Wednesday, 2 November 2011

(9.30 am)

DR JAMES SMITH (continued)

Questions by MS DUNLOP (continued)

THE CHAIRMAN: Good morning. Ms Dunlop?

MS DUNLOP: Thank you, sir.

Good morning, Dr Smith.

A. Good morning.

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

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

A. Yes.

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

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

A. Yes.

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

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

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

A. Yes.

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

A. Indeed. Can I just clarify one thing?

Q. Yes.

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

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

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

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

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

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

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

A. It is possible, yes.

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

Then you go on to say that:

"PFL started a crash programme ..."

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

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

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

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

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

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

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

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

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

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

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

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

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

A. The criticism was fair.

Q. Right. And then you say:

"On first publication in January ..."

I think that's actually January 1988?

A. Yes, it is.

Q. Yes. And we have mentioned this article already too, just to give the reference for it without going to it, it's LIT0010330:

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

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

A. Yes, 1990.

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

encouragement:

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

Then you go on to say that:

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

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

A. Yes.

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

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

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

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

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

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

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

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

which, through lightning processing is now in court book. I have the number. PEN0172468.

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

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

A. Yes.

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

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

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

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

order of 8 litres.

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

(Handed)

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

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

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

Q. Yes, right. And then obviously there is a lot of description in this article of the process, which I don't think we need to go through with you, and we can read it for ourselves, but what would the end product be? How much product would be achieved?
A. It would be six bottles of the size illustrated in Dr Foster's blood letter article.
Q. Right.
A. The same size as a blood plasma bottle with a rather smaller amount of freeze-dried material in them than you would have if it had been simply plasma.
Q. Right.
A. But only six bottles from 8 litres of plasma.
Q. Right.
A. Or 40 donors.
Q. Can you capture for us at all, even just an estimate, of the sort of number of bottles that an adult patient, needing treatment for a bleed might need, even just a range, Dr Smith?
A. An adult patient would almost certainly need more than one bottle and if he was being prepared for surgery or in recovery after surgery, he might require 2, 3, 4 batches, depending you how he was responding.
Q. Right. We did see a reference in medical records from the 1960s to a patient having had four flasks actually

of AHG, rather than AHF, prior to a dental extraction. To take the different initials first, would AHG be synonymous with AHF?

A. It means anti-haemophilia globulin. That term was in use more in the States than here.

Q. Right.

A. The "F" can sometimes stand for "fraction" or "factor". You will find many designations.

Q. But the same stuff?

A. Same stuff.

Q. What about the use of the word "flasks"?

A. That was a bottle. They were sometimes called "MRC bottles", "MRC flasks".

Q. So that doesn't surprise you, that little anecdote about a patient having four bottles prior to a dental extraction?

A. That's a relatively minor operation. In the 60s, we did not have the kinds of heroic surgery which began to be attempted in the 70s and 80s to repair damage, for instance, to haemophilic joints. Treaters were very, very wary of any surgical intervention but emergencies, of course, occurred, cranial bleeds, for instance, which might require much more than preparation for a dental extraction.

Q. I think the other piece of the jigsaw which I need to

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

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

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

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

A. Yes.

Q. Yes.

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

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

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

A. Yes.

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

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

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

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

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

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

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

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

THE CHAIRMAN: Could I just follow a little?

MS DUNLOP: Yes, certainly.

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

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

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

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

Does this --

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

MS DUNLOP: Thank you, sir.

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

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

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

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

THE CHAIRMAN: Mr Anderson?

MR ANDERSON: The same, sir.

THE CHAIRMAN: Mr Johnston.

MR JOHNSTON: The same, sir.

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

Questions by MR MACKENZIE

THE CHAIRMAN: Mr Mackenzie?

MR MACKENZIE: Thank you, sir.

Good morning, Dr Smith.

A. Good morning.

Q. Dr Smith, we will turn now to the topic C3, please. It may help, before we look at your main statement, to go back to your two-page supplementary statement, please, which is PEN0172198.

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

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

A. Yes.

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

remind us, of seeking to make a purer product?

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

Q. Yes, I'm sorry.

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

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

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

Q. Why?

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

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

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

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

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

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

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

Q. Thank you.

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

A. That's correct.

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

It's PEN0172206. This has only recently become available to us but I think this is a letter dated 9 July 1984, Dr Smith, from yourself to Dr Foster, enclosing prints from the film you took at PFC on 25/26 June 1984.

