Friday, 28 October 2011

(9.30 am)

(Proceedings delayed)

(9.48 am)

DR ROBERT PERRY (continued)

Questions by MR MACKENZIE

THE CHAIRMAN: Good morning.

Yes, Mr Mackenzie.

MR MACKENZIE: Thank you, sir.

Good morning, Dr Perry.

A. Good morning.

Q. We are considering topic C3 this morning, as you know, which is viral inactivation between 1985 and 1987 in particular, and, doctor, you have provided us with a statement which we can go to. It's [PEN0171219].

Of course, during this period you were the director of PFC and I think in fact you were director between 1984 and 2003. Is that correct?

A. That's correct, yes.

Q. Looking at your statement, we asked a number of standard questions to all of the witnesses and the first question concerns how and when did the SNBTS and PFC first become aware of the BPL/PFL product, that would become known as 8Y.

Could I ask, doctor, do you recall what was your first awareness of this work going on in England and this product?

A. I actually have a fairly hazy -- and as I have said in my statement, I am really unable to precisely identify the period but it was some time around, I think, early 1985 perhaps that I became aware of specific activities in this area, or information starting coming north of the border to tell us that something exciting was going on.

Q. How would information come north of the border to you? Would there be a particular route, would there be a variety of routes or what?

A. I think it would be primarily through our informal relationships that we had research scientists at PFL and BPL, particularly Jim Smith, who I think has been mentioned on a number of occasions, and Dr Foster had a very good relationship with Jim Smith and I think the information would have come through that route. It wouldn't have been a formal communication.

Q. Thank you. Then the written reply you gave us, you say you were unable to precisely identify the date on which the SNBTS/PFC first became aware of the BPL/PFL 8Y development. We can then see what you say also in your reply.

Moving on, please, to page 2, the second question we asked was:

"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?"

Again, before coming to your written response, could I ask, please, were you aware during 1985 of the results from the 8Y trial?

A. In late 1985?

Q. At any point in 1985.

A. At any point in 1985. I can't recall a point at which I started to become aware that the results were encouraging. I think having said that, it must have been at some time in late 1985 because I think, as we moved forward -- in 1986 I was drafting a paper for the SNBTS haemophilia directors meeting in early 1986, where I mention this development, and that was very early January that paper was being drafted. So it must have been late in 1985 that I was getting information, probably informally -- I don't think there was anything formal or there was no formal correspondence -- but through the various interactions we had with colleagues in BPL, we were beginning to understand that the trial was proceeding successfully.

Q. Presumably, looking at the phase 2 trial of 8Y or indeed

any Factor VIII concentrate undergoing phase 2 trials at this time for reduced infectivity for NANBH, one would have to wait a certain period after the first infusions of the product before one could really draw any initial conclusions. The point I think I'm seeking to get at is that one is looking after infusion of the product for elevated ALT levels?

A. That's right.

Q. So one would have to wait a certain period to be satisfied that a patient didn't appear to have elevated ALT levels as a result of infusions of the product. Can you give us an indication of the sort of period one would have to wait before one could say, "Well, initial results seem promising"?

A. Well, I'm really not an expert in this area. I'm not a medical doctor and I think Professor Ludlam, as others, have talked about the complexity of doing these studies because there was no direct test for whether the product was infective with regard to Hepatitis C.
I would have thought, however, that -- and I can't recall what the window period for incubation of non-A non-B Hepatitis was, but I would have thought that, you know, in around about six months, you would start to get the first early indications that there was no transmission. But it would depend very much on very

rigorous follow-up of patients, fortnightly testing of ALT samples, because my understanding is that in non-A non-B Hepatitis these ALT spikes that you get can be transient and if you miss a particular point in the follow-up, that could have been the point at which the ALT spikes.

Q. So as director of the PFC in 1985, if you had been given the initial results from the phase 2 trial of 8Y, your view would have been if the results had been perhaps one month after infusion, you would have said, "We cannot place any weight at all on these results"?

A. I would have said, "so what?"

Q. So what? The longer the period after infusion, presumably the more weight can be placed on the results. I think you mentioned six months perhaps as a period one might then start to place some weight on the result. Is that generally --

A. That's my view but as I emphasise and underline this, I'm not an expert and I'm certainly not a clinician but I have a broad understanding of these time periods.

The other important element, of course, is that in order to get a high level of confidence or an increasing level of confidence that the process was delivering a safer product or a non-infective product, you would want it tested in a number of batches, because you might

have been lucky with one batch, that there was no hepatitis or non-A non-B in that particular pool. So it has to be multiple batches, multiple patients and over a reasonably long time period, as you have described.

Q. That would have been your view as director as at the end of 1985?

A. At the end of -- yes, that would have been my view, I think by that time we were already seeing what I would describe as "false dawns" in terms of safe products and products that had been purported to be safe but were not so. So I think, as PFC director, although it wasn't our study, I would be looking for some really fairly substantive results before I would conclude that this product was beginning to approach a point at which you could consider it to be a safe product.

Q. And Dr Perry, presumably, as director of the PFC, the fact that BPL were able to manufacture a Factor VIII concentrate which could be heated at 80 degrees centigrade for 72 hours, presumably that was something of great interest and importance to you. Is that correct?

A. Yes, it was, yes. This was novel technology, although it -- I think it arose as a result of discussions and collaborations between PFC and BPL but it was of enormous interest, absolutely.

Q. Did you take any active steps to be informed of the results of the phase 2 trial of 8Y?
A. I'm pausing just to -- but I don't think I did, no. But we were getting sufficient information informally, I think, but I can't recollect what the particular route was but, no, I don't think I went down the formal route of seeking formal reports from BPL of their 8Y clinical trial from either Dr Lane or Dr Smith or our other contacts at BPL. So I think the answer is no.
Q. In the middle of 1985, for example, once you knew BPL were manufacturing this 8Y product, did you take any active steps to be even kept informally advised of the results of the phase 2 trial?
A. Well, I wouldn't say "steps" because that implies that I took some premeditated action, but we already had a very effective dialogue between people like Jim Smith who was effectively the senior scientist at BPL and PFL who had designed the product. So as time went on, we knew that we would have been updated by Jim Smith. So we didn't have to put in place a specific process to extract the information from BPL.
Q. Given what we discussed earlier, it may be that one would have to wait perhaps up to six months before any results were worth taking much notice of?
A. That's my view this morning, about six months, yes.

I wouldn't expect there to be anything significant before that time, although I have seen written statements that -- if I can recollect the wording -- which said, "We have now safely passed the point at which the first patients infused with products would be expected to have transient ALT."

And I think that would probably precede the six-month time period but it's a very, very soft indicator of product safety and I wouldn't have put much store by those sort of initial observations. I think I would have been interested and if it was my process and my product, I would have been very excited and optimistic but I wouldn't have drawn any further conclusions than that.

Q. In particular, it may, in terms of whether one changes one's course of action, depend whether one is a clinician prescribing a particular product to a particular patient or whether one is a director of a fractionation plant, which may have to completely change to a different manufacturing process?

A. Yes.

Q. But certainly we hear your position as director as to how much weight you would places on these sorts of results.

A. Certainly in mid 1985, probably well into late 1985,

I don't think I would have received any information that would have led me to change our course of direction. I think -- and actually there is a good practical reason for that. In an ideal world we would have been running parallel developments of pasteurisation and dry heat treatment and so on, but with the limited resources that we had, we had to choose one, and I think during that period our choice and the horse that we were backing was still pasteurisation as the most likely route to producing a product safe with respect to non-A non-B.

Q. Yes, and we will come back to look at when things changed shortly but if I could just go back to your written response at question 2, please, you told us that:

"The preliminary clinical trial of 8Y commenced around April 1985 in patients considered to be susceptible to hepatitis ..."

By "clinical trial" do you mean phase 1 or phase 2 study?

A. Sorry, where were we reading from?

Q. Sorry, it's your answer at the top of page 2.

A. Okay. Well, if it was patients -- in patients considered to be susceptible to non-A non-B, that would have been previously untreated patients and seldom treated patients, so I think that would have been what

I would describe as a "phase 2 study".

