, is a reference to the Mackintosh experiment we have just talked about?

A. Yes, and I think we may have repeated those experiments. We didn't just depend on one experiment. You normally

repeat them to see if you can confirm the results. That's probably the information that I was referring to.

Q. What's meant by the words "not unexpected"?

A. I think this is a parenthesis and, kind of with hindsight, you do see that, in plasma fractionation, where you are dealing with processes made up of a number of steps, that there can be interactions between the different steps. So why would -- thinking hard about it, maybe it is not unusual that the freeze-drying procedure might influence how the subsequent heat treatment performs. For example, the type of -- the composition of the cryoprecipitate that you get at the start of the process influences what happens with the heat treatment, which is about ten steps later on. So if that can influence heat treatment, maybe the freeze-drying can influence heat treatment.

Q. So the words in brackets, "not unexpected", are perhaps after the event comment?

A. Very much after the event, yes.

Q. Can we then, please, look at Dr Smith's response, which is [SNB0075458]. We will see this is a letter dated 11 December 1985 from Dr Smith to yourself, where he sets out the freeze-drying conditions at Oxford. It's fairly technical. I don't propose to go into that in any more detail.

So at this stage, mid December 1985, you have the freeze-drying conditions, certainly at Oxford, perhaps not for BPL -- or just Oxford?

A. This seems to be just Oxford.

Q. PFL? Thank you. Could I then, please, revert to page 42 of the briefing note? The second last paragraph, last sentence. You stated:

"The information supplied by Dr Smith confirmed that the new freeze-drying cycle devised at PFC was similar in design to that being used to freeze-dry 8Y, consistent with this being the key aspect of the 8Y process, rather than the degree of purification."

So is it really at this stage, doctor, October, November, December, 1985, that your thinking changes from being of the view that purification was the key to the severe heating of 8Y, to thinking that it may in fact be the freeze-drying process?

A. Very much the case, yes. If we can heat something at 80, which is much less purified, that seems to suggest it wasn't the purification that was important because the two freeze-drying processes now that we had devised appeared to be fairly similar and that seemed to point to that being the area that was more important in the 8Y process than the purity.

Q. Thank you.

Then carrying on, the bottom of page 42:

"In addition to this finding, a number of other items of information emerged in late 1985, which, taken together, caused the SNBTS to alter its R&D strategy to focus on the development of an 80-degrees centigrade dry-heated Factor VIII concentrate, similar to 8Y of the BPL, rather than the high purity NYU concentrate. This new information included ... "

Over the page you list the various factors. Firstly:

"A pre-publication report from the USA which found HIV to be more resistant to dry heat treatment and earlier experiments had indicated ..."

A reference to Prince paper:

"... leading to uncertainty over the margin of safety being provided by the current SNBTS dry heated Factor VIII concentrate."

What I propose doing, sir, is simply providing the reference for these documents, rather than going into them in detail because I think we could get bogged down a little in detail. The general point is made by Dr Foster that these reports gave rise to uncertainty over the margin of safety, and I don't think that statement is controversial.

THE CHAIRMAN: If it becomes controversial, I'll no doubt hear from somebody else, Mr Mackenzie.

MR MACKENZIE: Thank you, sir.

The Prince paper, for reference, is [SNB0075360]. That's the pre-publication version. It was, in due course, published in the Lancet on 31 May 1986, and that is [LIT0010339]. One can also look at document [SNB0075358], which is a letter from Dr Perry to Dr McClelland dated 5 November 1985, in which the pre-publication of Prince is discussed.

Then returning, please, doctor, to page 43, the second bullet point, you refer to a problem of instability that had been identified in a scale-up of NYU, which required to be solved. I don't think we have heard about that. Do we need to hear about that?

A. Very briefly. As we were making progress with this research, Dr McIntosh was gradually increasing the volume of preparation in order to get material to do freeze-drying studies, et cetera, et cetera, and in some of these experiments in the research laboratory, where he reached a volume of the experiment where the product became unstable, and it seemed to occur, I think from memory, at about a point where -- the equivalent of 100 litres of plasma.

If we were dealing with less than that, the product

was stable; if it was more than that, it was unstable. And it seemed to be that there was something in there that was reaching some critical concentration and was causing the instability of the Factor VIII, and that pointed out a problem that had to be solved and we didn't -- you know, this was another unknown, so it was something to bear in mind, that we didn't know how long it would take to solve. It might be solved in weeks, it might take months, it might take years. That was unknown. So it was just another concern that was emerging about the NYU programme.

Q. In the next bullet point, you refer to the difficulty in dry heating the high purity NYU product at 80 degrees centigrade. We have just discussed that. The next bullet point states:

"A recognition that the sophisticated equipment required for the production of the high purity NYU concentrate could not be obtained quickly and its operation would require revised staffing arrangements, the establishment of which was uncertain."

Are you able to briefly tell us about the question of the equipment and the staffing arrangements --

A. Yes, this was a multistage chromatographic process, which we were looking to have automated as much as possible, and we wanted to buy this equipment and have

it operational as quickly as we could, and Dr McIntosh sat down with the company Pharmacia, who supply this equipment, and he drew out our requirements with them -- and this was in October 1985. And it was that process of sitting down with the company that made this equipment that we learned that this was really much more sophisticated than they had ever done before. It was the first time that anyone had manufactured automated chromatographic equipment for the purification of proteins at this scale, and they told us that they couldn't deliver this equipment for something like, six to nine months.

So that was an obvious delay. We couldn't get the equipment. We thought we could have got it sooner. And also, working through the equipment, Dr McIntosh also worked out -- he realised that the operation of this was considerably -- would require a lot more effort and more manpower or womanpower than we had at the moment, and we would need also to have probably some form of shift-working to carry out the process because it wouldn't be completed in one day, and as we have discussed in the earlier sessions, we had failed to obtain shift-working at PFC. We had put forward proposals in the past and it hadn't been obtained, and it was something that was out of our hands. We weren't

in control of getting -- negotiating staffing arrangements.

So that was another issue that was causing us to think this NYU high purity product might take longer than we had hoped, and that was another aspect to take into consideration.

Q. Then the final bullet point:

"The 8Y produced at BPL has been found to be satisfactory in terms of clinical efficacy and tolerability."

Doctor, was pressure being created on PFC by the fact that the 8Y product was in production and had been in routine clinical use for a number of months, and on the face of it appeared to be more safe in respect of NANBH transmission than the PFC equivalent product?

A. I think, at this time, the knowledge on safety -- we have just been through all of that, and it's still embryonic. We are certainly very interested, obviously, and we are at a point where we are deciding whether to go with that horse or stay with this horse, and it's where do you put your priorities, and we are beginning -- we are debating -- getting into a debate about these issues at this point in time. And of course, we took a decision to change our direction.

Q. And it's really perhaps a combination of all of these

factors you have listed there, which led to the decision to --

A. I would say there was not one single factor but if I were to emphasise one single factor, it would be the first one, which was the concern about HIV.

Q. Interestingly, perhaps, doctor, you haven't included as a factor the preliminary evidence about the safety of 8Y in terms of transmitting infection or not. Was that a factor? Can you remember?

A. No, the driving force -- and you might come on to it. There is a memo that I wrote shortly after this where, at around about December 1985, I'm actually saying, "I think we should stick with pasteurisation and high purity," and Dr McIntosh was saying, "No, I think 80 degrees". So we were having that debate and we had differences of opinion. So we got together and had a meeting and developmentally we agreed that the HIV data from America was causing some uncertainty --

Q. I'll come on to that in a second. We are very interested in that. I'll perhaps just read on two more paragraphs in your briefing note and then we will come back to look at some of the documents and events in more detail. So go back to page 43, you explain that:

"A meeting of PFC managers was held on 23 December 1985 specifically to consider these matters

and it was agreed that a change in the strategy should be recommended to the SNBTS, with the development of a 80 degrees dry heat-treated Factor VIII concentrate as first priority and the development of a high purity Factor VIII concentrate as second priority."

Just reading on to the next paragraph:

"This new plan was endorsed at the next meeting of the SNBTS Factor VIII study group on 27 February 1986 and was agreed with haemophilia directors on 5 March 1986, the primary objective being to introduce a new Factor VIII concentrate as soon as possible, to provide a greater margin of safety against HIV. It was also important that there be no interruption in the provision of this essential product to patients."

Can we turn to look at some of the documents, doctor, starting with the memo you mentioned? It's your memo to Dr Perry of 18 December 1985, which is [SNB0136680]. We can see the subject is, "Factor VIII, progress and options". You explain:

"This is a brief summary of where we are at with the NYU Factor VIII project and the various options that are available to us to achieve a product heated at 80 degrees centigrade for 72 hours."

You deal firstly in the memo with the NYU project and explain that:

"We are currently trying to determine a product formulation which stabilises Factor VIIIC and enables heating at 80 degrees centigrade for three days to be achieved."

Just to pause there, doctor, why were you currently trying to determine a formulation which enabled heating at 80 degrees for three days?

A. By this time we were already issuing Factor IX heated at 80 degrees for three days and the dry heat treatment procedure was simpler than pasteurisation technically and therefore -- and we were very interested in having this high purity product as well. So heating the high purity product at 80 degrees for three days in the same way as we were heating Factor IX had become, I think, by this stage our first objective and was beginning to -- in terms of the order of things, replacing the idea of pasteurisation because it was technically simpler to do.

Q. By "pasteurisation", doctor, do you mean wet heating at any temperature, or by "pasteurisation" do you mean wet heating at 60 degrees?

A. Any temperature that would be effective against non-A non-B Hepatitis. You may have seen that we were exploring heating at different temperatures, as 70 degrees and so on, to try and get some comparability to albumin, which was seen as the benchmark for safety.

Q. Yes. Thank you.

Doctor, returning to your memo, you go on to say:

"The latest attempt at heating on 17 December 1985 has given a negative result."

You then go on to set out various things, including various options. The options are perhaps a little technical. I should perhaps say, doctor, that the question of the technicality of the various options for NYU in perhaps degrees of detail that we need to know, I think I'm happy to stick at a certain level. If others feels they need to know more detail, they can always drill down but I think I'll leave page 1 as it is.