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

So that's that.

THE CHAIRMAN: It doesn't look very automated.

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

MR MACKENZIE: Thank you.

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

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

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

Q. Is that a second precipitation?

A. Yes.

Q. Given for the purpose of?

A. Concentrating the Factor VIII.

Q. And removing?

A. To some extent removing the heparin, yes.

Q. And further removal of the fibrinogen and fibronectin?

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

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

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

any documentation of that.

Q. Yes.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

a period of months?

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

Q. Thank you. On that point. If we can revert to your supplementary statement, please, PEN0172198, and on page 2, please, under "Introduction of 8Y" we see:

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

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

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

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

A. Exactly.

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

"Clinical trials for virus safety: from April 1985".

I think that's what we have called the phase 2

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

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

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

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

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

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

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

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

Is "and" perhaps redundant in that sentence:

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

A. The "and" after PUPs is redundant.

Q. Yes, thank you. Reading on:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

A. At -- yes.

Q. So when --

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

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

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

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

Q. Thank you, Dr Smith.

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

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

Thank you.

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

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

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

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

We asked:

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

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

"At the time ..."

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

A. Yes.

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

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

LIT0010617. We can see this is a 1989 publication by Mrs Winkelman and others, including yourself. I think in short this publication relates to 8Y. Is that correct?

A. Yes.

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

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

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

A. Yes.

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

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

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

A. Yes.

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

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

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

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

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

"Production of 8Y concentrate ..."

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

have discussed that. And then over the page, please, the next step we see is "Precipitation of Factor VIII". Is this essentially the second precipitation step?

A. Exactly. After the heparin stage, the Factor VIII is in the supernatant and therefore of quite large volume. It's always an advantage if you can get the Factor VIII into a small volume and you do that by making sure it goes into the solid phase and the unwanted material stays in the supernatant.

Q. Yes, and that second precipitation takes place with glycine and sodium chloride?

A. Yes. That is something we had been working on as a second stage to another primary precipitation stage. We could just slot that in.

Q. I see. The next step is "Removal of Saline", that's just salt, is it?

A. Yes.

Q. The last stage is "Finishing", which no doubt involves various things but also in particular I think involves freeze-drying and also then the heating in a dry state. Is that correct?

A. Yes.

Q. I will come back to ask you just a little bit about freeze-drying in the next question but if we could for present purposes, please, go to the page 0621, the start

of the discussion. In the first sentence under "Discussion" it states:

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

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

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

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

A. Yes, mainly.

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

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

Is that correct?

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

Q. Oh.
A. Plainly we did not -- we knew that it had not been into patients before early 1985.
Q. Thank you. We can put that paper to one side, please, and return to your written statement, if we may?
A. Could I just --
Q. Yes.
A. -- give you another reason for stating that?

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

Q. Yes, we know that in October 1985 HIV screening was introduced in the UK, so --
A. Yes.
Q. I understand. Back to your written statement, please.
THE CHAIRMAN: Could I just ask, while there is something which again has interested me incidentally. You refer to some of the objections that have been raised to the success of 8Y and I seem to have read somewhere a comment that people around fractionators around the world were amazed at what had been achieved partly

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

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

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

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

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

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

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

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

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

MR MACKENZIE: Thank you.

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

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

To pause there, when you say today you:

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

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

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

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

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

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

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

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

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

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

fault, it's just the natural consequence of having a stop gap product which isn't ideal.

Q. Thank you, doctor. We come on to freeze-drying in question 2.

It might be an appropriate time, sir, to have a break.

(11.05 am)

(Short break)

(11.30 am)

MR MACKENZIE: Thank you, sir.

Before the break, Dr Smith, I asked you a question, why was 8Y able to withstand severe heating and that in 1984/1985 the thinking seemed to be primarily because it was a high purity product. You then gave an answer which I am afraid I didn't completely understand, so I should perhaps go back to that to try and clarify it. I think we have printed off a hard copy of your answer. I think we can bring it up on the screens as well. It is highlighted in red on the screens:

"Yes, I should perhaps explain the -- another relationship between yield ..."

And so on. Are you able, doctor, just to break down the main parts of that answer and explain exactly what you meant?

A. In the context of the intermediate purity concentrates,

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

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

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

A. Benefit of a very highly soluble product.

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

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

A. Yes.

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

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

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

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

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

THE CHAIRMAN: It is not getting out.