Q. Yes. Have you got that information from the documents you have looked at in preparing for this --

A. It's certainly not a recollection. So it's from documents and reading references and so on.

Q. Yes. You go on to explain:

"In the absence of a specific test for NANBH, such trials relied on rigorous, regular and frequent monitoring for abnormal liver function tests in suitable susceptible patients [including children. Such parents were] rare and required a long period of surveillance to provide reliable and meaningful results."

Also the question of requiring exposure to multiple batches:

"To ensure the effect of heat treatment was consistent and reproducible."

You say:

"Although early results in a relatively small group of patients were reported by Dr Rizza ... as encouraging ... "

I think that's a reference to the seventh meeting of the CBLA central committee for R&D and blood transfusion on 19 December 1985?

A. Yes.

Q. We looked at that earlier. Doctor, did you receive

a copy of these minutes at the time?

A. These are the CBLA minutes?

Q. Yes.

A. I can't recall. I think it's unlikely that I received them. I think they were seen -- it was an internal CBLA meeting and report. But I think there was some useful information that came up and I think I became aware of that around about December.

Q. You go on:

"It was not until the interim review point in this study in March 1986, reported in October 1986 to the UKHCDO, that the freedom of NANBH, HB or HTLV-III would have been described as 'likely'."

That's a reference to the interim review to Dr Smith's interim report, dated 30 September 1986.

A. That's correct.

Q. You say:

"Even at that stage such a conclusion would have been regarded as cautionary and unconfirmed."

A. Yes.

Q. Then you go on to say:

"The final report ... was published in October 1988 ..."

That's by Dr Colvin and others?

A. Yes.

Q. And you then say:

"Further studies complying with the internationally recognised ICTH guidelines were considered necessary and a new study was proposed in 1987 ... "

And the results published in 1993 -- that is the Rizza and others study we looked at earlier?

A. That's right.

Q. Thank you. The next question, question 3, we then go on to October 1985, when PFC discovered their existing intermediate NY Factor VIII product withstood heating at 80 degrees centigrade, and we asked why such heating of the existing intermediate product was not introduced immediately, and you explained that:

"There are a number of reasons why this laboratory observation did not lead to the adoption of a strategy for the immediate introduction of NY Factor VIII heated at 80 degrees."

The top of page 3, please. You have a subheading "SNBTS/PFC strategy for Factor VIII supply."

You tell us a little about that.

A. Yes.

Q. When you state:

"When it became known in 1984 that coagulation factor concentrates were implicated in transmission of HIV ..."

Do you mean factor concentrates produced by PFC or is that just a more general statement?

A. I think it's a more general statement about international references to transmission of AIDS by coagulation factor products, although, as is by now very clear, we did become aware in late 1984, in October 1984, that the PFC products themselves had transmitted HIV.

Q. You go on:

"The SNBTS and haemophilia centre directors' strategy to protect patients from infection with HIV included ..."

A number of key elements. Firstly a focus on self-sufficiency to avoid importing commercial US products. And secondly:

"The rapid and progressive development of manufacturing processes capable of inactivating HIV ..."

You say:

"In the period from 1985 to 1987, the SNBTS developed and introduced three new products."

Is that reference, doctor, firstly to the NY product heated at 68 degrees for two hours, secondly the NY product 68 degrees for 24 hours and thirdly to Z8?

A. Correct.

Q. I understand. The third key element, the question of

a batch dedication system to reduce the exposure of patients to multiple batches of products. You tell us:

"This system, introduced in early 1985, required the SNBTS to maintain high overall product stock levels to ensure that individual patients were treated with a single product batch for as long as possible. This had the important effect and goal of minimising the number of donors to whom patients would be exposed."

You go on to say:

"The key prerequisite to this strategy was the availability of high product and plasma stock levels (already achieved in 1984) and agreement that the successful development of new products would not necessarily require ... the immediate recall or change (and loss from the supply chain) of the superseded product."

Et cetera.

Over the page, please, doctor, at page 4. You return then to the initial discovery in a laboratory by Dr McIntosh, I think, in October 1985 that the existing Factor VIII concentrate could withstand heating at 80 degrees centigrade and various other matters we have discussed with Dr Foster. About half way down the page you say:

"In the absence of evidence that a severely heated

product offered protection against NANBH, the PFC proposed an alternative development strategy which would continue to protect all patients from the HIV risks believed to be inherent in commercial products and deliver a product (Z8) comparable in its properties to 8Y. This strategy was discussed and agreed with the SNBTS and haemophilia directors."

A. Yes.

Q. We have heard evidence about a meeting on 23 December 1985 at PFC between yourself, Drs Foster, Cuthbertson and McIntosh. Do you remember that meeting?

A. I can't say that I remember the meeting but I am aware of the meeting taking place but I can't position myself at the meeting at the moment.

Q. Do you remember the meeting taking place?

A. Yes, yes.

Q. Albeit you can't -- do you have a visual --

A. No, I don't, I have no visual recollection of what I felt like and so on.

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

A. Yes, it was about really realigning our developments for Factor VIII products. The fact that it took place on 23 December probably signifies that this was being given a fairly high priority, otherwise it would have waited

quite happily until the New Year. So it was about the possibility of moving away from our pasteurisation project and also the project that we had running with Johnson, with Professor Johnson, into a dry heat treatment process, and this really followed the observations by Dr McIntosh and Dr Foster that the demonstration in principle that with relatively modest changes to the product, we could produce a product that was comparable to 8Y.

Q. What was your view going into the meeting?

A. I can't remember.

Q. Do you remember the views of those attending the meeting, as discussed at the time?

A. I can't remember who was the proponent of the individual options. I guess there were two options: to carry on as we were or to recommend an alternative strategy, which was the development of an 80-degree, three-day heated product.

I think my concern -- and again this isn't from recollection, this is from reading various notes of meetings and so on -- is that I had some concerns over the 80 degrees three-day product. I think other witnesses have mentioned that around that time the efficacy of dry heat treatment, so-called dry heat treatment, was being called into doubt by some

organisations and my concern, as PFC director, was that although I thought there was very good science around heating a product at 80 degrees for 72 hours, I thought there might be a presentational issue, that other organisations and our competitors in commercial industry, might want to discredit the adoption of this particular process. So I had some concerns over that.

I think equally, I felt that this was likely to be a simpler route to a safe Factor VIII product, compared to the pasteurisation route, which, I think, as Dr Foster has described, was more complex. It required an in-process step, it required the addition of large amounts of carbohydrate stabilisers and then the subsequent removal of these and so on, compared with the heating of a product in its final container at 80 degrees for three days.

I think my feeling was this was beginning to look very attractive from an operational perspective.

Q. As director of the PFC at the end of 1985, did you feel any pressure from the fact that the 8Y product was subject to this more severe heat treatment? It was being produced by BPL, it was being routinely issued, the preliminary clinical results appeared promising and yet at PFC the NYU, high purity project still had not been completed. Did that create any pressure or

tension?

A. Well, I think during this period, I guess -- well, ever since I took over as director, I think we were under constant pressure, without trying to exaggerate here -- I think the world was beginning to move very, very quickly in terms of developing techniques and strategies for addressing the virus safety of coagulation factor products triggered by the HIV tragedy, and of course the emergence of a product which was showing good promise in England and Wales, I think, given the relationship, which was good, between England and Wales and Scotland in terms of scientific collaboration -- but there was an element of competition between the two organisations. So the notion of our colleagues and fellow scientists in England being slightly ahead of the game created an additional layer of pressure, of course.

Q. We have heard evidence that at the meeting, Dr Foster's preference was to continue to prioritise the NYU high purity project, whereas Dr McIntosh's preference was to prioritise a severe dry heat-treated Factor VIII?

A. Yes.

Q. Which camp were you in?

A. Well, I think you asked me earlier how I felt when I went into the meeting. I think I was genuinely open-minded, which was the reason for having the

meeting. I wanted to discuss it with colleagues around me and take their views. I'm not sure what particular camp I was in. I think I was very -- having listened to the discussions -- there was relatively new information from Dr McIntosh's experiments that he had been doing. I certainly remember coming out of the meeting reasonably confident that we had a strategy which had a very high probability of succeeding in perhaps a shorter timescale than the pasteurisation project.

Q. Yes. To what extent, if at all, did you feel you had to defer to the expertise of perhaps Dr Foster and also Dr McIntosh, as the R&D scientists working in this field?