A. I should just add that at this point in time I'm kind of speculating why is it that this material that we thought would survive heating hasn't and how can we explore this further.

Q. Yes. Over to page 2, please. You then talk about, in paragraph 2, the standard Factor VIII products.

I assume this is a reference to the intermediate purity NY product.

A. That's correct.

Q. Thank you. Really, three options are set out in that respect. 2.1:

"Heat our existing product at 80 degrees for

three days.

"Preliminary results suggest that this can be achieved with the more conservative freeze-drying regime that we are now using for the NYU product."

What do you mean by more conservative freeze-drying regime?

A. We called it conservative because it was a slower process. It took longer. It was more gentle.

Q. Thank you:

"The problem here would be a relatively long freeze-drying time, about one week, for a 40 ml fill --

A. I think that should say "one month" actually.

Q. Sorry?

A. I think this is a mistake and it should say one month, not one week.

Q. One month? Just for comparison purposes, what was the length of freeze-drying time for the NY intermediate purity Factor VIII being issued at that time?

A. I think it was about three or four days.

Q. Then paragraph 2.2, the second option in respect of the existing product:

"Purify our existing product a little further so that we can concentrate the solution (by ultra-filtration) and achieve a smaller fill volume and thereby reduce the freeze-drying time. This could be

done by zinc precipitation or cryoprecipitate (we have already heated this material at 80 degrees centigrade with good results). A little work would be required to optimise the ultra-filtration conditions."

Just to pause and to look at two separate documents, we saw that at the top of this page there is a reference to "preliminary results", under 2.1, and, under 2.2, a reference to "good results". I think we have some laboratory notes which we can perhaps briefly look at. Can we look, first, at [PEN0171378]? We can see, at the top right-hand corner, the date, 11 November 1985. Whose writing is this?

A. That's my writing.

Q. What's the reference to NY776? What product is that?

A. That would have been the established Factor VIII concentrate, intermediate purity.

Q. I see. So is this a record of -- we can see -- unheated and then heated at 88/72 hours?

A. Yes, this is all of the different types of material that we had studied with the different additives and temperature and time of heating. I had obviously taken photographs of all of these to look at the colour of the vial because that's one indication of damage that's occurring on heat treatment and it shows you the different concentrations of some of the agents that you

were adding to see how it would affect this material.
Q. So this is a record of the severe dry heating experiments being carried out on the existing product --
A. That's correct.
Q. -- as at November 1985? Thank you.

Again for completeness, please, a separate document, [PEN0171379]. We can see the date at the top, 21/11/85. What document is this?
A. This is Dr McIntosh's first experiment, I think, to -- I'm not sure if it's his first but it's one of his experiments to see if the material that we had been working with for our pasteurised Factor VIII product could be adapted to a dry heat-treated material, and so this is the method sheet for the pasteurisation material, ZHT, and you can see, as you go down it, that he has crossed various things out and as you get further down, he has deleted all the stuff that leads you into pasteurisation and he is just modifying some of the solutions to see if he gets a material that can be capable of dry heat treatment.
Q. So is this the beginning of Z8?
A. It is the beginning of Z8, yes.
Q. I see. Could we return to the memo, please, paragraph 2.1, the reference to "preliminary results"? Is that a reference to the first document we have just

looked at, the one dated 11 November 1985?

A. I'm not sure --

Q. It may not matter.

A. -- if it refers to that one or not, I'm sorry.

Q. How about then the document that's dated 21 November 1985, which was the beginning of what turned out to be Z8?

A. That would be paragraph 2.2 here.

Q. That would be 2.2, I understand. Thank you.

Then paragraph 2.3, other options:

"Copy the BPL method."

You have set this out in some detail, I think, in your briefing note, which we will come to shortly, but just to stick with the memo, you state:

"This was derived from our own work in zinc. precipitation and glycine/NaCl precipitation. The process involves a difficult centrifugation step (Sharples centrifuge) and difficulties with poorly soluble contaminants were not resolved by us. I would estimate that a fair amount of work would be needed to finish this project off and it is not an attractive proposition for transfer to production."

We will come back to look at that in more detail shortly, Dr Foster, because you have set it out in your briefing notes. So I'll just put that to one side for

just now, the question of copying the BPL method.

Continuing with the memo, you state:

"Unfortunately, all of these options compete for resources, particularly Factor VIII assays, still the rate limiting factor."

What do you mean by that, Factor VIII assays being still the limiting factor?

A. As we discussed a little bit earlier, these assays were very laborious and difficult to perform and we had a specialised laboratory for that purpose that did all of the coagulation factor assays for PFC, for production as well as research and development, and they basically worked flat out all the time. It's always easy to take lots of samples and do lots of experiments but actually making the measurements and doing the assays is what takes the time. So that is almost always the rate limiting factor. We were seeking to always enhance our capability but however much we enhanced our capability, we could always give them more samples to test.

So that is really all I'm referring to here. The assay situation was always going to be a major factor in how much progress you can make and how quickly.

Q. Am I right in thinking this was the position, that at PFC there was a laboratory which undertook Factor VIII assaying and the purpose of that was to test Factor VIII

concentrate to see how much Factor VIII was in the product?

A. They would do the assays for Factor VIII and Factor IX. They would be testing samples at every stage in production, they would be testing samples from research and development and they would have banks of samples waiting to be tested and they would have staff working flat out.

Q. So at the main PFC manufacturing plant, which was routinely producing Factor VIII, IX or whatever, there would be samples or vials taken from that routine production and sent off to this laboratory for Factor VIII assaying, to test how much Factor VIII was in it.

A. That's correct.

Q. As a quality control measure perhaps.

A. Exactly.

Q. But on top of that work your research and development laboratory was also producing Factor VIII samples which you would want to undergo this Factor VIII assay?

A. Yes, and we believed that it was important that the one laboratory did all of the assays so that we were having assays done to the same quality and standard as the production material.

Q. Yes. Then, going back to the memo, in the final

paragraph you say:

"My own recommendation is to give options 1.1 and 1.2 top priority but to continue on 1.3 and 2.2, so that we can either change tack on the NYU project if progress is slow or produce a modification of our existing product if pressure on heat treatment demands it."

Perhaps two queries, doctor. Firstly, at this time am I right in thinking that your preference was to continue to give the NYU project top priority, ie to try and fix any difficulties with it, but plan B would be as set out in 2.2 of your memo?

A. That's correct. I should say that -- I'm not sure it has been mentioned very much, but one of the factors in my thinking at this time was the knowledge that the haemophilia directors were very keen on having higher purity products and they were concerned about the possibility that there might be some immune disturbance in patients as a result of the lower purity products. So that was an added aspect to consider with this higher purity material.

Q. Yes. The final question, Dr Foster, in this regard: the reference at the very end of that memo:

" ... if pressure on heat inactivation demands it."

What did you mean by that?

A. I was referring to the work from Dr Prince in the

United States. He had questioned the effectiveness of dry heat treatment against HIV and we were getting information on the grapevine, if you like, from the United States that people were beginning to think this dry heat treatment doesn't work. So, for us, one possibility was would you have to take that into consideration because, if it's a concern in America, it's going to be a concern in the UK as well.

So that's the pressure I'm talking about: Does this dry heat treatment work against HIV? And, of course, at this time it's HIV that is the overwhelming concern for everyone. Looking back now, we kind of see non-A non-B as equal or even perhaps of more concern but at this point in time it was HIV that was driving everyone's thinking.

Q. Thank you. Sir, that takes us up to the meeting in -- yes.

(1.00 pm)

(The short adjournment)

(2.00 pm)

MR MACKENZIE: Dr Foster, one query has arisen in my mind in relation to your evidence on your memo we looked at before lunch, the memo dated 18 December 1985 to Dr Perry.

I think you said in your evidence that, "I'm

actually saying, 'I think we should stick with pasteurisation and high purity'," and Dr McIntosh was saying, "No". It's a reference to, "We should stick to pasteurisation".

I think in the memo we don't see the word "pasteurisation" appearing. I'm simply wondering whether your view at that stage was that pasteurisation was the only option for NYU and you had essentially ruled out the possibility of severely dry heating it or whether, at the time you wrote your memo, your preference was to prioritise NYU and you were leaving open whether it could be heated by pasteurisation or severe dry heating?

A. Yes, I think that's correct. I was emphasising what I thought was the importance of the high purity product and its possible compatibility with pasteurisation and with dry heat treatment or other techniques like solvent detergent that were emerging. And I think at that time I still would have thought that pasteurisation had more evidence to support it in terms of achieving a safe product. So that's why I said "pasteurisation", but you are correct that it was really the high purity process that did have those other avenues that I thought we could go into if they were required, either the dry heat or the solvent detergent.

Q. Could I then, please, doctor, move on to this meeting of 23 December 1985. Can you tell us firstly, please, who was at the meeting?

A. There was myself, there was Dr Perry, Dr Cuthbertson and Dr McIntosh.

Q. The Inquiry, I think, has asked to see any records of the meeting and I think this is another example where there are no records in existence now. Is that right?

A. To the best of my knowledge, it was very much an informal meeting and I'm sure we all took notes at the time but they were just rough notes as an aide memoire as to what we had -- the conclusion we came to at that meeting. But I can't find any record of those now.

Q. You did again provide us with a copy of an extract from your diary. Could we look at that, please? It's [PEN0171383]. I think on Monday, 23 December. Is that 2 pm or 3 pm?

A. It's 2 pm.

Q. "Factor VIII meeting."

I think we can perhaps then see, one then goes into the Christmas holidays, is that right?

A. It's basically Christmas Eve, yes, we go on to.

Q. Was it considered that there was some urgency to hold this meeting before the Christmas break?

A. Yes, I think the memo that I wrote was trying to bring

together the strands of all of the thinking that was going on, and we had the evidence from Dr Prince's manuscript that was causing concern, and I think it was probably Dr McIntosh who said, "Let's have a meeting. We need to go through it," and it was convenient to do it immediately on the Monday, so we did.