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

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

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

A. Yes.

THE CHAIRMAN: Thank you.

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

THE CHAIRMAN: No, not at all.

MR MACKENZIE: Thank you, sir.

Thank you, Dr Smith.

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

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

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

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

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

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

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

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

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

Q. And how is heat applied to the shelves?

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

Q. So the shells are heated --

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

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

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

Q. To the product?

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

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

Q. Yes. So that is a freeze-drying step at PFL?
A. Yes.
Q. What was the --
THE CHAIRMAN: Could I --
MR MACKENZIE: Yes.
THE CHAIRMAN: I think what interests me is not the detailed discussion of what happens once you get into the

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

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

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

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

THE CHAIRMAN: Yes, but not in the specification.

A. No.

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

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

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

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

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

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

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

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

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

Q. Yes.

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

Q. I understand. Then you --

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

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

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

Q. Thank you.
THE CHAIRMAN: That's a washing machine approach to it at that stage, is it, introducing liquid at an appropriate temperature?
A. It means you can go from freezing to cooling -- I'm not sure if it was the same fluid but without having to pre-freeze.
MR MACKENZIE: But, doctor, the liquid, is introduced within the shelves like a radiator, a closed system, or is it circulating around about the vials?
A. No, the vial is sitting dry on the dry shelves and as you aptly point out, it is like heating five or six radiators on top of each other, on each of which sits a batch of vials.
Q. Yes. Simply for completeness, I think we have a photograph of the freeze dryer at PFC. It might be worth just looking at that for completeness. It's page 18 of PEN0121695. The first page, if it helps, is 1695.

I don't have a date for this photograph, doctor --
A. That's at either PFC or BPL.
Q. Yes, I think it's PFC. Is the freeze dryer shown in these photographs similar to the type of freeze dryer, at least in looks, as that at BPL?
A. The geometry of the chamber seems to be very similar. There is some evidence that it's circulating fluid in

the shelves because of the nature of the plumbing.

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

A. Yes.

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

A. Yes.

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

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

Q. Thank you.

Moving back, please, doctor, to page 3 of your written statement and your written apply to question 2 was:

"Here too, I remain agnostic. It is conceivable that the traditional freezing and drying conditions

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

You refer to an event in about 1986. You:

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

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

A. Indeed.

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

A. Essentially, yes.

Q. Yes. If I were to ask the question in a different

way -- do you accept as a general principle that the freeze-drying step is a relevant factor to a concentrate's ability to withstand severe dry heating? -- what would your answer be to that more general question?

A. That ...

Q. That freeze-drying step --

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

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

A. In response to occasional failures.

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

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

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

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

identifiable variables as possible in every experiment."

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

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

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

A. It was more complicated than we had thought.

Q. I see.

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

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

A. Again, you would have to perhaps distinguish the controlled ones from the ones which happened by drift or plant aging or changes in the specification of the

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

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

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

You explain your:

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

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

A. It was our assumption, I think, in the public service --

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

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

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

Q. And --

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

Q. Okay. You go on to explain that:

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

You explain:

"This was much regretted but I was reassured that

PFC, although adopting a different procedure to protect intellectual property ..."

And the reference to SNB0074479 we don't have to go to. I think it's Dr Foster in July 1984 writing to Research Disclosure, an American publication, with an invention. But you explain that PFC understood your embarrassment and that:

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

And:

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

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

application didn't cause him to change direction. Would you have expected him to have expressed a lot of interest or changed direction on receipt of the 8Y patent application?

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

Q. Thank you.

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

"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?"

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

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

Q. Yes.

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

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

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

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

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

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

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

Q. Yes. On that last point, could we please go to

a document SNB0015484.

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

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

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

Q. January 1985, yes.

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

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

A. I see.

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

It's January 1986 this is written, because there was a meeting at PFC on 23 December 1985, where it was

decided to change priority and this memo was written in January 1986. So you are quite right, thank you, you are quite right.

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

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

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

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

A. I don't recognise the direct quotations.

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

"Likely it would depend on who is writing/speaking and who is listening. The references in footnote 3 are intended to be helpful but I accept no responsibility for opinions which do not have my mark on them. Subjectively, I started to surmise (for public consumption at least) in mid 1986 that it was looking

quite good and I probably eased up on plans to revert as soon as possible to pasteurising or even to explore the solvent-detergent option with more determination."