A. In coming to my decision?

Q. Yes.

A. Well, I was going to say "totally" but that would be an exaggeration. These were the people in PFC whose job it was to organise -- develop the project and develop it on budget, on time, against the pressure that you have described and so on. So I had to take a lot of account of their particular views but it was a collegiate discussion, it was a collegiate view, but I think also -- I think you may be coming on to this -- it wasn't a decision in the gift of the PFC director to take an executive decision on this. So it was the first

part of a process towards proposing an alternative strategy.

Q. And could it be said that the fact that it may not have been an easy or clear choice to make is reflected in the fact that the two R&D scientists had different views? Dr Foster's preference was to continue with the NYU, whereas his colleague, Dr McIntosh's view was that there should be priority for the severe dry heat treatment?

A. Absolutely, but having a different view on what is the most appropriate development isn't unusual in the industry. I think if these decisions were simple, then everyone would be doing the same thing and they clearly weren't.

Q. Doctor, I'm about the to leave the questions on the meeting. I'm not sure if, sir, if there are further questions you wish to ask about the meeting?

THE CHAIRMAN: I'm quite content.

MR MACKENZIE: Yes. Could I ask one follow up question, please, doctor?

You said in your evidence that although you thought there was very good science around heating a product at 80 degrees for 72 hours, you thought there might be a presentational issue.

A. Yes, I think --

Q. Hang on, sorry. You said:

"... other organisations and our competitors in commercial industry, might want to discredit the adoption of this particular process. I had some concerns over that."

A. Yes, I think this is the whole issue at that time, and I don't have a vivid recollection of this but there was a period around that time of organisations -- because dry heat treatment had already been introduced by organisations. It was one of the first techniques to be adopted by the commercial industry, albeit at very low temperatures for relatively modest periods of time. And there was evidence that these processes were not effective against non-A non-B Hepatitis. I think the presentation -- what I'm describing now as a "presentational issue" is that the whole generic issue of dry heat treatment could have been potentially discredited simply on the basis of these early forms of heated product, which had been shown to transmit both HIV and non-A non-B Hepatitis. And my concern was that for those that we had to discuss these options with, they might have taken the view that this was just another version of a dry heat-treated product and they have already been shown to transmit non-A non-B Hepatitis. So why is this one going to be different?

Q. Yes. I think Dr Cuthbertson yesterday told us that in

a way 8Y was an outlier because the commercial fractionators didn't go down this severe dry heat-treated route?

A. Yes, that's right.

Q. After the meeting, doctor, what happened next?

A. I believe what happened next was that I took that decision and no doubt thought about it over Christmas and came back in the New Year and discussed it with -- my instinctive and natural course of action there would be to discuss it with Professor Cash with a view to him advising on what process we should then engage in to get, I guess, collegiate approval for our particular preference.

Our preference -- my preference at that time, my recommendation as PFC director, was clearly to go down the route of 80 degrees for 72 hours. So my next step was to discuss this proposition with Professor Cash.

Q. Do you have a recollection of discussing that with Professor Cash?

A. No, I don't.

Q. Do you think it's likely you may have gone to see him rather than written a letter, for example?

A. I think it's inevitable that I would have gone to see him about it.

Q. Professor Cash yesterday accepted that he was the

ultimate decision maker on an issue such as this and is that in accordance with your understanding?

A. I think, in a sense, yes. I certainly -- I wouldn't have wished or certainly gone into a process of changing a strategy for what was arguably one of the most important products and services that the SNBTS offered, without Professor Cash's support. So having his support and agreement was absolutely vital. Had Professor Cash said, "No, I don't like that idea," then that would have had an effect; we would have gone back and rethought our recommendations, but I think my understanding -- and again, it's not a recollection, I don't remember the conversation but I'm absolutely sure that it would have taken place. Professor Cash at the end of the day was supportive of our proposition.

Q. So in short, both yourself and Professor Cash were in agreement as to the best way forward on this?

A. Absolutely.

Q. Yes. Could I then, please, look at one or two documents? The first one is [SNB0015469]. Can we go to the last page, please? We will see, Dr Perry, the document is dated 10 January 1986 and we see your name there. Can we go back to the front page, please? We can see this is a report you prepared for the SNBTS and haemophilia directors meeting in March 1986?

A. Yes.
Q. The date of the report slightly puzzles me, Dr Perry: 10 January 1986. What was likely to have been the process for creating this report, ie at that time would you have sat at a computer and typed it up yourself, would you have dictated it to a secretary?
A. No, I would have written it out on sheets of paper with a pen and pencil and then given it to a secretary, who would have typed it up and made the necessary corrections and so on. We didn't have computers then. We might have had early forms of them but ...
Q. Given the time of year, can you make any informed guesses as to when you may have written the document and when it may have been typed up?
A. None at all other than my practice at the time -- this was an important annual event, the annual meeting of the SNBTS and haemophilia directors, and it was always necessary and required that PFC and SNBTS presented a report for the meeting, which was, I think, seen as very helpful. So it could well have been I started the process of writing this, or parts of it in terms of the quantitative supply -- what is described as the supply and demand section. That could well have been written in late 1985.
Q. Yes. Because the only slight puzzle I have, Dr Perry,

is that there doesn't appear to be any reference in this report to the important meeting on 23 December and the recommendation/decision to change the development focus?

A. No, if we could scan the document -- if I can see what the headings are, I think the simple explanation -- and I'm not sure I can offer a better one -- is that it could well have been that Professor Cash was away in early January and I hadn't had the opportunity to speak to him. So I can't place my meeting -- the meeting that I can't recall with Professor Cash, which I know will have happened -- I can't place that in a timescale compared to the writing of this particular report.

Q. Could we, please, go to page 4? I think it's worth just looking at what is said under paragraph 3, "Heat Treatment of Coagulation Factor Concentrates":

"3.1 Factor VIII."

We see about half way down the paragraph:

"Most recently unconfirmed reports have emerged which suggest that HTLV-III may be less susceptible to heat inactivation [than] was originally thought."

I think that's a reference to the Prince publication --

A. That's right.

Q. -- paper:

"In response to these reports, PFC has recently

recalled all residual stocks of 68-degree/two hour material. Directors will be aware that the Blood Products Laboratory are currently issuing a Factor VIII product, which has been heated at 80 degrees for 72 hours, and preliminary clinical data indicates that this material is non-infective with respect to HTLV-III, NANB and Hepatitis B. While it is unlikely that the current PFC product could be successfully treated under these conditions ..."

To pause there, in October 1985 Dr McIntosh had found in the laboratory that the current product possibly could withstand these conditions. Is there any tension in what you have written and in what Dr McIntosh discovered or is this all happening about the same time or what?

A. I think it's all happening around the same time. Dr McIntosh's discovery was certainly around late 1985 and this document was clearly being written on 10 January. The meeting with the haemophilia directors was actually in March, and at that meeting we did put forward the proposal to change --

Q. We will come to that in a second.

A. So my explanation -- and again this is a reconstruction of the past, it's certainly not from memory -- is that this document was written -- it was still valid in the

sense that it was providing useful information but the proposal to change courses -- to change course towards the 80 degrees/72-hour material, I think was put in or submitted, although I don't have all the documents in front of me and I haven't looked at them recently -- presumably that was done as a separate exercise to the main report which was still presumably done --

Q. I suppose, to be fair to you, Dr McIntosh's observation in a laboratory in October 1985 was just that; it was a very initial --

A. Absolutely, and Dr McIntosh used to make many observations on many occasions. He was a very hard-working and productive scientist. So -- but I think the observations, as I think I have said in my report, that he demonstrated the principle that a relatively impure product could be heated at 80 degrees for 72 hours in a laboratory experiment, didn't actually set the world alight as far as I was concerned. It was interesting.

Q. I'm also interested in the next passage, Dr Perry. You say:

"A major development programme has been underway for 12 months with the view to the production of a high purity Factor VIII product which can be formulated and heat-treated under conditions which give comparable

levels of viral inactivation. Such treatment may not require such vigorous heating conditions."

This is a reference, I think, to the NYU product?

A. It is, yes.

Q. And it's really what you mean by saying:

"... under conditions which give comparable levels of viral inactivation and such treatment may not require such vigorous heating conditions."

What was the basis for these statements?