Q. Was the PFC shut down between Christmas and New Year or would you have been back in at PFC between Christmas and New Year?

A. PFC, in terms of production, there was no production taking place but we would usually have some people coming in to do work that could be scheduled, such as maintenance work. But I wouldn't normally be planning to come in at that period, no, and those lines going through the diary suggest that I wasn't planning to come in.

Q. Do you have a recollection of what was discussed at the meeting?

A. Yes. I think we had a very good discussion about the various options and I have to say I'm sure -- I was actually persuaded by Dr McIntosh and -- that we should focus on developing severe dry heat treatment as the first option, rather than the second option that I had suggested. And I remember that Dr Perry was particularly concerned about the reports of the HIV data

from Dr Prince and we felt that we needed to do something as quickly as we could to try and enhance the degree of heat treatment to get a more secure position with regard to HIV, and the quickest way of doing that was judged to be developing a severe dry heated product now that we knew how to do it. We thought we knew how to do it because we had discovered that the freeze-drying was the trick, rather than the purification. We thought we could complement that. That was the quickest thing we could do.

Q. When you say Dr McIntosh was advocating prioritising a severe dry-heated product, for the avoidance of doubt, why was he of that view, for the reasons you have just explained?

A. We would talk about these things and it was a very fine judgment but I was very much on the -- still thinking that the clinicians were wanting a high purity product and we should focus on that and Dr McIntosh, having made the discovery that we could heat lower purity material at 80 degrees, was keen to progress that and he -- in that discussion he persuaded me of his point of view and there was one aspect that Dr McIntosh highlighted. It's a detail but it's an important detail, and that is that the dry heat treatment is carried out on the product in its final sealed container, and so there is no risk of

any cross contamination after the heat treatment, whereas with pasteurisation and with solvent detergent treatment, those processes are carried out in the middle of the process and therefore the process has to be contained thereafter to prevent any infection getting back in.

So that's technically a much more difficult and sophisticated thing to do. So Dr McIntosh was emphasising that point as well. He saw it as being pharmaceutically a very good process step. And so there was -- all of these issues were discussed at this meeting and we all came out agreeing that we should move as quickly as possible to developing a severe dry heat-treated product.

Q. Of intermediate purity or perhaps slightly purer than the existing intermediate purity?

A. Slightly purer. I think I explained it in the memo: in order to make it feasible and practicable, it had to be more purified. So we would have to put in place the procedures to do that. But Dr McIntosh had done some preliminary work to show that that was achievable.

Q. How long did the meeting last roughly?

A. I can't remember. I would say maybe a couple of hours.

Q. It was quite a lengthy discussion?

A. Oh, yes.

Q. And the outcome was the agreement that you have mentioned. What was envisaged at that time would then happen?

A. I took from the meeting that we would immediately begin to focus our -- as a priority, our attention to severe dry heat treatment and Dr McIntosh would draw up a programme of work to do that, and meanwhile Dr Perry would discuss this with Professor Cash to see if he agreed with that change of direction.

Q. Do you know whether that discussion took place?

A. I think it must have taken place but you would have to ask Dr Perry that.

Q. Dr Perry and Professor Cash about that.

Just stepping back a little, was that a decision which PFC were able to take alone?

A. No, it was a recommendation, I would say, rather than a decision. It was an SNBTS decision and we were simply recommending this was what we should change our priorities to.

Q. The full question was going to be this: was that a decision which PFC were able to take alone or did that require outside approval, whether from the Common Services Agency, the SHHD, Professor Cash, SNBTS, coagulation factor study group, the SNBTS directors or what?

A. It certainly required to be taken beyond PFC and certainly to the SNBTS, and by that it would be Professor Cash -- would be the key person there and if he felt strongly, then he would say clearly -- the other directors would go along with that. There would be no difficulty but Professor Cash would also want agreement with the haemophilia directors.

So ultimately, if the haemophilia directors had said, "No, we don't want you to do that, we would rather you carried on with the high purity work," then we would have taken notice of that.

Q. Thank you.

I would like to then just look at some documents which followed that meeting. Could we firstly, please, go to [SNB0015469]? I think we have looked at this before but if we go to the last page again, please, we can see this is Dr Perry, 10 January 1986. If we go back to the first page again, please, we saw before, from the title, this was a report for the meeting of the haemophilia and SNBTS directors in March. If one goes to pages 4 and 5, page 4 in particular, this may be a question I have to ask Dr Perry, doctor, but in short, where this report is dated 10 January 1986, there is no reference, I think, in it to a decision having been taken on 23 December 1985 to prioritise severe heated

dry product.

Are you able to offer an explanation for that or should I simply ask that question of Dr Perry?

A. I would need to read this again, I think. I'm sure it was discussed at that meeting with the haemophilia directors.

Q. Yes, this is a report which appears to be dated 10 January 1986, prepared in advance of a meeting of haemophilia directors on 5 March 1986. There may be nothing in this but on the face of it, it's perhaps slightly curious that there is no reference in the report which bears to be dated 15 January 1986, to this important decision.

A. As I said, it wasn't a decision, it was a recommendation, which would go to Professor Cash and it may be that Dr Perry hadn't had time to go over that with Professor Cash by the time he wrote this.

Q. Yes, but there is not even, as I can see, a reference in this report to even that recommendation. But it may be that's just something I have to discuss with Dr Perry.

A. Well, yes, he wrote this and I can't really answer that question. I can only speculate that it's possible that he hadn't had the discussion with Professor Cash by the time that he wrote this and that -- of course, consideration with Professor Cash is recorded in the

minute of the meeting of February, subsequently, where we go through the various recommendations.

Q. I'll explore that with Dr Perry but just to continue this chain of documentation, the next document is then [SNB0015484]. Again, I can perhaps discuss this with Dr Perry but this appears to be an addendum to Dr Perry's report we have just looked at, where one can then see discussion of this. It says:

"The heat treatment procedure now being applied to Factor IX concentrates ... may well be effective in ensuring non-infectivity of products. It is generally believed that heat treatment of this severity can only be achieved with high purity products (eg BPL ...) However, recent research at PFC has shown that this is not the case and that severe heating can be tolerated even at low purity if key process steps are carefully controlled prior to heat treatment. This information will enable a non-infective product to be achieved using intermediate purity material without compromising the development of the very high purity product noted in paragraph 5.1. The advantages of this course of action are ..."

They are set out:

"It is likely that a product of that type will be available for evaluation in April 1986."

Again, I can ask Dr Perry about this but the tone of this is that a decision has been made that this will happen, this is now the new plan of action. Does that seem fair?

A. Yes, that's correct.

Q. Yes. I can perhaps discuss with Dr Perry the precise chronology. It may be that at the end of the day nothing turns on precisely what happened when, but if we are able to clarify that, I think we should at least try to.

A. Certainly, at least from my perspective within PFC, we had already begun to change the priority of our work and Dr McIntosh was focusing almost entirely on the severe dry heat treatment, rather than the high purity work.

Q. When?

A. He had begun really in October and -- but certainly in January that was his -- he changed his priorities, but again, you can ask him that when he gives evidence.

Q. Yes. Again, simply to continue this chain, [SNB0015454]. Dr Foster, go to the bottom of the page, bottom left we can see the document appears to be dated February 1986 and I think we can see from the initials in the right that Professor Cash, I think, is the author of this document, and again we can see from the title, these are notes for the haemophilia centre

and transfusion service directors meeting in March 1986. Dr Foster, would you have seen this document at the time?

A. Yes, I probably would have seen that at some point.

Q. Why would you have seen this one?

A. Because I attend these meetings.

Q. I see. And then if we can go to page 6, please. As I say, nothing may turn on this but if we can look under the reference to the high purity product, please, subparagraph (v), the last sentence states:

"Accordingly, a decision has been taken to introduce an interim solution ..."

As at February 1986, it certainly appears a decision has been taken to follow the recommendation at the 23 December meeting. Do you have any view as to whether a decision has been taken and what that refers to? Does that refer to what came out of the meeting on 23 December or does that refer to something after that?

A. My understanding is this is very much the recommendation that we made at the 23 December, it was then passed on by Dr Perry at some point to Dr Cash, and he seems to have approved that and now regards this as a decision that has been taken by SNBTS. If the haemophilia directors were to come back and say, "No, we disagree," I'm sure Professor Cash would have reviewed that

decision.

Q. Thank you.

The next document in the chain, please, is [SNB0075596]. These are the minutes of the meeting of the coagulation factor study group on 27 February 1986. Were you a member of this group, Dr Foster?

A. I was, yes.

Q. If you go to page 3 under "Fractionation Update", an overview from Dr Perry, he states:

"Current plans for changes in Factor VIII product ... "

In particular the phase 3, I think is what became known as "Z8":

"Improved freezing plus zinc treatment to allow smaller fill volume and improved freeze-drying: 80/72 [to] manufacture from April 86. Issue from January 87."

It's the reference to "current plans" I think is perhaps consistent with the decision having been taken to adopt the recommendation from the December meeting. Does that seem correct?

A. That seems correct, yes.

Q. Just as a side question, doctor, under phase 2, a reference to "improved freezing", 68 degrees for 72 hours, three months' stock. Is that a reference to an intermediate purity NY, heated at 68 degrees for

72 hours?

A. It would be, yes, and you may remember that one of the companies in America, Cutter, were heating their product at 68 degrees for 72 hours, whereas ours was only 68 degrees for 24 hours and it's possible that we had done some research that suggested that we might be able to get to 72-hours but ultimately that was just an extra diversion and we didn't go down that route.

Q. For completeness, was that phase 2 product ever issued to patients?

A. No, it didn't -- I don't even remember it getting very far at all. So it didn't get to patients.

Q. I understand. The last document, if I may, in this chain of documents is [SNB0015448]. These are the minutes of the meeting on 5 March 1986 between the haemophilia and SNBTS directors. We can see you were present at this meeting, doctor, and then at the top of page 3:

"High purity product. Dr Cash informed members ... Dr Perry explained ... he said that difficulties have arisen in relation to the heat treatment of the new high purity product and it has been decided to introduce an intermediate stage: a product which is only 2 to 3 times purer than the existing intermediate Factor VIII but can be dry-heated at 80 degrees for 72 hours. It is hoped

that this intermediate product will be available for clinical evaluation in April and for routine clinical issue within three months."