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

A. Yes.

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

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

Q. That's the solvent-detergent method?

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

Q. Yes. Because the use of the word "revert "in this statement is perhaps interesting, doctor, in that it may

suggest that during 1985 at least you regarded dry heating as essentially an interim or temporary solution. Is that a reasonable inference?

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

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

A. Exactly.

Q. And then reverting to your written answer -- we don't have to go to it, SNF0011123. We have looked at it before. It's your written interim report of 30 December 1986, you say:

"That was a little more upbeat but not much. Even then, tentative exposure of our NANBH clinical data throughout 1986-87 was heavily criticised (see, typically SNB0017768... "

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

"It was gratifying that more England and Wales clinicians were supporting our new, more rigorous trial by 1987. Following a wave of NANBH and even HIV failures in dry-heated commercial products, 8Y became briefly the best game in town and they may have sensed

the some risk if they did not fall into line. However, using the only product which hasn't failed yet does not necessarily denote confidence that it's going to be 100 per cent successful. Note the extremely cautious wording of the Colvin publication in 1988 more than three years into trials."

We have looked at that before:

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

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

A. HIV -- there was word coming through from the US products that even 60 degrees for 72 hours or 68 degrees for 24 hours in the hands of respectively Baxter and Cutter, appeared to be successful so far in inactivating HIV in a plasma supply which was almost certainly, by that time, heavily infected. The natural inference is, therefore, that if you can go to 80 degrees for

72 hours, you are going to be home and dry with HIV or at least you have introduced an additional margin of safety for what that's worth. If you get hepatitis or HIV, you have got it and the margins don't matter to you very much.

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

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

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

Q. Thank you.

The next question, please, if we go on, if we may, doctor, to page 5 of your statement. This is to do with the contact and exchange of information between PFC and PFL/BPL. During this period. It's a topic we have covered at some length in the Inquiry, Dr Smith.
I don't want to take too much time on it, which is why I think I propose taking your answer on page 5 (a), simply taking that as read but asking you two points.

The first point is this: you say:

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

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

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

Dr Cash may have felt that he was being kept at arm's length from some developments at PFC and in Mr Watt's time there may have been some justification in that feeling. But Dr Cash is a very responsible National Medical Director, as well as National Director. He would naturally have felt responsible for the quality and in particularly the safety of any product coming through PFC and being issued with SNBTS's name on it.

So it was not at all my view that Dr Cash's vanity or potential to control-freaky caused his interest and lasting interest in getting around the problem between the two respective directors.

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

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

I'm particularly grateful for his achievements in bringing together a world class group of scientists in

his central R&D lab and I have referred several times in my testimony to the assistance received not just from PFC but from Dr Prowse, Dr Pepper, Dr Dawes, in fact almost all the people in the central lab. That central lab would never have been set up, would never have existed to help us and the rest of the world if it had not been for Dr Cash's energy.

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

Thank you for indulging me.

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

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

I'm not sure we have really heard about this but we have heard about the structure in Scotland, where essentially there were a number of transfusion directors, a national medical director and a director of PFC, who I think all essentially were responsible to one body, the Common Services Agency.

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

A. Yes.

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

A. Indeed.

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

A. Exactly.

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

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

A. I knew it existed.

Q. Yes.

A. And I'm fairly sure I was invited to assist Dr Lane, who was a participant, to prepare reports or mini reports, for that. Until the Inquiry has revealed these

documents, I don't think I ever saw a minute of the R&D committee.

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

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

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

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

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

exactly as one would expect from its original remit to advise CBLA -- not CSA ..."

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

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

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

SGH0024677. But we should perhaps go to Dr Forrester's response.

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

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

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

I think, again, I'll simply propose taking this as

read because I think we have covered, I think, much of the ground set out there. I think it's an interesting and important response but as I say, I think with a view to avoiding unnecessary repetition, I'll simply take that as read.

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

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

"See SGH0018783."

Just to explain for the record, that is a document relating to PFC revenue development proposals for 1982 and 1983, including in particular expansion and work required as a result of the medicine inspectors' report.

You also go on to refer to annual reports. I think that's a reference to annual reports of BPL and PFL. I think we have previously clarified with the SNBTS that PFC did not at this time produce annual reports.

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

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

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

"In these circumstances ..."