A. The description of "under conditions which give comparable levels of viral inactivation" would be a selection of a time and temperature profile, which I think -- in using model viruses, which the Inquiry has heard about previously, would give comparable levels of inactivation of a particular virus that you used as a model to test the process.

Q. Would "conditions" also refer to wet heating rather than dry?

A. Yes, absolutely. It would be time/temperature, in solution or as a lyophilised product or other methods as well, as subsequently became developed.

Q. So in the final sentence where you state:

"Such treatment may not require such vigorous heating conditions."

Is that again a reference to the model virus

studies?

A. It was a reference to a notion that I think existed at the time that if you were able to purify a product to a higher level of purity than the contemporaneous, intermediate products were, you could reduce the time and temperature and achieve a comparable level of virus inactivation. And I'm not saying this is a fact. There was a notion that that was possible. So our thought at that time was that if we succeed in producing a relatively high purity product, we may be able to achieve the same level of inactivation as other leading products, which at that time was 8Y but using lower time and temperature.

The benefit of that, of course, would be in yield. So it's not mentioned here but in terms of being able to lower the severity of the heat treatment, you stood the chance of actually improving the yield of the production, which for all of these developments was still vital.

We must remember that these virus inactivation procedures were all being undertaken against the background of: we must continue to supply a sufficient supply of products for patients in Scotland. So they are not being carried out in isolation; at least 60 per cent of my interest was in making sure that the

process that we selected stood the highest chance of delivering a product yield that would continue to allow us to supply products in Scotland.

Q. We should remember that so we don't consider the question of heat inactivation too narrowly. There is a wider context to it all.

A. An absolutely vital context -- yes, that self-sufficiency was the goal. I think in many senses there were two key goals. One was to provide a product -- and you have mentioned the pressures to do that, and I think they were very real and they were very proper. Our job was to deliver a safe and effective product.

Q. Presumably, if the goal was self-sufficiency --

A. But also -- self-sufficiency, but delivering a product which would only deliver half the yield of its predecessor and result in only 50 per cent of the patients in Scotland being treated would not have been considered by me or anybody else as a good result, however safe the product was.

Q. I was going to say, presumably the ultimate goal was self-sufficiency in safe products?

A. Absolutely.

Q. The two go hand in hand in a way?

A. Yes.

Q. Over the page, please, at page 5. We will see, just in passing, paragraph 4, "Batch Dedication of Factor VIII" that:

"A system of batch dedication of Factor VIII has now been in operation since early 1985 and has operated successfully. This system of product issue will continue until a safe non-infective product is at routine issue."

Just for completeness in paragraph 5.1 under "Factor VIII":

"Directors will be aware that PFC has been pursuing the development of a new Factor VIII product which is high yielding, high purity and non-infective. This programme of work has been afforded the highest priority over the past 12 months. A pharmaceutical manufacturing process has now been developed which gives access to Factor VIII with a purity of greater than 50 international units per milligramme of protein and in high yield. Work is now in hand to formulate this material into a form suitable for a viral inactivation process which gives comparable levels of viral kill to the current BPL product, which so far has proven to be non-infective. A programme of in vitro characterisation and animal studies has been initiated, and it is likely that the product will be ready for phase 1 clinical

trials in April 1986."

So just looking at that last paragraph in terms of the meeting in December 1985, how close were you to having NYU Factor VIII available? If the decision had not been taken at the meeting in December 1985 to prioritise severe dry heating and if you had stuck with NYU product, was the expectation at the meeting in December 1985 that the product would be ready for phase 1 clinical studies in April 1986?

A. Well, that's what this particular paragraph suggests.

Q. Yes.

A. And I'm not sure that that was -- and had that been the case, I think you are absolutely right. If the programme had been that advanced, that we were only four months away from delivering a safe, relatively high purity product, then I have to conclude that this was perhaps an over-optimistic statement concerning the NYU product.

Q. But also the reference to the product, which will be ready for phase 1 clinical studies, would that be a product produced in the research and development laboratory, in the pilot scale production in the main plant or full-scale production in the main plant?

A. That couldn't have been full-scale production, and given the timing of the drafting of this particular document

and the estimated date in which we might be able to do phase 1 studies, this would be a product manufactured at pilot scale.

Q. So even if this course of action had been followed and even if it had been proved possible to have a pilot scale product ready for April 1986, one would still have had the further, not insignificant step of scaling up that process to full-scale manufacture?

A. Absolutely. I think that's right. I think that's exactly right.

THE CHAIRMAN: Can I ask a question?

I find it difficult to envisage Dr Foster yielding in December 1985 to the alternative approach if work on the pasteurised product was as close to fulfillment as this suggests.

A. Well, he didn't yield easily, I don't think. But he was very capable of listening to colleagues and being persuaded that an alternative strategy was likely to have a higher probability of a successful outcome, if I can put it like that.

THE CHAIRMAN: I think having listened to him, I can understand all those various elements but still wonder whether, had success been as imminent as this suggests, he might have resisted more vigorously.

A. I think the judgment that we took -- and I can't

reconstruct all the various considerations that were discussed at that time -- but I think it was probably quite a closely run thing, and I think, as Mr Mackenzie has suggested, my balance of preference came down to a process which I perceived as being more likely to be successfully operated; it was a simpler process.

I personally liked the idea of what has been described as "terminal heat treatment", that is heating the vial in its final container because then there is no opportunity for contamination after that step has taken place. So pharmaceutically I had a strong preference for that particular option.

MR MACKENZIE: Thank you, sir.

We should then, I think, doctor, move on to the addendum to your report, which is [SNB0015484].

I assume you drafted this addendum, Dr Perry?

A. Yes.

Q. We don't know the date of it but I assume it must have been drafted some time between your previous report of 10 January 1986 --

A. That's correct.

Q. -- and the meeting on 5 March 1986 with the directors?

A. Yes.

Q. When do you think it was drafted, January, February, or is it simply guesswork?

A. I have no idea.
Q. It's worth, I think, looking at what you say. It is headed "Factor VIII intermediate purity non-infective". You say:

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

A reference to Smith, personal communication. So certainly by this stage you have received some communication from Dr Smith to that effect?
A. I think our degree of optimism, confidence, was beginning to rise. I think again we have to bear in mind at that time there was no -- there was no gold standard for this. There was no route that you could follow that would give you certainty of outcome. Everyone was engaged in trying to develop products which would result in non-infectivity. So one's strategies were based on informed opinion of -- and relatively soft evidence, which was beginning to emerge at that time.
Q. You go on:

"It is generally believed that heat treatment of this severity can only be achieved with high purity products (eg BPL Factor VIII is 5 iu/mg). However, recent research at PFC has shown that this is not the case and that severe heating can be tolerated even at

low purity if key process steps are carefully controlled prior to heat treatment."

I assume that's a reference to the work of Dr McIntosh?

A. It is.

Q. "This information will enable a non-infective product to be achieved, using intermediate purity material without compromising the development of the very high purity product noted in paragraph 5.1."

That will be a reference to NYU?

A. Hm-mm.

Q. Then you say:

"The advantages of this course of action are:

"1. Provides non-infective Factor VIII product more quickly than will be possible with the very high purity product."

What you mean by "non-infective"? As in non-infective in relation to which virus or viruses?

A. All viruses.

Q. All viruses?

A. Yes.

Q. So did you have a particular virus or viruses in mind?

A. Non-A non-B Hepatitis was the target and obviously HIV and Hepatitis B. I'm not saying it would definitely be. I was saying, on the basis of the evidence emerging from

the BPL, work on 8Y and the clinical trials there, this product was likely to be comparable.

Q. We have heard of the concerns emerging at the end of 1985 as to whether dry heat treatment was effective in producing or in killing HIV, and I think Dr Foster's position was that that was one of the main factors for the decision made at the meeting in December 1985, and really what I'm wondering or asking is: the decision to change the priority of the development work at the end of 1985, was that largely with a view to increasing the safety of the product in respect of HIV? Was it more to try and produce a safer product from the perspective of NANBH or was it a combination of both or what?

A. I think it was probably a combination of both. There was certainly the beginning of concern that the dry heat treatment at the relatively low temperatures was not as effective as we thought against HIV. I'm not sure whether that was subsequently proven to be the case but nonetheless, it was sufficient to -- any information like that would have destabilised our position.