Which I think would take things to about July 1986. But the reference to:

"It has been decided to introduce an intermediate stage ..."

Again, I think, is consistent with your evidence that the decision was taken.

A. Yes.

Q. It also occurred to me, looking at this, to what extent did the haemophilia directors have input into that decision and that course of action? It rather looks like a fait accompli, but is that incorrect?

A. No, I wouldn't say that. I would say that SNBTS had come to a view and that's what Dr Cash is calling a "decision", but if anyone at that meeting -- and this is why he has brought it to the attention of all these different people -- had said, "We don't agree with that. We would rather you did something else," Professor Cash would have taken that into account and reviewed that decision.

Q. But certainly there was no dissent from the haemophilia directors at this meeting about that course of action.

A. No.

Q. I understand, thank you.

I would like now, please, doctor, to return to the briefing paper and to continue with the chronology of what happened in Scotland. So I think we had finished at page 43 of the briefing note and at the bottom of that page we had got to the paragraph -- and this comes back to the point we touched upon earlier, whether the option of copying the BPL process for 8Y. At the bottom of the page, you say:

"The option of directly transferring the methods and technology used by BPL was not chosen because a number of uncertainties remained, in particular, the use by BPL of a chemical (heparin) at a concentration which interfered with the routine method used by SNBTS for measuring Factor VIII activity; uncertainty over the practicality and time required to replace the SNBTS method of measuring Factor VIII activity with the method used by BPL."

That's essentially a reference to different Factor VIII assay methods?

A. Yes, correct.

Q. Over the page at page 44, the next bullet point:

"Uncertainty over the omission of aluminium hydroxide adsorption in the BPL process and the possibility that minor process variations might result

in an instability to Factor VIII."

I'm not sure we need to know more about that other than to notice a concern. Then the next bullet point:

"Difficulties previously experienced by the SNBTS in the use of precipitation/centrifugation to recover purified Factor VIII from dilute solutions."

So are these really technical concerns?

A. Yes, they are largely technical concerns and the question we were faced with was, what could we do most quickly, or what did we think we could do most quickly. And that was the judgment that we made, that we could do it most quickly using procedures we were more familiar with and that were more compatible with our operation.

Q. And the factors you have listed in these bullet points would all be things that may slow you down?

A. That's right.

Q. The last bullet point:

"The need to purchase, install and become familiar with large-scale size exclusion chromatography in Factor VIII processing."

If PFC had wished to copy the BPL 8Y process, would that have involved having to order, purchase, install, new plant and machinery?

A. Yes, it would, yes.

Q. And would that have been off the shelf items or items

that would have to be specially designed or what?
A. The equipment that Dr Smith was using, I think, had been certainly specially selected and possibly even influenced by himself, and it would have taken time to purchase that. I can't say how long it would have taken but it would have taken some time, and of course, we would have had to get the funding to do that as well.
Q. Would any equipment have to have been specially made for PFC or could it have been simply ordered, or do you not know?
A. We would have had to, I think, see exactly what Dr Smith was using and how he had obtained it, and it's conceivable that it might have been possible to order it off the shelf, as you say, but even then the delivery times for these types of equipment are not immediate and you do have to wait a period of time, and also it was not inexpensive equipment, so we would have had to make bids for funding -- possibly a new bid for funding --
Q. I suppose you also lose control of the exercise, do you, in that if you follow the Z8 option, then do you perhaps retain more control than having to go to outside suppliers of equipment, outside bodies for funding and what have you?
A. I think we had the capability to progress the Z8 option really in hand, if you like. Although we did have to

buy more equipment, we were more familiar with that because we were using techniques that we were already familiar with and, for example, the size exclusion chromatography was not something that we had experience with. So that would have been a new learning process in itself.

Q. Is there an element of better the devil you know?

A. You could put it that way, yes.

Q. And you do say in your statement:

"Therefore, to minimise uncertainty, it was decided to base the method of preparation of the new SNBTS product on technologies with which the SNBTS was already familiar but which were broadly equivalent in their outcomes to the processes being used at the BPL."

You then explain:

"The new SNBTS product was named Z8 ..."

I'll just pause briefly to look at the relevant document. It's [SNB00075608]. This, we will see, is a memo dated 5 March 1986 from yourself to Dr Perry and Dr McIntosh, and it's to do with the question of naming. If we could go over the page, please. Subparagraph (iii):

"Product 3 involves precipitation of the cryo extract (zinc) and concentration. We have previously used the term ZHT but as heating is now an integral part

of virtually all processes, it may be better to use the simpler form Z8. This would be my preference."

Is it really from that date, from March 86 that the term "Z8" is used for this process?

A. I think that must be the case.

Q. Just to pause on this point, going back to ZHT, the essential step there, as I understand it, was that zinc was used to precipitate fibronectin?

A. Fibrinogen and some fibronectin as well.

Q. Yes, to produce a purer product. Going one step back to the unheated NY intermediate purity product, was anything used to precipitate -- was zinc used in that product?

A. There was no precipitation step but there was an adsorption of aluminium hydroxide, which was a standard procedure in virtually all methods of manufacture. As you saw a few minutes ago, that was something that Dr Smith would have left out and caused us a little bit of nervousness in his 8Y process.

Q. So zinc precipitation to create a purer Factor VIII, that really we should think of in terms of ZHT for the first time. Just developing that a little, so was Z8, in a way, a continuation of the ZHT project, in that, what seems to be similar to both ZHT and Z8, is the use of zinc to precipitate?

A. Yes, that's correct and in a way 8Y was also a variation of the ZHT project.
Q. So in a way there is no clear delineation between the different products and projects?
A. There is a lot of similarity in the techniques that are being used. Variations and -- to fine-tune them to do slightly different things.
Q. It's a process of evolution perhaps?
A. Yes.
Q. I understand. Going back to page 44, I think you set out some of the main steps in the preparation of the Z8 in some helpful bullet points. The first bullet point:

"The recovery of cryoprecipitate via continuous thawing."

Secondly:

"Partial removal of fibrinogen and fibronectin from cryoprecipitate extract by precipitation with zinc and heparin, using a much lower concentration of heparin than BPL."

That step, is that developed from the ZHT?
A. Yes, it's very much the same step.
Q. I understand. Third step:

"Removal of destabilising coagulation factors by adsorption to aluminium hydroxide."

Fourth step involving calcium, and the next bullet

point:

"Recovery and concentration of Factor VIII using ultra-filtration technology."

I think this again seems to have been a development of the ZHT project?

A. That's correct. We had done quite a bit of work on that in the ZHT project and that was the procedure that we thought was most suitable for the Z8 project also.

Q. The next bullet I'm not going to go into, and then the last bullet point:

"Freeze-drying of the product using a new type of freeze-drying cycle that had been designed by PFC scientists in October 1985 in order to freeze-dry the high purity NYU product."

So again, that's going to be an example of where the work on NYU helped produce Z8.

A. That's correct.

Q. This isn't, of course, a full account of how Z8 was manufactured, and perhaps for completeness I can simply give the references in your briefing note to where you do give a full account. In particular -- I just give this for reference -- between pages .1869 and 1873, one sees a full account of the Z8 manufacturing process.

Also, if we can, perhaps, go to a flowchart at page 1852 -- sorry, this is a different document. The

full reference for this document is [PEN0121852]. This is a document you produced for the B3 hearings. Could we have that document up, please? [PEN0121852]. It's between pages 1869 and 1873 of that document. One sees a full narration of the Z8 process but if we could go to page 1852, hopefully a flowchart should appear.

THE CHAIRMAN: I think we are on 1852.

PROFESSOR JAMES: We are on 1852.

MR MACKENZIE: 1885? I think in the right-hand column we can see a flowchart that applies to Z8. Is that correct?

A. That's correct.

Q. And perhaps we can go to the bottom of the column and we can see C19 and C20. C20 is the freeze-drying step and then the separate final step is to dry heat at 72 hours at 75 degrees or 80 degrees centigrade. Is that correct?

A. That's correct.

Q. Sir, I don't propose going through the processes in any more detail than this. If you would like me to ...?

THE CHAIRMAN: I don't think so. I think the structure of this was gone over when we looked at the first two columns in particular and I don't see any need to go over it.

It is noted that with Z8, we are on to method 2 of

freeze-drying. As a change, I don't know whether you want just to underline that. But I think the rest of it follows through quite clearly.

MR MACKENZIE: I'm grateful.

We can put that to one side now, thank you. Return to the briefing paper, please, at the bottom of page 44. You mention:

"A visual comparison between Z8 and the earlier NY products as shown below ..."

We will come to that in a second.

"Both vials contained 250 international units of Factor VIII activity. The vial of the NY product on the left was freeze-dried from 40 ml of solution while a vial of Z8 on the right was freeze-dried from 10 ml solution."

A. That should actually be 15 ml. That's my mistake.

Q. It should be 15 instead of 10?

A. That's correct.

Q. I'm grateful.

Over the page, please, to see these pictures. I was hoping for colour but I am afraid it is black and white, but certainly we can get an indication of the volume of the product in the vial, I think, from the picture. At page 45, looking at the picture, in short, NY is on the left and Z8 is on the right. Is that correct?

A. That's correct.
Q. Is there the same amount of Factor VIII activity in both vials?
A. Sorry?
Q. Is there the same amount of Factor VIII --
A. Yes, they are both designed to give the same dosage.
Q. But because the Z8, the vial on the right, is purer, there is less volume in the vial?
A. That's correct.
Q. I see. Then continuing with the text, you explain:

"Suitable process conditions for the manufacture of Z8 were determined in small volume laboratory experiments that were performed during the first quarter of 1986 ..."

Is that a reference to the work of Dr McIntosh in the research laboratory?
A. It is, yes.
Q. "... and translated to pilot scale operation in the second quarter of 1986."