Then the next sentence:

"Once a settled pattern has evolved ..."

The next one:

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

And to pause to explain the reference to SNB0073635, that is a reference to Dr Foster's memo to Mr Watt of 3 May 1983 in respect of a possible acceleration of the heat treatment programme in response

to AIDS.

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

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

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

The top of page 10, please. There is a reference at the top of page 10 to, I think, staffing, employment and remuneration aspects. I think in short, Dr Smith, we note all that you say and while staffing, et cetera, may have been a factor in events at PFC, it doesn't seem from the evidence we have heard so far that it was a determining factor or indeed was at the forefront of decision-making. So I think, for that reason we will simply take what you say at the top of page 10 as read and no doubt, if anyone disagrees with what I say, then a point can be made in submissions to the chairman in

due course about that issue.

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

Q. I understand.

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

"A priori objections."

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

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

This is the heparin as a precipitant:

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

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

"The supply of reliable Factor VIII assays has always been the most serious limitation when every

laboratory's development of improved concentrates ... "

Then the next sentence:

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

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

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

Q. I understand. Thank you.

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

A. You are waiting for the assays to confirm that what you intended to achieve by changing a variable has in fact had that result, and you cannot proceed until you have

rationally -- until you have determined that. It slows down progress.

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

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

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

A. This is where the art comes in.

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

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

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

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

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

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

THE CHAIRMAN: Right. Yes, thank you.

MR MACKENZIE: Thank you, sir.

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

You explain the difficulties in attempting to quickly duplicate methods from another laboratory, even

provided with a lot of detail. You say:

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

That's back to the unknown unknowns perhaps:

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

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

If we could perhaps start at page 6 of your report. I think, doctor, you have had a chance to look at it previously, although it may have been some time ago in

preparation of your statement. Is that correct?

A. Yes.

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

"Following the completion of small scale laboratory studies, a number of experts have been carried out at pilot scale."

Under 3.1.1:

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

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

I'm not going on ask you about the details, doctor, but I think in short one can see the different process stages and the target for the efficiency of Factor VIII and the results of the experiments, I think, all with a view to seeing how much Factor VIII was lost at each step in the process and whether yield levels could be maintained with the ZHT process, and Dr Foster referred in the body of the report we just looked at to results from the zinc precipitation step, "step 1: disappointing", but I think we can see for ourselves that in fact in all of the steps, if one takes an

average of the figures, the recovery of Factor VIII is, I think, less than the target figures. So I really just put that to you to put it into the record of the Inquiry rather than ask you to comment in detail on it.

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

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

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

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

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

A. Yes.

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

"Pasteurisation. Heating in solution with sorbitol as a stabiliser is the preferred option at the moment but severe heating of the freeze-dried powder may be

possible (Dr Smith unpublished results) and may be of interest."

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

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

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

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

Then:

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

This is really post-Groningen explaining the evidence based approach to introducing dry heating at that time. I think, in short, Dr Smith, from this report Dr Foster is explaining the introduction of dry

heating of the intermediate PFC product in late 1984 but also that the research work would continue to seek to develop a high purity Factor VIII concentrate with pasteurisation being the preferred heating method but not closing one's mind to dry heating.

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

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

Q. And would that have remained your view --

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

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

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

Q. Thank you. Could I return then, please, to your written response. I think we had come to 3, "Limitations in

PFC's resources."

You do say that:

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

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

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

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

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

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

At what stage in the 8Y process were these centrifugation steps used? Was that during the initial

extraction from cryoprecipitate or ...?

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

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

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

I do not know in fact whether PFC had a Sharples centrifuge on the premises. They would therefore have

had to learn how to collect this fine precipitate in a Westfalia centrifuge, which is not ideally adapted for this task. Both these centrifugation steps would therefore have caused PFC trouble.

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

A. Indeed.

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

"At an important desalting stage ..."

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

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

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

A. Yes.

Q. And paragraph 3.5 we can see what you say and paragraph 3.6 again, going back over some ground we have been over before. 3.7, a point of detail in the text in italics. You asked you do not know at what point PFC ordered commissioned and validated precision ovens, and I think the answer is the ovens were ordered in January 1985 and were delivered in July 1985. And

our reference for that is Dr Foster's briefing paper, page 38. That's a point of detail.

Then 3.8:

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

Then in the last paragraph there you say:

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

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

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

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

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

I assume that's to inactivate NANBH.