So obviously I think HIV at the end of 1985 was still the driver, was still the driving force for everything we did. So we were trying to increase margins of safety. But also we have to remember that the original dry heat treatment -- that the original

virus inactivation processes being developed by all manufacturers in the world were driven by non-A non-B Hepatitis. That's where the process started. It wasn't ... so I think at the end of 1985, that prospect was also coming into sight and was coming to be recognised as a realistic possibility.

Q. And then (iii), other advantages of that course of action are set out, the second one being:

"That will allow the new, very high purity product to be properly assessed and phased in without undue haste."

And two other factors I won't go to at present. You finish by saying:

"It is likely that a product of this type ..."

And I think this is a reference to what became Z8?

A. Yes.

Q. ... will be available for evaluation in April 1986 ..."

When you say "a product of this type ... available for evaluation", is that a product produced in the laboratory at pilot scale production or at full-scale production?

A. I think this would be somewhere between a laboratory and a pilot scale manufacture, but I think it also may help us -- the question you asked earlier about when this was written. Clearly this was written relatively early in

1986. If I had been writing it in March, then I would have been wildly off course in terms of my estimates. This was written relatively early in the year and with what I would now recognise and concede is a slightly optimistic timescale for the actual development.

Q. Yes. We will come back to that last point shortly.

Thank you, Dr Perry. Just to complete this chain of documentation, if I may, can I quickly take you to this please, [SNB0015454]?

We can see the bottom left-hand corner the date February 1986 and then bottom right-hand corner, "JDC". I think these are Professor Cash's notes for the March meeting. Can we, please, go to page 6? Under (v), "high purity product". I'll let you read it for yourself, Dr Perry. Then you will come to the sentence:

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

And I think this is a reference to a decision taken at the meeting in December 1985, which you then took to Professor Cash, who agreed with the recommendation?

A. Absolutely. That's correct.

Q. We can then put that to one side, thank you. Back to page 4 of the statement, please. The next question in the bold typeface, we asked:

"Why did it take until May 1987 before intermediate

Factor VIII manufactured by PFC and dry-heated at 80 degrees for 72 hours was available for clinical use?"

You refer to the briefing paper Dr Foster produced and we have gone over that evidence with him.

You then say:

"The development of the Z8 product commenced at the beginning of 1986 as part of an agreed SNBTS plan to develop a reduced infectivity, NANBH product available to all patients in Scotland as the third phase."

Just to pause there, the reference to "an agreed SNBTS plan," what's that a reference to?

A. Well, certainly at the very least it indicates that this is something that PFC has obtained support of from its national medical director, but I think Professor Cash typically would have taken it or -- in some way -- I can't remember whether there was a formal meeting or part of another meeting, but he would have had it discussed by SNBTS directors. He was, I think -- for something as important as this, I think he would have been -- I think he was very confident of his decision and his support for it but he would have typically taken a board --

Q. So that's a reference to events at the end of 1985 and beginning of 1986?

A. 1986.

Q. I understand. But also the reference to "develop a reduced infectivity, NANBH product", and again, as I say, I understood from Dr Foster that the main factor was to provide more protection against HIV. So I just wonder why you just say "NANBH" there?

A. I think everyone had a different perspective on this. I think Dr Foster is right. I think also -- I think at that stage in early 1986, I think we were beginning to become fairly confident. We had effective tests in place for HIV. So we could monitor patients or haemophilia doctors could monitor patients, and there was beginning to be a high level of confidence that the HIV problem had been effectively addressed. We also knew that HIV was easily inactivated, relatively so, so if -- I think the assumption in this is that reduced -- if you achieve reduced infectivity or non-infectivity for non-A non-B Hepatitis, you are almost certainly going to achieve non-infectivity with respect to HIV. So non-A non-B Hepatitis was still the gold standard at the time, even though the urgent clinical and scientific target was HIV.

Q. Okay. Over the page at page 5, please, doctor, in the third line down, the sentence commences:

"In contrast to BPL, the SNBTS had adopted a phased development plan involving the progressive development

and introduction of heated products, without interruption of supply."

It's a reference to "in contrast to BPL"; what did you understand the position to be in England at this time?

A. I'm not sure. But they certainly didn't start at the point that we started at, and we started at the point of (a), the given assumption in all our planning was continuity of supply because even without heat treatment, the belief was that products made from volunteer donors in Scotland would be safer than anything you would get from the US from paid donors, and the reference to a phased development plan was (a), the 68-degree material for two hours, with an expectation that would be followed by a 24-hour material. So we had a phased programme which provided continuity of supply and progressively safer products being delivered.

BPL, as I think we have heard from others, didn't have the benchmark of continuity of supply as part of their specification, and I think, as we have heard, there were periods where they simply stopped supplying. So they didn't have that additional pressure of maintaining a continuity of supply.

Q. And in terms of the SNBTS phased development plan, presumably -- let me know if I'm wrong -- when the first

NY heated product at 68 degrees for two hours was brought out, you said the plan was then to have an increased heating of that product?

A. Yes.

Q. But also, I think, at the same time, of course, Dr Foster was undertaking his research work in NYU, so that would have been the next phase?

A. Yes.

Q. And we have discussed that that part switched to a different phase?

A. I would simply make the small point that when we began this process in 1984, and we did have an expectation of there being a phased development programme but we weren't quite sure of the timing and the specific content of these phases, other than our strategy against the backdrop of having good product stocks would be that we had the opportunity of developing products which are progressively safer whilst at the same time maintaining supply.

Q. Yes, I suppose ideally one would want, firstly, a plan for the future but, secondly, flexibility, so one can change course and revise's one's plan according to circumstances?

A. Yes.

Q. And just returning to your statement, please. In the

last sentence of the first main paragraph commencing:

"This strategy required the PFC to continue to routinely manufacture NY Factor VIII at 68 degrees for 24 hours until the Z8 product had been developed, validated at scale, transferred to routine production and safe working stocks established ..."

To pause there, I wonder if that sentence is strictly speaking correct, and as you then go on to tell us the manufacture of the 68-degree/24-hour product was stopped in July 1986 at a time, I think, when the Z8 product had been developed to the stage of pilot scale production, but it certainly hadn't, at that stage, been:

"... validated at scale, transferred to routine production and safe working stocks established ..."

A. I think you are correct.

Q. Just a point of detail.

A. There is a slight disconnect between those two statements, although to an extent they were true. But you are absolutely right, we hadn't established at scale, we hadn't established safe working stocks of Z8, and the reasons for discontinuing were to release resources and capacity to do large-scale studies.

Q. But certainly you go on to say that:

"In July 1986, the routine manufacture of NY Factor

VIII at 68 for 24 hours was discontinued to allow the PFC to focus its development and manufacturing resources on the final development stages of Z8 and to subsequently build working stocks ... for distribution in the batch dedication system."

So certainly in July 1986, the initial pilot scale production of Z8 seemed to work and, because of that, I think, routine manufacture of the existing product stopped?

A. Yes, I think we had a high level of confidence that we were on the right track. We had a very high level of expectation that the development would be successful within the sort of timescales that we had established.

Q. Yes, and the problems which arose with Z8, they didn't arise between transfer from the laboratory to pilot scale production?

A. No, no.

Q. They arose between transfer from pilot scale production into large-scale, full production?

A. Exactly, yes.

Q. Thank you. Then you do say:

"At this point ... "

This is July 1986:

"... it was estimated that sufficient stocks of NY Factor VIII were available to meet planned requirements

until the spring of 1987, which was, therefore, the estimated date for the transition from NY Factor VIII to Z8."

I think the next two documents to look at are quite interesting in that regard. May I firstly, please, go to [SNB0075910]. This is the letter we have seen before from Dr Boulton to yourself, Dr Perry, dated 4 July, asking:

"Is the enclosed a clear representation of our telephone conversation yesterday?"

If we can go on to the next page, please, I'm sorry, it's another page. I'll give the reference in a second. (Pause)

I think the enclosure is a different number. It's [SNB0075911]. Could we turn it round? Thank you.

I think this has been produced by Dr Boulton, Dr Perry, is that right?

A. It looks as though -- it certainly has not been produced by myself.

Q. Yes. I think what's quite interesting, if one can see phase 2 -- and that's a reference to the NY 68-degree/24-hour product.

A. Correct, yes.

Q. And one can see under "September 1986" an entry:

"Production stops."