"Translated to pilot scale operation", is that a reference to the work moving off the research lab and into the main manufacturing part of PFC?
A. It is, yes, but it's -- work in the main manufacturing part, that's done still in relatively small volumes because we don't want to consume huge quantities of

plasma unnecessarily.

Q. I understand. Perhaps two documents will just confirm matters, if I may, document [PEN0171411]. We can see from the top of the page:

"Preparation of immediate purity Factor VIII for heating: Z8-6-001. Pilot run, 23 June 1986."

Is this essentially a record of the first pilot run of Z8?

A. It is, yes.

Q. The reference "Z8-6-001", what does that mean?

A. That gives you a batch number, if you like. "Z8" is the product type, "6" is the year, 1986, and "001" is the first preparation of that type of material.

Q. I understand. Could we also, please, for completeness, look at [SNB0079049]. We can see, I think, from the heading "batch Z8-6-002," dated 28 July 1986. So this is a second pilot run of Z8?

A. That's correct.

Q. Were there only two pilot runs, do you know, or were there more?

A. I think there were only two at this volume. It's really volume-related, and here we are talking about maybe 200 litres of plasma, I think, and when we get to full-scale, we are talking about thousand litres of plasma or something close to that.

Q. Thank you.

Returning, please, to the briefing paper, about half way down page 45:

"By July 1986, progress in the pilot studies was encouraging and there were good stocks of existing 68 degrees/24-hour heat-treated Factor VIII concentrate available. It was therefore decided to cease production of the existing product ..."

This is a reference to the existing intermediate NY heat-treated product.

A. Yes, that's correct.

Q. Thank you:

"... in order to release production staff and facilities in order to fast track the development of Z8 at large scale. Preparation of the first production trial batch of Z8 was begun in August 1986."

The reference to "the first production trial batch of Z8", is that a reference to scaling up the production to full-scale production?

A. Yes, it would have been pretty much up to the large volume of plasma that we would typically make a batch of Factor VIII from.

Q. I understand, and again, two references for completeness: firstly, [SNB0079072]. These are the notes of a steering group meeting on 30 July 1986:

"The following decisions were made: 1. No further old-style Factor VIII (NY) will be made for the time being. 2. A large-scale production run of the new Z8 process was approved for Monday, 4 August 1986."

It's really very much what is said in the briefing paper, Dr Foster, and the other reference, if I may, is [SNB0076048]. This is the letter of 7 August 1986 from Dr Perry to Dr Boulton in relation to Z8. He says:

"Just a note to let you know that we have now successfully manufactured two batches of the above product and assuming all is well on the QA front, we are well on target to make product available for a clinical trial end of August/beginning of September. All looks well at the moment ..."

One question, Dr Foster, the reference to "successfully manufactured two batches of the above product," is that a reference to the pilot scale operation, the full-scale operation or perhaps both?

A. At this date it would be the pilot scale batches would have been -- completed their quality control and you could say they were successful. The first large-scale batch would have been processed but it wouldn't have completed analysis by this time, I don't think.

Q. Thank you. If I may put that to one side, please, and return to your briefing paper, you explain in the middle

of page 45 that:

"Further fine-tuning of conditions for the preparation of Z8 was required at the much larger scale of operation with the new freeze-drying process requiring particular attention. Only a small number of vials had been produced in each pilot batch, whereas at full-scale, the number of vials was large enough to fill the freeze dryer shelves. Under these conditions, a significant number of vials failed to withstand 80 degrees centigrade dry heating."

You go on to explain:

"Differences in the crystalline structure of the frozen plug were observed to be associated with this behaviour. Vials with a plug of a uniform fine crystal structure could withstand 80 degree C dry heating, whilst those with plugs containing larger crystals or a mixture of fine and large crystals did not. This is illustrated in the photograph in figure 2 below, which shows three vials of Z8, all of which were dry-heated at 80 degrees C for 72 hours."

This doesn't come over well in black and white, I am afraid. I'm sure we are going to get a colour copy available to the chairman and others but for present purposes, you describe that:

"The first vial on the left exhibits a plug of fine

crystals, which I don't think we can see on this copy, and the middle one has a mixture of fine and large crystals, while the third one on the right exhibits large crystals, and only the vial on the left was able to tolerate dry heating at 80 degrees for 72 hours, and the failure of the other two vials to withstand severe dry heat treatment is illustrated by the degree of discoloration present."

We certainly need a colour copy to see that and we will arrange that. We will take your word for it for present purposes.

A. You have got the colour copy. You can analyse that.

Q. You go on to say on that page that:

"Differences in crystal structure are determined by the rate of freezing and it was postulated that the uniform formation of fine crystals might be a result of supercooling, a condition at which the vial contents remain liquid below the freezing point of the solution. In this situation, a small disturbance is sufficient to cause instantaneous crystal formation (ie freezing) with fine crystals being formed."

Just pausing there, doctor, am I right in thinking that in the pilot scale production there weren't that many vials going into the freeze dryer, whereas when matters were scaled up to full-scale production, the

freeze dryer was full of vials, and that difference in how full the freeze dryer was seems to have made a difference?

A. Yes, because the freezing takes place inside the freeze dryer, the vials sit on a shelf and the refrigerant is inside the shelf. So if you have many more vials there, then the way that material freezes is going to be quite different to when there are only a few vials, because the few vials get all the refrigerant, whereas with all of the vials, you haven't got as much availability of cold to freeze the material in the same way.

Q. Then at the bottom of page 46, you explain that:

"Experiments confirmed this hypothesis and a two-stage freezing procedure was designed whereby the necessary fine crystal structure could be obtained throughout every vial of every batch of Factor VIII concentrate on every occasion."

And that:

"Subsequently, careful examination of the product temperature profile obtained during the freeze-drying of a sample of BPL's 8Y exhibited a sharp rise in temperature at the point of freezing."

Just to pause, Dr Foster, and to display my ignorance again, it seems counter-intuitive that there would be a sharp rise in temperature at the point of

freezing, one would have thought there may be a sharp fall in temperature, but that's simply wrong?

A. When a material freezes it changes from a liquid state to a solid state and it does so because it is more stable in the solid state. When it reaches that solid state, because it is more stable, there is this release of energy, it is an exothermic process. If that happens gradually, you don't see that because that energy is so gradual, it's dissipated very -- and you can't detect it. But if it happens -- in order to mature at the same time, it actually shows up as a rise in temperature, and you can see that in the figure below, where you can see a distinctive rise in temperature when this change of state takes place and the molecules are in a more stable configuration, so they release energy and the temperature rises.

Q. I see. You go on to say that:

"A sharp rise in temperature at the point of freezing is a characteristic feature of supercooling, indicating that supercooling may have occurred advantageously with 8Y."

You then make reference to that being illustrated in figure 3, which I don't think I'll go into. Two letters I would like to then look at, please. One, [SNB0076080]. This is a letter dated 29 August 1986

from Dr Perry to Dr Boulton in relation to trials of phase 3 factor VIII. This is Z8.

THE CHAIRMAN: Are you leaving the topic that you were on?

MR MACKENZIE: I am, sir, yes.

THE CHAIRMAN: Look at the preliminary report, please, at page 507. Could we have that? It was an exchange with English scientists at about this time over the question of freeze-drying. I'm just looking for a little bit of explanation of what happened. I'm hoping you will remember some of this when you see it, Dr Foster. Page 507.

It should be about 82, I think, on there. You see at paragraph 11.319 there, there is a reference to a report on the BPL model and it includes a reference to your work and then it says:

"Note was taken of the Scots research in relation to Factor VIII. In the context of Factor IX, the conclusion was that there is no information yet on how different softening conditions are affecting Factor IX but it will be interesting to look for differences if only to convince ourselves that there are none."

Then there is a letter from Dr Smith to you, reporting on developments after that report, saying that pre-softening had been a major variable.

How does that fit in with what you have been telling

us?

A. It doesn't. It's a different topic and it's to do wit the preparation of cryoprecipitate and how the plasma is prepared before you thaw the plasma to prepare cryoprecipitate, which can also have an effect on what happens afterwards.

But we did -- after we had realised and discovered that freeze-drying was important, of course we had let Dr Smith know this, and at PFL they did start a project themselves on freeze-drying and they began to look at it in much more detail, and that became quite a large project from their point of view because they did accept that freeze-drying was important and they had to begin to better appreciate that themselves, and we had a number of reports from them about their work. So they were beginning to investigate this too from their perspective. They recognised its importance.

THE CHAIRMAN: Did you get anything out of this? Was there anything positive that came out of this so far as PFC's procedures were concerned, or was it a case of you supplying information that affected the way the English --

A. No, I don't think we learned anything from it ourselves but it was useful to know that they were agreeing with what we were doing and they were doing the same sort of

thing.

THE CHAIRMAN: So far as the softening is concerned, did that contribute to the effectiveness overall of the procedure or is it wholly incidental?

A. It's not incidental. It's important because if it's not done correctly, you can end up with too much fibrinogen in the product and that doesn't survive heating. So it's part of the process that has to be done correctly.

THE CHAIRMAN: Thank you.

MR MACKENZIE: Thank you, sir.

Dr Foster, could we then please go back to [SNB0076080] to continue the chronology of what was happening in Scotland at this time, the letter from Dr Perry to Dr Boulton of 29 August 1986. He states:

"While we now have material which can be used for trial beginning of September in Dr Ludlam's patients, I am not at this stage convinced that it has a proper GMP pedigree or that it represents our definitive process. We have recently encountered an eleventh-hour problem with freeze-drying, which we are now addressing with some considerable urgency. The result of this is that we will not be able to meet the target dates of early September for clinical trials but I am confident that the delay will be measured in weeks rather than months. As soon as I have a new trial target date,

I will contact you. I would be grateful if you informed Dr Ludlam of this unexpected delay, but at the same time assure him that we will be back on course in the very near future."

The reference to the eleventh-hour problem with the freeze-drying, is essentially reference to what you have discussed here and what's set out in your briefing paper?

A. Yes, I think it must be.

Q. Yes. It's envisaged here that the delay in commencing the evaluation of the product, Dr Perry hopes that will be measured in weeks rather than months. I think as things turned out, it wasn't until, I think, December that Z8 was available for clinical trial?