A. That would also include some HIV failures.

Q. I see.

A. The Armour product, for instance.
Q. "... and reputable doubts about its efficacy against even AIDS virus ... "
A. Sorry, that's part of the --
Q. Yes. So is the first part, "In the wake of seemingly endless failures of dry heating between 1983 and 1985", a reference to NANBH?
A. Indeed.
Q. I understand. Et cetera.

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

The final document, please, if I may, is LIT0010648. We see this is a paper published in June 1987 by Dr Prince and others. If we look at the abstract, we will see, just half way through the first paragraph:

"This review summarises detailed information which is now available establishing the viricidal potency of these procedures, particularly with regard to the contaminating viruses of most concern: Hepatitis A,

non-A non-B Hepatitis and the AIDS virus."

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

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

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

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

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

The first entry, I think, relates to Factor IX, so we can put that to one side perhaps, but then the next entry relates to Behringwerke's Factor VIII. If we then go to the right-hand columns, in terms of the proportion of patients infected in the clinical studies, we can see for this product, for NANB, two out of 31 patients infected, although I think there may have been later

a question mark about that, but below that 0 out of 21 in another trial and, for the Hepatitis B virus, 0 out of 31 patients and then 0 out of 11, and for HIV one can see 0 out of 21 patients and then 0 out of 18.

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

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

Over the page, please, finally, look at table 4. Table 4 is headed, "Efficacy of processes involving heating in a lyophilised state".

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

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

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

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

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

A. He would see that, as far as non-A non-B transmission was concerned, (inaudible) product's heated in solution (inaudible) the only product heated in solution -- had been more effective in inactivating non-A non-B Hepatitis than any of the dry-heated concentrates

investigated so far, the only one to have a clean sheet still being 8Y.

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

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

A. Sorry?

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

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

Q. Yes, it was June 1987.

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

Q. I see.

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

Q. Thank you. Doctor, I've really finished -- yes, sir, I was going to say I really have finished with the rest

of Dr Smith's statement. I think I'd propose simply taking that as read. So really --

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

MR MACKENZIE: Powder dry.

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

(1.10 pm)

(The short adjournment)

(2.00 pm)

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

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

THE CHAIRMAN: That's fine. My source was Lindsay and if you can't add to that, I'm content. Thank you very much.

Yes, Mr Mackenzie?

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

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

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

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

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

THE CHAIRMAN: Mr Di Rollo?

Questions by MR DI ROLLO

MR DI ROLLO: Thank you, sir.

Dr Smith, I think in the last day or two, amongst other things, we have been looking at the development of Factor 8Y in England and some of the reasons why PFC did not develop a similar product until a bit later on. What I would like to ask you about is the question of whether or not 8Y might have been made available in

Scotland -- that is to say English 8Y -- and the knowledge that Scottish fractionators and clinicians might have had in relation to the safety margin that 8Y may have had in early 1986.

If we look at one document, DHF0030476 -- I think reference has already been immediate to this. This is the issue of 8Y in England.

This document is indicating that the 8Y is being issued or to be made available generally, and if we look further down, we see that clinical trials at six haemophilia centres are in progress to gain evidence of reduction or elimination of the 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.

Then it goes on to say that:

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

Then the final paragraph on that page says:

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

likely to benefit most from the security inherent in 8Y."

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

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

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

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

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

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

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

Q. The date for this document was 10 January 1986. This is

a draft of a report by Dr Perry for the SNBTS haemophilia directors for their annual meeting, which was to be held a number of weeks later.

The next document I want to put to you is 17 March 1986, which is SNB0075664. I think this is a meeting at PFC on 17 March 1986 and we see that a number of people appear to have been present, I think including yourself. Is that right?

A. Yes.

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

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

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

What I would like to ask you, looking at these documents, is obviously there is a difference between asserting publicly that something is safe or anything of that kind, but it does appear that from the information

available there was likely to be an increased margin of safety insofar as non-A non-B Hepatitis is concerned in using 8Y as opposed to other products. Is that a reasonable proposition?

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

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

A. Paragraph 5, you will see Dr Perry's words. He is interpreting perhaps a five minute review and his take on that is in terms of, while results cannot be considered conclusive at this stage, I don't think in any forum at this time I would have come out so much in

favour of optimism.