A. Yes.
Q. Although that may be July. It doesn't matter, I think, too much. But what's interesting, one then sees:

"Phase 2 product being used up."

A. Yes.
Q. And that continues until perhaps the end of March 1987 and it then states:

"No more phase 2 available."

So that was the prediction as at summer of 1986, that NY/68/24 product would continue to be used up until the end of March 1987, and if one goes down to the reference to the phase 3 product being produced -- and that's a reference to Z8 -- one can see that production is estimated to commence perhaps September 1986 and then to continue -- am I right in thinking, Dr Perry, that really between September 1986 and March 1987 the intention is essentially to stockpile Z8?
A. Yes, it was a period of building stocks and gaining operational experience of a new process.
Q. Yes.
A. And that was the strategy. I think these decisions to discontinue manufacture of one product and introduce another one are always -- always carry an element of risk but that indeed was the strategy, but also Dr Boulton points out that there was a requirement

within this plan to have the clinical evaluation of the Z8 product conducted some time between September and December 1986.

Q. Yes. During the period of stockpiling Z8, between September 1986 onwards, presumably after the phase 1 evaluation had been undertaken, I assume the intention would be that the Z8 product would be available to any previously untreated patients during the stockpiling. Is that right?

A. That was the expectation and the intention that, as far as the PFC equivalent of 8Y, ie the Z8 product, came into play, we would have a product which had a comparable level of virus safety to 8Y, and indeed that could then be used to treat even before the point at which it was going to be routinely introduced into practice because we had previously agreed with haemophilia directors, and certainly within the SNBTS that the new Z8 product would be introduced only after the existing stocks of 68-degree/24-hour material had been exhausted. Yes, I think there is correspondence between myself and Dr Boulton that suggest that.

Q. I suppose I'm just trying to be quite careful about what is meant by when Z8 would be introduced, in that my understanding is that after Z8 had undergone the phase 1 clinical trial, I assume it would have been available to

treat previously untreated patients but that for those patients who had already been prescribed a batch of the NY/68/24-hour product, they would continue to receive that NY product until that batch had been used up?

A. That is exactly how the batch dedication system was intended to work and facilitate the introduction of a new product.

Q. Yes. I think we can put that to one side.

It would certainly be a suitable time to have a short break.

(11.03 am)

(Short break)

(11.26 am)

THE CHAIRMAN: Yes, Mr Mackenzie.

MR MACKENZIE: Thank you, sir.

Dr Perry, I would like to continue with your statement, please. We had reached page 5, about half way down.

We can see:

"Z8 material for clinical evaluation was available in December 1986, approximately two to three months later than originally planned as a result of unexpected problems arising during the early stages of large-scale manufacture."

A. That's correct.

Q. We heard about that from Dr Foster:

"The clinical evaluation of Z8 was not conducted until March/April 1987 until the SHHD reassurances concerning patient compensation had been received by the haemophilia directors."

I'll deal with the question of compensation with other witnesses. Then:

"The overall timescale from January 1986 to April 1987 ..."

That's about 15 months:

"... for the design, development, scale-up, transfer to routine production and clinical evaluation of a new and innovative Factor VIII product, whilst concurrently maintaining uninterrupted supply of NY Factor VIII and avoiding exposure of patients to imported Factor VIII products was in my view neither excessive nor unexpected."

Over the page, please, question (c) about changes in the manufacturing process Dr Foster has dealt with. The next question, (d) asks:

"What was the original timescale for the production and introduction of Z8? If that timetable was not met, when and why did it slip?"

You respond that:

"From the preliminary laboratory studies in early

1986 it was considered feasible that the new Z8 product could have been available for clinical evaluation in April and routine issue three months later."

That's about July 1986 for routine issue:

"This assessment was presented to the meeting of the haemophilia and SNBTS directors in March 1986."

You say:

"This was a preliminary (and clearly over-optimistic) estimate and ... "

Just to pause there, Dr Perry. January to July, I think is what's being suggested, in early 1986 being the time period to reach full production of the product. Is that correct?

A. Yes, I think that was the original -- the original plan and strategy, yes.

Q. Which was about seven months?

A. And that's what I'm describing as "over-optimistic".

Q. How does that compare with the previous page where, in the final paragraph, you stated:

"The overall timescale from January 1986 to April 987, 15 months, was not unexpected."

Is there a tension or inconsistency there?

A. I'm not sure that there is an inconsistency. I think the -- on the previous paragraph, I think that's with the benefit of hindsight and knowing what's now

involved. We were in new territory here, whereas the original timescale of January to July was, as I say -- I think it was over-optimistic -- I can understand the point about there being an inconsistency but my retrospective analysis of 15 months or 12 months for the development, reduction to practice and introduction at large-scale for a manufacturing process as being 12 months is, I think -- I think is a retrospective analysis. I think it was a very substantial achievement.

Q. Yes. At page 6 of your statement you say:

"The preliminary (and clearly over-optimistic) estimate ..."

For Z8:

"... was subsequently revised in the light of experience (by June 1986) to September 1986 for clinical evaluation and introduction into routine use in early 1987, following consumption of NY Factor VIII stocks as agreed with haemophilia directors."

Then you explain:

"Unforeseen freeze-drying problems during scale-up and the additional work required to solve these ... delayed the availability of the product for clinical evaluation until December 1986."

We heard from Dr Foster about those problems and

their resolution. Then:

"The planned clinical evaluation of Z8 in December 1986 was not carried out until March/April 1987, when the necessary assurances were received ... concerning indemnification of patient volunteers."

I think the interesting paragraph is at the end, that:

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

That perhaps brings us back to the document we looked at just before the break.

A. Yes.

Q. Which was, produced, I think, in June or July 1986?

A. Yes.

Q. You do come back to this point over the page a little bit as well. So we could go over to page 7, please. Page 7, question 4. We asked whether:

"... PFC's work on the development of a high purity Factor VIII ... (NYU) ... resulted in any delay in the

introduction of Z8."

I think your answer in short is no, and we can take that as read.

A. Yes.

Q. One further question, doctor, and even answering this with the benefit of hindsight, if you want: could it be said that the decision taken in December 1985 to change priority to a Z8-type product should have been taken some time earlier?

A. I don't think that decision would have been able to have been taken that early. I think the key -- I think the key information that allowed us to take that decision was the experiments conducted by Dr McIntosh and the realisation that we understood how you could heat a relatively low purity product at 80 degrees for 72 hours, and that information wasn't available to us prior to that.

Again, it is with hindsight. I think our belief prior to that was that pasteurisation remained the best option. And colleagues from BPL to an extent actually agreed with that because there was some experience from the Behringwerke product that pasteurisation was likely to deliver a safe product. So we still felt that was the best option.

So it was a fairly quick change and change of tack

in December but I think there were specific events -- specific pieces of information, and a general sense of increased pressure to make -- bring this -- a safe product with respect to non-A non-B Hepatitis forward as quickly as possible.

Q. The next question, please, Dr Perry, is question 5. We asked:

"Did any difficulties in commencing clinical trials of Z8 ... result in any delay in the introduction of Z8."

You then say:

"As discussed above, there were delays in subjecting Z8 to clinical evaluation arising from the compensation/indemnity issue, but for the reasons described above, it is unlikely that this resulted in a delay in the phased introduction of the product for all patients in Scotland. Earlier completion of the clinical evaluation would have made the product available for specific patients identified by the haemophilia directors, eg those with little or no previous exposure to coagulation factor products."

I think we discussed this point before the break?

A. Yes. I think the point that I have made here and actually previously is that the date of routine introduction of Z8, ie for all patients in Scotland --

set aside the previously untreated patients for the moment -- was actually determined in July 1986 because that was the point at which we discontinued manufacture of the preceding product, we knew how many -- how much stock we had, we knew the rate of usage and at that point we knew that the introduction of the new Z8 product in terms of superseding the NY product would occur around March time.

Q. And one would have had to have departed from the batch dedication system?

A. Yes.

Q. To have brought forward the use of Z8 for all patients?

A. Well, you would have had not only to depart from that but you would also have to destroy very substantial stocks of material to which patients had already been exposed, ie the NY product. And I think all of these progressive developments in terms of new generations of product, were possible because we had safe -- actually relative to many other organisations, certainly in Europe and probably the world, we had very good stocks of product and it allowed us this flexibility of moving from one product to another. But had we chosen to introduce Z8 as soon as it was available, that would have resulted in the destruction of very large stocks of the previous NY product and we would have lost any

opportunity -- and I think we would have probably failed to supply against that scenario.