A. I think 2 December was when the batch was released -- it was made available for issue, yes.

Q. Just to continue matters, could we then please look at document [SNB0076144]. This is a meeting --

A. Before you go on to that, could I just add that of course it's important to appreciate that it takes two or three months to manufacture a batch of Factor VIII. So even if the batch was released or available for release in early December, we had actually prepared in October, and it took the period after that to carry out all of the tests. So it takes quite a long time to prepare one

batch of Factor VIII. So in fact the timescale to have the material available is not that long after Dr Perry's letter, that he wrote to Dr Boulton.

Q. Could you perhaps just talk us through that period in terms of the manufacturing period, how long that takes, and how long it takes for any subsequent testing?

A. It would take about a week to process the material until you had the product in the vial and perhaps heated, and then you are really talking about two to two and a half months after that to carry out all of the tests that have to be done; the full quality control is very extensive.

Q. So as at 1986, October 1986, what were the type of tests that were undertaken?

A. Oh, there would be a very large range of tests to do with the biochemical characteristics, the biological characteristics, the Factor VIII content, the microbiological content; samples might be sent to NIBSC. You are better asking Dr Cuthbertson because this was his department, not mine, but some of these tests involved doing bacteriology to establish if there was any growth of bacteria in any of the materials, and those tests, simply to wait and see if bacteria grow, take quite a long time. So there is an inbuilt time element that you just can't avoid.

Q. Yes, and that may tie in, perhaps, with the minutes of this meeting, a meeting of the coagulation factor study group, on 14 October 1986. I think you were present, doctor. If we can look, please, at page 3. This is at page 3. There is an update on Z8 and then, paragraph 3, "The Introduction to Routine Production". I think we can see a reference to lots 1, 2 and 3 and then:

"In view of the above ..."

That must be a reference to some of the problems perhaps:

"... modifications were made to the freeze-drying cycle."

Lots 4 to 8, full-scale. Et cetera. Top of page 4, we can see a reference to:

"Failure at full-scale production was due to varying performance of the freeze dryer and a change in product composition (increased fibronectin) at batch 4. In an effort to overcome these problems, work was continuing in the following areas:

"1. Modifications to procedure to improve extraction."

Is that a reference to part of the freeze-drying process?

A. No, this is when the cryoprecipitate is being dissolved and there is some separation of unwanted fibrinogen at

that point.

Q. I see:

"2. The establishment of freeze-drying parameters to cope with worst case scenario.

"3. Reduction of weight of cryo/L plasma to 1984 levels."

What's that a reference to, number 3?

A. The amount of cryoprecipitate that you get from the plasma can be influenced by a number of things, including the softening process we have just discussed. There is an optimal weight of cryo per litre of plasma to get a good yield without losing too much Factor VIII, but not get too much fibrinogen or fibronectin carried over, and it's a matter of finding that optimal position. And we perhaps had moved slightly away from that and needed to give that a bit more attention.

Q. There is a reference to:

"It was thought that it was unnecessary to heat at 80 degrees for 72 hours, and studies on product heated at 75 degrees for 72 hours had yielded approximately 300 iu Factor VIII/L plasma."

It was really the reference to:

"In an effort to overcome these problems, work was continuing in the following areas."

Do you know approximately when these problems were

solved?

A. I think that we begun to introduce what we called the "two-stage freezing", that solved the problem in terms of the crystal structure in October -- that's my best -- I can say, from this point in time, without going back into batch files -- I mean, Dr McIntosh might remember this better than I can but it was around about then that we introduced the two-stage freezing procedure which resolved the problem.

Q. And you had given evidence previously --

A. It might have been slightly later than October, actually.

Q. I just wondered, when you said earlier that in fact, Z8 was available on 2 December for trials, I think you thought it was probably produced in October. Is that still your view?

A. Yes, the material that was available in December for trials. Some of that was processed in -- as early as October. But I think that was only heated at 75 because it didn't have the right crystal structure. We did have material that was available at the end of December that did have the right crystal structure. So it must have been processed around about, maybe the end of October/early November. We can go back and look at the exact dates, if that would help you.

Q. I don't think it matters.
THE CHAIRMAN: I was just about to ask how do you feel you are getting on in terms of use of the day.
MR MACKENZIE: I think I'm getting on very well.
THE CHAIRMAN: I not looking for a qualitative assessment, merely in terms of time.
MR MACKENZIE: I did mean in terms of time actually. We have almost come to the end of 1986 and the period is to --
THE CHAIRMAN: 87.
MR MACKENZIE: Early 87, but Dr Foster doesn't really speak to clinical trials. That's outwith his area. Sir, I would certainly finish my bulk of questioning of Dr Foster today. I may not finish all of my questioning of him by certainly by 4 o'clock, I would have finished the bulk of it.
THE CHAIRMAN: Is there spare capacity tomorrow?
MR MACKENZIE: Yes, there is. Dr Foster is helpfully available tomorrow morning. We also have Dr Cuthbertson and Professor Cash, but they are speaking to much narrower matters.
THE CHAIRMAN: My only concern is whether we should try to have a relative briefly break.
MR MACKENZIE: That might be helpful, yes.
THE CHAIRMAN: Relatively brief then.

(3.07 pm)

(Short break)

(3.23 pm)

MR MACKENZIE: Thank you, sir.

Dr Foster, before I move on, the chairman had mentioned a point about plasma conditioning, I think, before we had the break. There may be two further documents which may just help complete that point. Could I firstly, please, put to you [SNB0076275]?

We can see this is the letter dated 8 December 1986 from Dr Smith to yourself, and he says:

"[The enclosure] may help to shed some light on old empirical observations. Please treat it in confidence before publication ..."

Et cetera.

I think if we try [SNB0076276]. This is the enclosure. It's headed "8XA."

What's that? Is that 8Y, or is that something else?

A. I don't know, I'm sorry.

Q. So it's not clear what that relates to but we can see the title is then, "The effects of plasma conditioning on subsequent cryoprecipitation and cryo-extraction."

We don't have to, I think, know more today than this relates to plasma conditioning, but if we could then, please, go to your response, which is [SNB0076296], and

this is a letter from you, Dr Foster, dated 16 December 1986 to Dr Smith, and you thank him for his report on plasma conditioning and say:

"We have also confirmed our previous observations and your findings seem to fit in with our experience precisely. We have been doing intensive work on freezing and freeze-drying over the last three months. When we scaled up the Z8 process, we came across two problems: one, our large production dryer was performing differently to our small production dryer and our pilot dryer and two, variations in final product, total protein (because of plasma conditioning et cetera) gave major batch to batch variations in solubility ... we now believe that we have overcome all of these problems (only time will tell) by means of a special freezing technique and by designing our freeze-drying cycle more carefully. Freezing turned out to be the most critical area."

Is that correct, freezing or freeze-drying?

A. Yes, I would say so.

Q. "Freezing turned out to be the most critical area. Poor results (solubility) were linked to the presence of a crystalline structure after freezing and the degree of crystal formation increased with increasing protein concentration ..."

Is that essentially consistent with your evidence earlier in answer to the chairman's questions?

A. This is talking about freezing of -- this final paragraph -- freezing of the product. So that's what I am describing here, whereas the very first line, which was the report on plasma conditioning, was the thawing of the plasma. So they are quite different things but they do all have an effect on the final product.

THE CHAIRMAN: I think that my interest was in the contribution that two different processes were making, not an attempt to link them as one, but are they properly seen as two things that were being developed by you, roughly along the same timeframe, each of which was contributing to the quality of the final product?

A. Yes, it was a learning process on both our parts and we were learning from BPL and they were learning from us.

MR MACKENZIE: In the second last paragraph on the page, when you say that:

"We now believe that we have overcome all of these problems by means of a special freezing technique and by designing our freeze-drying cycle."

The special freezing technique, for the avoidance of doubt, what step in the process is that carried out?

A. That's the freezing of the product in the freeze dryer, where I talked about achieving supercooling to obtain

fine crystals and we had a two-step freezing process that was designed to achieve that.

Q. Yes. I understand. So really what you are saying is that the whole freeze-drying procedure, that was the most critical area, rather than the prior step of plasma conditioning?

A. Yes, although the plasma conditioning was not unimportant, but the most critical thing was the structure of the frozen material in the vial that is being freeze-drying.

Q. I think that's entirely consistent with what you explained earlier. I'm grateful.

Moving on, please. Could we then look, please, at [SGH0016672]? This is a note of a clinical trial review meeting on 1 December 1986. Could we, please, go to page 4? Item 9:

"Z8 heat-treated 75 degrees/72 hours. Dr Perry reported that this product 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 coordinating this study."

I think that's consistent with what you said about the product being available for clinical trial, I think you said 2 December?

A. Yes, that's the date on the official batch record.

Q. Yes. So if we could then, please, go to the batch record, which is [PEN0171437]? I don't think we have looked at this in the Inquiry before. Can you explain to us what this sheet is in general terms?

A. This is a sheet that records, for each batch of Factor VIII, what the batch number is, what the product is, if you like, in the top left-hand corner, who has authorised it to be issued, and then the date that it has been placed to issue, and it also states the expiry date, which in this case is two years after the date of issue.

It tells you how many vials were placed at issue, the volume of the material in the vial, the biological content, which in this case is 220 international units of Factor VIII, and then in the table below, you see the number of vials issued and the date that they were distributed and where they went to.

Q. Thank you.

You mention the expiry date was two years after the date of issue. Is that right? Is it two years after the dated of issue or date of manufacture or what?

A. It's -- it will be the -- you would have to ask Dr Cuthbertson to get a precise answer. It may be the date that the manufacture was completed.

Q. Yes.

A. But I'm not certain about that.
Q. We will ask Dr Cuthbertson but we can see this document and in the top right corner somebody has written "75 degrees".
A. That's correct.
Q. So this presumably relates to the batches of Z8 which were manufactured at 75 degrees for 72 hours?
A. That's this one particular batch and it was heated at 75 degrees for 72 hours.
Q. I see. We can then see the date placed at issue, 2 December 1986. I think we can then see that date, 22 December 1986, number issued, 20. It may be, Dr Foster, I should leave my following questions for Dr Cuthbertson. Presumably this is within his area?
A. Dr Cuthbertson and Dr Perry, yes.
Q. Yes, well, I think we have asked you a lot of questions so we will keep some for others.