Q. So you wouldn't --

A. The first -- could I?

Q. Yes.

A. The first part of your question.

Q. Yes, indeed.

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

Q. So are you saying that it would not be reasonable to think that at this time -- this is March 1986 -- that 8Y provided -- and this is insofar as non-A non-B Hepatitis is concerned; that's when we are interested in specifically -- an increased margin of safety over, say, the available Scottish product at that time, which was, I think, known definitely to transmit non-A non-B.

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

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

Q. I understand that you cannot say it's safe.
I understand that. What I'm asking you to do is to look at one product, 8Y, and say, one, the existing Scottish product will definitely give you hepatitis, non-A non-B Hepatitis, but the English product will not definitely do that. One can't know whether the English product will do that and there has not been any recorded case up until that point, despite 12 months of use. I'm asking

you which one has the best margin of safety or the better margin of safety?

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

Q. Yes, I do.

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

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

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

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

A. More patients exposed, more batches exposed.

Q. And at what point would you say that there becomes

a worthwhile statistical benefit, if you like, of having 8Y as opposed to the existing Scottish product? What does that --

A. Worthwhile to whom?

Q. Worthwhile to a previously untreated patient?

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

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

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

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

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

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

Q. Can I ask you about one or two documents in relation to

1986? Maybe that will help. If you go to SNB0075799.

Can you just put this document into some sort of context?

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

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

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

Q. When was that done?

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

Q. Right. We see that this has been discussed obviously in correspondence on 9 May 1986. If you just go to SNB0075801, as I understand it, this is what's appended to this document. It's the protocol. Again, if you just scroll down, that's dated 30 April 1986. Am

I right in thinking that this is the same process that you have just described in terms of testing --

A. Yes, exactly.

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

A. With a variety of surrogate viruses.

Q. Indeed.

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

"It was agreed that Dr Smith would liaise with Dr Cuthbertson with a view to establishing a level of virus inactivation achieved by BPL 8Y material. This would involve the transfer of samples between BPL and PFC and the development of a protocol which accurately

simulated routine BPL formulation and treatment conditions."

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

A. Exactly.

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

A. Exactly.

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

MR DI ROLLO: It does, thank you.

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

A. I do.

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

A. I was telephoned, I believe, by Mr Pettet, who was Dr Lane's right-hand man in the business of allocating resources and who I took would be relaying Dr Lane's wishes. Mr Pettet was asking me to send, I think, about 50 vials of 8Y to Dr Perry. My understanding was that this was to provide material should any

haemophilia centre in Scotland acquire a patient in the category we have spoken about, who might benefit most from what we regard as our safest product at the time.

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

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

A. That was probably the inference to be drawn from the request but I do remind you that back in 1984 we had a request for heated intermediate material at a time when, if it had not been from specially vetted donors, the product might very well have transmitted hepatitis. It comes again to your definition or your understanding of a "margin of safety". It may be more imagined than

real. It would become more real perhaps during the course of 1986.

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

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

Q. Indeed. I think there is some contemporaneous material relative to this and perhaps we should have a look at that. SNB0075980. I'll just take you through this. This is a letter from, is it, Dr Pettet or just Mr Pettet?

A. Mr Pettet.

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

"Following your letter on your requirements for 'virgin' haemophiliacs in Scotland and Northern Ireland,

I tried to contact you by telephone last Thursday in order to begin supply as soon as possible. As you were down in London, it was obviously difficult.

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

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

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

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

Then he goes on:

"There is one point, however, that you need to consider. Current batches of 8Y on issue, are not made

from certified anti-HIV screened donations. The first individually screened product will not be released for issue until August. Subsequent batches will all be made from screened plasma."

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

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

Q. Of course.

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

Q. No, I understand.

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

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

A. Yes, Mr Pettet is trying to say that if you, Dr Perry, would prefer that for speed, it goes straight to Aberdeen haemophilia centre; it would go on the plane. But our understanding will be that we will be in full

touch about this and you will have blessed the transfer of this material straight to the haemophilia centre, instead of it going through the official routes through the PFC stocks --

Q. I understand.

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

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

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

MR DI ROLLO: Just to follow some correspondence through, just so that we see it, 28 July 1986, SNB0075986.

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

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

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

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

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

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

Then if we go to the next letter, 1 August 1986, SNB0075990, I think this is a letter from you on this occasion:

"Dear Bob,

"As requested in your letter of 24 July and agreed verbally by Dr Lane, I'm sending the 50 vials of 8Y 3312, in case you wish to protect category 1 patients before your Z8 is ready."