Q. And if Z8 had been made available as soon as it was available and if existing stocks of the NY product had been destroyed, might that have threatened self-sufficiency, ie for a period might there have been a need to purchase commercial concentrates?

A. That's right. That's right. Absolutely. And that's why we had a previously -- a previous agreement between SNBTS and haemophilia directors that the subsequent -- that the continuous introduction of progressively improved products would be introduced and -- via the batch dedication system, which meant that as a result of delays in patients moving over to the newer product, you didn't necessarily increase their risk as a result of doing that because the batch that they were receiving -- they had received prior to the introduction of the new product. So it wasn't increasing the risk; they weren't being exposed to additional batches of product.

Q. Yes. Returning to your statement, doctor, you say that:

"However, PFC had, at the request of Dr Ludlam, obtained small stocks of 8Y from BPL/PFL in 1986, which were made available for the treatment of patients (eg newly diagnosed, previously untreated or allergic reactions to existing product) for whom 8Y would be

considered preferable until Z8 became routinely available."

I think you even provided a statement to the Inquiry in relation to topic C3A on that matter?

A. Yes.

Q. Then question 6. We moved on to another issue. I think we provided two documents to you which we have looked at previously and I don't have to go back to now. But we said:

"Did any wider management, organisational or other issues result in any delay in the introduction of Z8?"

The two documents we had referred you to were a memo from yourself to Dr Foster of 22 December 1988 and a letter by Dr Foster to Dr Prowse in 21 November 1990. I don't want to go back to them now. You were shown them earlier and your answer at the top of page 8, you say:

"Product developments such as Z8 were typically led by a senior manager of the PFC development department. The management of the Z8 project involved a multidisciplinary project team with a membership drawn from development, production, quality and engineering departments."

Your recollection is that:

"The Z8 project manager ... "

Is that Mr McIntosh?

A. Yes, Dr McIntosh.

Q. " ... was closely involved in all stages of the development, including its transfer into routine production."

Et cetera.

A. Yes.

Q. I should perhaps ask you, Dr Perry, the two documents we have provided to you as the basis for this question -- firstly, your memo to Dr Foster of 22 December 1988 -- would it be helpful for you to actually see that on the screen, doctor?

A. It would actually, yes.

Q. I'm sorry, it's [SNB00067120]. Can I just take a minute to look at that, doctor. It's a memo from yourself to Dr Foster and others. The subject "Modification to Z8 Freeze-drying Cycle". In the second paragraph you say:

"Less reassuring is my personal observation (shared by others), that this particular process modification was proposed some considerable time ago and could have been introduced many months ago."

A. Hm-mm.

Q. Really on the basis of that we asked the question:

"Did the sort of consideration set out in this memo apply to the development of Z8 in 1986?"

A. No, this post-dated the -- this particular incident, which I do remember, not vividly but with some clarity because, you know, I remember being fairly frustrated, but at the period at which the Z8 was being developed, I think, as I have described in my witness statement, it was under very effective management and it was probably the highest priority project within the PFC, and both myself, Dr Foster -- it was led by Dr McIntosh, but both Dr Foster and I were very closely involved in the management and the monitoring of that particular project, including the release of resources from various departments throughout the centre.

Q. And does this memo really relate to once Z8 is up and running, it is being routinely produced by PFC? There is then a question of fine-tuning and modification of the process as time goes on?

A. That's right.

Q. And if a modification is proposed, what's the system or process for that being considered and actioned?

A. Absolutely. What I'm expressing there is a frustration that things that could have been done sooner but for a variety of reasons weren't done -- I was (a), expressing my frustration and (b), suggesting that we needed to put in a better system for managing changes in individual processes but I don't think this particular issue here

had any impact on the Z8 development itself.

Q. Thank you. I don't have to take to you Dr Foster's letter in November 1990 because he has spoken to that and he is the author of it.

Then, please, question 7, returning to your statement. Question 7 concerns the contact and exchange of information between PFC and BPL and PFL. As background to this question, we had identified a letter from Dr Cash to Dr Lane in December 1982, I think in relation to cooperation in respect of heat-treating Factor VIII concentrate or perhaps coagulation factors more generally. But also in particular, doctor, Professor Cash had produced background notes in January 1984, which spoke of difficulties between the then directors of PFC and BPL. Do you remember those documents or would it help ...?

A. Is this the one in which Professor Cash describes the furtive management arrangements?

Q. Yes. I should perhaps just go to them so you have them, doctor. The first one is [SNB00043163]. We see this is a letter dated 17 December 1982. It's from Professor Cash to Dr Lane.

A. Yes.

Q. It's to do with the hepatitis-reduced Factor VIII concentrates and the questions, I think, of clinical

evaluation in British, previously untreated patients and the commercial companies wanting to do that. But page 2, for our purposes --

A. Yes, okay.

Q. I think you will have seen this before?

A. Yes, indeed.

Q. It's the last sentence of that paragraph.

A. Hm-mm.

Q. "I do not regard the existing furtive arrangements as regards Factor VIII between Jim Smith and Peter Foster, however good they may be, as a sound basis upon which the NHS fractionators can combat the commercial people."

I should perhaps then also just briefly refresh your memory by going to [SNB0065138].

Dr Perry, we can see this document is headed:

"Background notes for the chairman (on the occasion of the meeting between [the Common Services] Agency and CBLA colleagues: 20 January 1984)."

The author of this document from the bottom right-hand page is Professor Cash, "JDC"; do you see that?

A. Yes.

Q. If we go on the next page, please. The next page again, please. Do you see the paragraph at the top beginning:

"It would be appropriate to conclude that the formal

relationships between BPL ... and SNBTS have not been satisfactory over the years."

Does this document start to ring a bell now? I appreciate you probably didn't see it at the time.

A. I didn't see it at the time, no.

Q. I think your attention was drawn to it with the statement request?

A. Yes.

Q. Did you have a look at it then?

A. Yes.

Q. I'm grateful.

Then over the page, please, we can scroll down, please. Over the page again, please. The top of page 4, if we could blow that up a little, please? Thank you.

We can see "The rationalisation of research and development programmes". But in short, Dr Perry, Professor Cash alludes to difficulties between the then directors of PFC and the English counterpart, I think Mr Watt and Dr Lane?

A. Yes.

Q. And that really forms the basis of question 7. I should perhaps ask before I come to your answer, doctor: before you became director of PFC, were you aware of any difficulties between Mr Watt and Dr Lane?

A. Yes. I think the answer is yes. I think it was -- I was going to say it was widely known but I think the nature of the relationship between the two organisations was fairly well understood. They were both -- Mr Watt was a fairly flamboyant sort of character and in some senses very exciting to work with. But I think it was -- I think it was recognised in PFC and probably in BPL that Dr Lane and Mr Watt, for all sorts of reasons, which I never took the trouble to find out what they were, but there were some issues. There were some conflicts. Maybe it was competition, I don't know. But, yes, they were not the best of friends.

Q. Yes. Putting personalities to one side, I think we have heard evidence that there were substantive differences between the directors, for example on issues such as whether Scotland should fractionate plasma from England. That's a real issue and one can see perhaps people may have different views on that.

A. I think there is a long and -- a long history on that particular issue and I think, yes, my understanding, when I joined, was that the PFC was established to fractionate, I think, for what was then described as "North Britain", which I think was for the population north of Manchester. And indeed funding -- I cannot provide any evidence of this but my understanding was

that DHSS then at that time provided funding for PFC, or part funding for it as well. I think subsequently it was decided that this wasn't the case and I think the view taken by Mr Watt and perhaps others, and maybe with some justification, I don't know, was that this had been the result of direct involvement and opposition by people like Dr Lane and his predecessor.

Q. Okay.

A. Who considered the PFC development to be unnecessary.

Q. I'm about to come back to the topic C3 but one final question: when you became director in 1984 and from then on, how was your relationship as director of PFC with Dr Lane?