Then just to complete this chain, please, could we then go to [SNB00079130]. The notes of the meeting of the Z8 steering group of 18 December 1986. Just out of interest, we see the following points were agreed:

"1. Plasma conditioning is still seen as a problem which requires attention."

So that was an ongoing matter to some degree. Is that correct?

A. That's correct.

Q. Then paragraph 6:

"All batches manufactured in 1986 will be heated at 75 degrees centigrade for 72 hours with 20 vials from each batch being heated at 80 degrees centigrade/72 hours."

Over the page, we can see paragraph 8:

"No clinical feedback has yet been received."

I'll cover that with other witnesses:

"If none is forthcoming in the near future, then we may have to revert to the manufacture of NY."

So really at this stage, the lack of clinical trials of the Z8 product was becoming an issue?

A. I think we were certainly concerned about this because, as this memorandum states -- this minute states, the stock of product was running down and we were worried that we might actually run out.

Q. Yes. Again, just to continue this chain, please, the final document in this respect, [SNB0015507]. If we go to the last page, please, we see again this is a note by Dr Perry of 15 January 1987. The first page again, please. Again, this is an example of Dr Perry's notes for the meeting of the haemophilia and SNBTS directors. This meeting took place in February 1987. Then one:

"Introduction of new Factor VIII product (Z8)":

"Plans are now well advanced for the introduction of a new Factor VIII preparation."

Then specifics of the product is given in comparison with the existing NY product. I think we can see in the right-hand column for the new product Z8, for the heating regime, 80 degrees centigrade, 72 hours, but initial supplies will be heated at 75 degrees for 72 hours. And we can then see, two paragraphs under the table, the statement that:

"Product development has required that initial batches of product are heated to 75 degrees for 72 hours. All batches manufactured since January 1987 are heated to 80 degrees for 72 hours."

It's the reference to "product development has required", is that a reference to the difficulties in particular for freeze-drying and plasma conditioning?

A. Yes, I think so. The early production batches couldn't withstand heating at 80, and it was found that they could withstand heating at 75, and the view was taken that this was still superior to anything else that was available in Scotland at that time and therefore those batches should be heated under those conditions.

Q. Can we then please return to your briefing paper, just to continue with the chain of events. We are now at page 48, please. The second paragraph tells us that:

"A period of about three months was required to prepare and fully test a batch of Factor VIII concentrate, therefore it was not until December 1986 that the first batch of Z8 was available for clinical evaluation."

I see. So the reference to "fully test the batch of concentrate" is a reference to what you have told us earlier about the various tests in PFC that Dr Cuthbertson was responsible for?

A. Yes, it's testing and its review of all the documentation, to be sure that everything has been done correctly. There is a quality assurance process that takes place as well.

Q. But that's not a reference to the clinical evaluation --

A. No, it's not a clinical evaluation.

Q. Thank you.

Then under "1987", you tell us -- in short, Dr Foster, once you have achieved production of Z8 and its full-scale manufacture at PFC, I think really the question of clinical evaluation of the product and questions of compensation and indemnity are really matters I can ask others. Is that correct?

A. I think that is correct, yes.

Q. But you do helpfully just set out events at the beginning of 1987 in any event, but I'm not going to

detain you in that. But at the bottom of page 48 you do say that:

"At the PFC, most batches which could not withstand 80 degrees/72 hours dry heat were found capable of withstanding heating at 75 degrees for 72 hours. As this degree of heat treatment was superior to that being applied to alternative Factor VIII concentrates available in Scotland at the time, it was decided that it would be preferable to release this material."

You say that:

"No cases of HIV, NANBH, or HCV transmission have been associated with 75-degree/72 hours dry-heated ... Z8, suggesting that this procedure was effective in preventing transmission of these viruses."

Pausing briefly there, were studies undertaken in that regard or are you simply relying on the fact that there may have been no reported cases of transmission or what?

A. My memory is that some of the 75-degree batches were included in studies at that time and they were not found to transmit non-A non-B Hepatitis or Hepatitis C, but this was a very long time ago and I'm really just going on my memory now.

Q. Right. Who would be best placed to speak to that?

A. Probably Dr Ludlam.

Q. Thank you.

Then in your briefing paper you look at the period 1988 to 1990, and you tell us that there were further revisions, I think, made to Z8. Is that correct?

A. Yes, that's correct and this is not unusual. All manufacturing processes like this in plasma fractionation require fine-tuning and -- so this was no different, it was no exception, but there was quite a bit of fine-tuning required, as we learned more and more about the process and how robust it was to variations, the day to day variations that occur in these sort of situations.

Q. Yes. Correct me if I am wrong but presumably, in respect of the period 1988 to 1990, was it the case that any deficiencies -- if they can be called that -- in the product in that period did not cause Hepatitis C infection?

A. No, the product would have been heated at 75 or 80, and to the best of my knowledge those products didn't cause any infection.

Q. Thank you.

Then in the remainder of the briefing paper on this page and over the next page, you then continue with further developments on different products up until 2006. I don't propose, sir, to read that out. I think

it's of interest as background but I think it does take us outwith the scope of this topic C3 but it is all set out there. Thank you.

That completes the briefing paper, Dr Foster, at this stage. I think I would like to return now to your statement, please.

THE CHAIRMAN: Are we just taking the Factor IX --

MR MACKENZIE: I will come back to that at the end, sir.

THE CHAIRMAN: You are coming --

MR MACKENZIE: Yes.

Your statement, doctor, was at page 5 of [PEN0171556].

Doctor, this is only page 5 of a 33-page statement but I wouldn't be disheartened because we have covered most of the ground that I wish to cover and we can skip some of these pages and certainly I won't be referring you to any number of the same other documents, so I'm fairly confident -- lawyers always say this -- that we can deal with what follows much quicker than what has gone before. I think we were on to question 3, doctor, which was:

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

And we asked:

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

I think the answer is probably clearer to us all from what you have said today, but you have helpfully summarised matters below in your response and I don't propose reading that out with a view to avoiding any repetition.

Over the page. I think the answer in short, Dr Foster, is that it wouldn't have been possible to immediately switch to heating the existing intermediate NY Factor VIII product at 80 degrees for 72 hours. Is that not the short answer?

A. No, if we had wanted to do that, we would have had to bring in additional freeze-drying capacity, which would have taken a lot of time and I'm not even sure we could have fitted it into the building. It would have required so much freeze-drying space.

Q. Yes. We have gone over that, thank you. Then at page 6, question (b):

"Why did it take until May 1987 before [Z8] was available for clinical use?"

Again, we have gone over the detail of this but you do give a helpful summary that typical phases were a:

"Design of the process ... in the research laboratory ...

"Scale up ... to pilot scale operation ..."

We have looked at that:

"Scale-up of the whole process to full-scale operation ..."

We have looked at that. The question of clinical evaluation. I'll ask others about that. Et cetera.

Then page 7. Again, we have gone over this:

"A number of unexpected problems emerged during the development of Z8."

In particular the freeze-drying. We don't have to go back over that, I don't think. Then page 8, subparagraph (c), the question was:

"What changes in the manufacturing processes were made and when to enable ... Z8 to be dry-heated at 80 degrees for 72 hours?"

You tell us that the production of Z8 required a new manufacturing process to be established from the recovery of cryoprecipitate paste onwards, and these changes have been described in an earlier witness statement. Simply for the record, I think that's a reference to [PEN0121852]. That's your B3 statement, in particular pages 1869 to 1875.

Then question (d), we asked:

"What was the original timescale for the production and introduction of Z8? If that timetable was not met,

when and why did it slip?"

We have looked at some documents in that regard and I think I will take Dr Perry through some documents in that regard, but in your response you say that you had:

"... originally advised Dr Perry that material might be available for clinical evaluation in April 1986 ... included in a briefing note for the haemophilia directors ... written by Dr Perry in February 1986."

But your estimate was wrong for a number of reasons. Firstly you 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 ... 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. [You were] not involved in this decision as this was the responsibility of [Dr Cuthbertson]."

I will ask him about that, but the point that occurred to me, Dr Foster, is that even if a phase 1 clinical evaluation had taken place off the pilot scale Z8, given the difficulties which were encountered in scaling up the product and the changes in procedures which required to be made, in particular to

freeze-drying, is it not the case that a further phase 1 clinical evaluation would have been required in any event for the scaled-up Z8?

A. Yes, you might well be right. I think we did make some changes, once we came across these problems. That might well have led people to think we must do the clinical evaluation again but, of course, that was in the future. So I hadn't anticipated that.

Q. Yes. And then you also refer in the other bullet point to a number of unexpected problems which emerged, all of which took time to solve, and we have gone over that in some detail. Page 9, please. We asked whether:

"... PFC's work on the development of the high purity Factor VIII concentrate NYU resulted in any delay in the introduction of Z8?"

And your response is that you don't believe that was the case. You say:

"Once the decision had been taken to develop Z8 ..."

And that would be in late 1985/early 1986:

"... this product was given the highest priority and research on the development of a high purity Factor VIII concentrate was effectively shelved."

Certainly, I think, one can see that once it had been decided to develop Z8, the product was available within about a year. But could it be suggested that the

decision to develop Z8 should have been taken earlier?
A. If we had taken a decision earlier, without knowing of the importance of freeze-drying, it's my opinion -- and it can only be an opinion -- that we would have failed. We would have struggled to reproduce the 8Y process, because that is the experience of other manufacturers who tried to do that without understanding the importance of freeze-drying.
Q. This is all hypothetical but if a decision had been taken to develop Z8 earlier, let's say in July 1985, would subsequent events then have run essentially the same course, in that the problems which were discovered with freeze-drying, would they have been discovered about six months earlier, for example?
A. No, because we wouldn't have known that freeze-drying was a critical part of the process and we would have been exploring other aspects of the process to try and find out what the problem was without understanding that it was freeze-drying and freezing that were important, and that's precisely what happened in Australia and in America, when they tried to reproduce this process and they failed.
Q. So why was the discovery in about October 1985 -- sorry, I'm talking about different things.
In October 1985 it was discovered at PFC that it was

the freeze-drying process that was important in achieving severe heat treatment rather than purity.