What did you understand category 1 patients were?

A. These would be pure virgins, previously untreated --
Q. Right. Again, it does looks as though your understanding in this letter is that this was to protect these against, presumably non-A non-B Hepatitis; is that right?
A. And incidentally HIV, but I don't believe that the current Scottish product would have transmitted HIV either.
Q. Yes. We are principally concerned with non-A non-B Hepatitis. You say:

"Please issue one of the attached copies of the trial protocol to the responsible physician in each event and let me know whom I should nag for data."

The quid pro quo from your point of view or the English point of view here is that data is going to be obtainable on virgin patients not having developed non-A non-B, which is the best data you could possibly have.
A. Just to qualify that, I'm not exactly sure what our category 1 would have included. It may have included up to a certain number of cryos, maybe about ten but as I sit here, I cannot give an exact definition.
Q. I understand that, Dr Smith, I'm grateful to you.
A. Good prospects for a clean trial --
Q. Indeed. Did you get any Scottish data?
A. I don't believe -- I can't remember -- our publications,

I think, never included any data from Scotland. I would have to -- would you give me a minute to check?

Q. Of course.

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

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

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

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

Q. Thank you for that, Dr Smith.

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

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

Q. Right.

A. And appeared on the last of people to be acknowledged in the papers.

Q. So --

A. They would have appeared --
Q. They would have appeared and you don't think there is anyone?
A. I can't recall anyone.
Q. Right.

Thank you, Dr Smith.

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

MR DI ROLLO: I'm obliged sir.

THE CHAIRMAN: Mr Anderson?

Questions by MR ANDERSON

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

Do you remember this morning Mr Mackenzie was discussing the general issue of 8Y in England for clinical use in about December 1985. Do you recall

that?
A. Yes.
Q. He sought your views on the proposition that upon introduction, effectively only about one third of the demand was being met. Do you remember that?
A. Yes.
Q. In your response to Mr Mackenzie's questions, you talked of satisfying the needs of the UK --
A. I'm sorry.
Q. I wonder if that's a slip and you meant England and Wales?
A. Absolutely. I apologise for that.
Q. Just for the record, sir, that's page 33, line 22 and just after that at page 34, line 16, again, I think you made reference to the whole country and I take it again that's a reference to England and Wales?
A. That's a slip.
Q. I'm obliged to you.
THE CHAIRMAN: Even expatriate Scots make that mistake, do they?
MR ANDERSON: So it would appear, sir.
Just related to that, Dr Smith, finally, can you look with me at the final paragraph of your statement, which we find on page 12 of PEN0171130. You say there, reading short, that:

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

Which you underline and then go on to say:

"[This] phrase is far from trivial".

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

A. Global.

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

A. Yes.

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

A. Exactly.

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

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

Q. I'm obliged to you.

THE CHAIRMAN: Mr Johnston?

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

Further questions by MR MACKENZIE

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

Dr Smith, in relation to the question as to Scottish participation in the clinical trial of 8Y, were you looking at one point for the later paper by Rizza and others, the 1993 paper?

A. Indeed.

Q. We can bring that up. It's SNB0045996. If we look at the bottom left-hand part of the paper, we can see a list of names --

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

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

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

Q. I think the one name I recognise is Dr Hann, who had been at Yorkhill but I think at this point he was down in London at Great Ormond Street. I don't think I recognise any other Scottish names but I may be wrong.

A. The difficulty is they did move around a bit, especially the younger directors in those days, and several of them had experience in both Scotland and England.

Dr Franklin, he would have been only in Scotland.

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

A. Then it's inconclusive.
Q. Yes, thank you.
A. Dr Ludlam's name does not appear.
THE CHAIRMAN: Dr Smith, thank you very much. As you know, your name appeared many times before your appearance and I think we were all looking forward to hearing what you had to say, you have been very helpful. Thank you very much.
A. My privilege.
MR MACKENZIE: Sir, there are no further witnesses today but we have a fuller day tomorrow. We have Dr McIntosh and then Mr Murray and Mr Macniven tomorrow.
THE CHAIRMAN: I don't think we can anticipate any of that. We will rise now.
(2.55 pm)
(The Inquiry adjourned until 9.30 am the following day)

I N D E X