A. That's correct.

Q. So if a decision had been taken in July 1985 to prioritise Z8, your point is that the discovery in October 1985 would not yet have been known.

A. It might never have been made. We might never have found out.

Q. Could that discovery in October 1985, about the importance of the freeze-drying process, have been discovered earlier?

A. It was -- we discovered it as part of the NYU high purity project and it was only because we had redesigned the freeze-drying process to freeze-dry high purity Factor VIII that we actually got to that point. If we hadn't redesigned our freeze-drying process, we wouldn't have found out.

Q. I understand. So even if the decision to develop Z8 had been made earlier, the separate NYU project would have run the same course in time? It wouldn't have been advanced?

A. Sorry, can you repeat the question?

THE CHAIRMAN: Would it have been continued at all or would you have abandoned --

A. We probably would have abandoned that, yes.

THE CHAIRMAN: So there would have been a discontinuation in that and then, I suppose, if you tried to follow the patented prescription, you would have failed, as others did?

A. That's the best of my judgment that I can make. Dr McIntosh was a brilliant scientist, so maybe he would have succeeded, but my view is we probably wouldn't.

THE CHAIRMAN: But if you then had to go back to Dr Johnson's process, after having failed to achieve the Winkelman result, you would have been delayed even further, on one view.

A. That's correct, yes.

MR MACKENZIE: I'm grateful, sir. I follow that now.

Then returning, please, to page 9, you really explain that, I think, by saying:

"I believe, on the contrary, that the development of Z8 would not have succeeded without the knowledge gained from working with Professor Johnson and in particular the discovery in late 1985 that freeze-drying was the critical step in achieving heating at 80 degrees centigrade rather than the degree of purity of Factor VIII. The importance of the freeze-drying method had not been appreciated at PFL/BPL."

Then (iii):

"In the absence of this knowledge, I am not aware of

any organisation that succeeded in achieving 80 degrees centigrade dry heat treatment of Factor VIII based on the findings of BPL."

You give examples of two organisations which attempted to do that and failed.

Question 5 relates to the commencement of clinical trials and I'm going to ask other witnesses about that rather than you, Dr Foster, if I may, so we can just skip over that, please.

Then page 11. At question 6 it moves on to another matter and asks:

"Did any wider management, organisational or other issues result in any delay in the introduction of Z8, for example by R&D staff not being sufficiently involved in the manufacture and production of products and processes that had been developed by them?"

I should refer to two documents which are really the basis for that question. Firstly [SNB0067120]. This is a memo dated 22 December 1988, so really outwith our main reference period for this topic. It's a memo from Dr Perry to yourself and others on the subject of modification to Z8 freeze-drying cycle. The memo states:

"It would appear that a modification to the Z8 freeze-drying cycle (primary to secondary drying) has

led to a major improvement to product quality and perhaps also yield ... Less reassuring is my personal observation (shared by others) that this particular process modification was proposed some considerable time ago and could have been introduced many months ago ... I would suggest that there are lessons to be learnt from these observations which may avoid future delays. The lessons are:

"1. A need to review the management mechanisms by which such changes are introduced;

"2. A need to explore the possible benefits of some form of scientific audit of manufacturing processes alongside QA audits;

"3. Clarify the role of R&D staff in the surveillance of such processes."

Dr Perry ends by saying:

"It is of course possible that my assumptions are incorrect but in any event I believe the topic should be discussed at the heads of department meeting."

So in short, Dr Foster, are there concerns expressed here by Dr Perry of any relevance to what happened in the period 1985 to 1987 in the development and production of Z8?

A. No, these comments apply to the routine management and production of the product much later. This is end

of December 1988 and it's what I alluded to earlier, that in these types of processes there is fine-tuning that goes on, sometimes, for many years. The way that is progressed is that where there are observations that perhaps an improvement can be made, a proposal has to be made formally to the head of the departments concerned, who are the head of quality and the head of production. That document we called a "process modification", which would lay out the request for a change and give the rationale and the evidence to support it. But it wouldn't proceed until it was approved by the head of quality and the head of production, and that was the established GMP time process. That was the management process in place.

In this case a process modification had been submitted but I think it's probably by Dr McIntosh. It had taken some time to be dealt with and I don't know what the delay was. I know that both Mr Prowse and Dr Cuthbertson were extremely busy people and maybe they had other priorities which had to be looked at but -- and this had been brought to Dr Perry's attention because he was the line manager for all of the heads of department and if their priorities needed to be reviewed, then he was the person to do that.

Q. Yes. There is perhaps a question about the involvement

of research and development staff in the initial pilot-scale production of a new product and then the full scale-up manufacture of a product and then, once a product has been issued, any future modifications of the product -- am I right in thinking that this memo is to do with the third stage, any future modifications?

A. That's correct, yes. In the first stage that you mentioned, which was the pilot, plant and the early development, that was led by development staff, and we had a project manager, who was Dr McIntosh. So he was basically in charge of that. Anything that is done in production has to be approved by the production manager, obviously, and by the quality manager.

Q. How about the second step, the scale-up to full-scale production?

A. Dr McIntosh was involved in all of that and he was leading that process.

Q. I understand.

Then the other document which we had seen was this, [SNB0077576]. This, doctor, is a letter dated 21 November 1990 from yourself to Dr Prowse, the director of the SNBTS National Science Laboratory, of 21 November 1990. So again we see it post-dates the period we are considering. Can we go, please, to page 3, paragraph 1.6, the question of delivery. The

letter states:

"You state earlier in the paper that our poor performance concerning Z8 and S8 was complex and multifactorial, yet here you imply that these problems will be resolved by management changes in the context of PFC product development. I have to disagree. The management changes that I think you are referring to do not address any of the issues required to improve the overall PFC performance."

Over the page:

"There are fundamental issues which relate to operational constraints (eg hours of work) and to the control and supervision of manufacturing operations. While the first of these is being addressed ... I see little or no prospect of improvement elsewhere. In these circumstances, the only way of significantly and favourably affecting our future performance will be to allow R&D staff a stronger role in the overall design, specification and implementation processes. In the past it has been PFC policy for R&D to withdraw sooner rather than later, leaving manufacturing staff to tidy up any loose ends. In retrospect, this has been self-defeating and has been the root cause of many of the problems experienced with Z8, which then followed through to S8."

Can you explain what you were meaning in that

passage, please?

A. Yes. In the development of any product which originates in a research department and ends up in a manufacturing department, there is this transition from research to manufacturing. How that was managed is the subject of many textbooks. One method is called "over the wall", which is not a method that we used.

We worked closely with our production colleagues but we didn't want to put them in a position where they wouldn't have ownership of the process. So there is a transition, where there is a gradual handover and the production staff take on ownership and the research staff withdraw. My preference was to encourage the production staff to take ownership as soon as they possibly could, but as the processes got more and more complicated and more vulnerable to minor changes, then my judgment was that the R&D staff needed to spend longer in production or give more time to that than they had done previously, and that was what I was reflecting in this letter to Chris Prowse in that particular paragraph.

Q. When you refer to the root cause of many of the problems experienced with Z8, what were the problems experienced with Z8?

A. Well, there were relatively small variations at various

points in the whole operation that with the previous Factor VIII product were of no consequence but which with Z8 became important and reduced the yield, perhaps even made the product unable to withstand heat treatment.

So the staff who were used to the old procedures hadn't really fully taken on board that procedures had to be much more closely defined than they had in the past and, in order to make sure that happened, you needed stronger supervision and management. That was a learning process that we all went through as we discovered the degree to which the Z8 process was a very difficult process to operate. For example, how the plasma was stored could affect how the process performed, things like that which had never been a problem before. We had procedures that were quite appropriate and we suddenly found that we had to tighten our limits, if you like, on storage conditions.

Q. Did any of the problems referred to in this letter affect the viral safety of the product?

A. No.

Q. Put that document to one side, thank you, doctor, and then go back to your statement, please, page 11. I think you have really answered the question 6. In (i), in short you say:

"I do not believe that any wider management, organisational or other issues resulted in any delay in the production of Z8 (other than those described [above] ..."

In subparagraph (iii) again you tell us the project to develop Z8 was led by Dr McIntosh of R&D and fully involved all relevant staff from the various departments, et cetera. I don't think we need to detain ourselves further with that answer, thank you, other than at page 12, subparagraph (v), you again confirm that:

"It was the degree of involvement of R&D in these later activities, after the production of Z8 had been established, that was the subject of comments in the documents ..." we have just looked at.

Sir, it's five past four. I can go on a little. I'm not sure if that suits others. I suspect I may have in total another hour to an hour and a half.

THE CHAIRMAN: I think that raises the question of the amount of time that Mr Di Rollo and others might need because if we take another hour/hour and a half tomorrow and then there is an appreciable interest from others, it becomes progressively more difficult to manage the other witnesses tomorrow. I don't want to require people to sit any longer than necessary but I think

I need to know what you all have in mind.

Mr Di Rollo, do you have any information that might be of assistance in this?

MR DI ROLLO: I don't think I will have a large number of questions for this witness. Certainly it wouldn't be, as presently advised, more than about five or ten minutes.

THE CHAIRMAN: Mr Anderson?

MR ANDERSON: I will be about five or ten minutes less than that, sir.

MR JOHNSTON: I don't expect to have any questions sir. I certainly don't at present.

THE CHAIRMAN: That's probably a more accurate answer than Mr Anderson's, to the same effect.

Well, I think, if that's the case, we can probably take the risk and break at this stage. It has been a long enough day. So I think we will take the risk and I look forward to seeing you in the morning.

A. Okay.

(4.08 pm)

(The Inquiry adjourned until 9.30 am the following day)

I N D E X

DR PETER FOSTER (continued) 1

Questions by MR MACKENZIE 1