A. I had no prior form with Dr Lane, so I could start from a clean sheet, as it were. It was absolutely fine. As was my relationship with Dr Smith and Dr Snape, and there was no historical baggage, as it were, in my position and indeed I used to meet Dr Lane on regular occasions and latterly he used to visit PFC. He would come up maybe a couple of times a year for informal discussions and so on. So it was fine. I wouldn't say we had a vigorous exchange of views on every topic and so on but we freely communicated.

Q. But certainly, once we come to look at the period under consideration for topic C3, perhaps the second half of

1984, 1985, 1986, 1987, in this period you are the director of PFC and your relationship with Dr Lane, your counterpart, is fine?

A. It's absolutely fine. I don't think it was -- I don't think it was necessarily regular and so on. This was in the early days of me taking over as director, but there was absolutely no problem between myself --

Q. Coming back to question 7 and really the topic-related question, we recognised there was clearly informal contact and exchange of information between PFC and BPL/PFL, in particular Drs Foster and Smith, and we asked whether any difficulties hinted at or expressed in the document, for example from Professor Cash, between the then directors, inhibited in any way the exchange of information in respect of the development of 8Y including severe heating of the product. I think your answer in short was no?

A. Absolutely none.

Q. No. Then the next question, please, question 8, concerns the CBLA central committee on research and development in blood transfusion, which first met on 21 June 1983. Could I pause, Dr Perry? Were you aware of the existence of that committee at the time?

A. In 1983?

Q. Yes.

A. Probably not.
Q. How about when you became director? Did you become aware of it?
A. It wasn't one of the first things that I discovered, no.
Q. Do you think that PFC should have been represented on this committee?
A. I think it was a -- I'm not sure. I wasn't aware of the political background to it. Even with hindsight, I'm not sure that I have got a clear answer on this.
I think it was -- my own view, informed by many years of experience, is that this particular committee -- I'm not sure how productive it was. It was very much -- sort of reflected what was happening rather than provided any forward looking strategy and so on.
Q. We will come on to your written response in that regard and I think you have had a chance to look at some of the minutes of the committee?
A. Absolutely.
Q. To get a feel for it?
A. Absolutely.
Q. Thank you.
A. It was a CBLA committee meeting. It was about research undertaken by the units and the organisations under the Central Blood Laboratories Authority. So there is no real reason that an organisation in Scotland under

completely separate, different, distinct administrative arrangement should have membership of a committee which is serving the needs of BPL and the reagent manufacturing units.

Q. I understand. If we go over to the top of page 9, I think that's essentially that is your answer to question (a), that essentially it was an English committee given the CBLA served England.

A. Yes, absolutely.

Q. Yes. Then I think perhaps you have an interesting observation in the second paragraph in your answer, where you say:

"I am unable to comment authoritatively on the value and importance of this committee from a Scottish, English or UK perspective. However, my impressions ..."

Are these your impressions of reading the minutes for the purpose of this Inquiry or were these impressions you formed at the time you were director?

A. Absolutely. Well -- no -- I think I became aware of this meeting and I knew it existed and we did have access, although the meetings were fairly confidential. I don't think they were strictly confidential in the sense that we didn't have means of obtaining these things or they came our way, but I certainly regarded it as -- if you read through the minutes -- and at the

time, from the discussions I had with colleagues at BPL, they saw it just as a means of Dr Lane informing board members of basically what he was doing, but the strategies, the plans, I think the key decisions were taken by the BPL director.

Q. I understand. You say in your statement:

"The committee exercised a primarily observational and reactive role in relation to policy, scientific or operational decisions taken elsewhere."

A. Absolutely. For example, if you look at the minutes of the meeting, you will see very little detail on the 8Y development and what the options are and what the strategy should be. It's simply Dr Lane reporting on progress.

Q. I think Dr Foster, when questioned on this point, said he would rather have received the information on 8Y first hand from Dr Smith than second or third hand through attendance at some committee.

A. Yes, with an inbuilt delay.

Q. One can understand the logic of that.

Then question (b), we can see your written answer. Thank you. We don't have to go over that. Page 10, please. I think question (c), we will again just take your written answer as read. We have really discussed these issues, I think.

Then page 11, question 9. I think we will just again, if I may, take your answer as read, answer 9. This is a slightly more general question, which I think departs a little from what is at the heart of topic C3 and we can see your answer. On page 12, please, question 10 concerned why Factor IX was able to be severely heated before Factor VIII and we have Dr Foster's answer and you, I think, very concisely say that:

"As described in this paper and unlike Factor VIII, it was not necessary to establish a new manufacturing process to render the existing Factor IX product tolerant to heat treatment. It was only necessary to modify the product formulation and to conduct an animal safety study, which took place as a collaboration between PFC and BPL ..."

I don't think we need to say any more on that.

Then we had some additional questions. Question 11(1) we have covered already. That took us back to the report we have looked at, your report of 10 January 1986, the meeting of the SNBTS and haemophilia directors. We don't have to say any more on that, thank you.

Then question 2 at page 131, really a point of clarification. Dr Boulton has a letter of 20th, not

22nd, I think it's 20 August 1986 to Dr Perry concerning a particular batch. It wasn't clear to us from the batch number whether that was the NY intermediate product or Z8 or something else. And you have checked the records and the reference in that letter is to the intermediate purity NY Factor VIII with the result that we don't have to detain ourselves any further in respect of that letter.

Question 3. The 11th hour problem of freeze-drying when scaling up Z8. We have covered that at length with Dr Foster. So we can leave that. We have a new point at page 14, a new document anyway. Question 4 states:

"In his minute of 26 August 1988 to the chief medical officer, Mr J Hamill, SHHD, notes that from speaking with Dr Perry, Mr Hamill learned that collaboration between PFC and BPL/PFL 'was not all that it might be'."

We should go to that document, I think. It's [SGH0024677]. One can see this is a minute or memo internally from Mr Hamill, addressed to the chief medical officer and copied to Dr Scott and Mr Macniven:

"Blood products.

"1. Finland/Holland/Scotland."

I think in short the SNBTS were liaising or discussing things with their Dutch and Finnish

counterparts and I think Mr Hamill, who I think had come into post quite recently, was querying these links, and in paragraph 2 he says:

"There may be a background to these links of which I am unaware, but coming new to the subject I don't for the life of me understand why our top priority should not be ensuring that there are adequate links between our service and its English counterpart and in particular between PFC and the English establishment at (I think) Elstree. Speaking to Dr Perry recently (and he seems very open with us) I learned that collaboration between the two establishments was not all that it might be: and I wonder whether there is a risk that these foreign contacts will lead us down a road towards greater 'independence' from England when what we should in fact be considering is ways in which we can maximise the return to Scotland from their research and product-testing efforts."

So Dr Perry, do you remember this discussion with Mr Hamill at the time?

A. No, I don't, I am afraid. I did not have many discussions with Mr Hamill. I think I met him on a couple of occasions. This wasn't a specific conversation; this was a cup of tea conversation, I think, after perhaps a CSA subcommittee meeting or

something of that --

Q. Which you probably didn't expect would reappear some 20 plus years later at a public Inquiry.

A. No, there are lots of things that I hadn't expected but this is probably one of them.

THE CHAIRMAN: I'm sure Hamish Hamill didn't expect it either.

A. I'm sure Hamish, who is a very nice man, will not remember having this conversation either.

MR MACKENZIE: I think that's the gist of his statement to us to be fair.

A. I'm disappointed that he doesn't remember --

Q. He doesn't even remember the cup of tea.

There is perhaps, Dr Perry, potentially a serious point behind this, in that this seems to be a suggestion by you to Mr Hamill of 1988 that, certainly in Mr Hamill's words, links between PFC and BPL were perhaps not all that they might be.

If you had said something to that effect, can you tell us what you think you may have meant or been referring to and in particular whether it's relevant to the development and introduction of Z8?

A. Well, I don't, and this will have to be a reconstruction, but I think from the words I have used, "they were not all it could be", there were

a number of areas in which I felt at that time that a closer working relationship might have been helpful.

I think we were at a time where we were introducing an immunoglobulin product, for instance, and I think our colleagues at BPL either were about -- no, they had at that time failed to introduce a product or they had introduced it and sadly it transmitted non-A non-B Hepatitis to a number of patients at Northwick Park. So they abandoned their development.

My view at the time was we had a very good intravenous immunoglobulin process in place in Scotland and it would have been, I think, beneficial to the UK had there been a more productive dialogue about the probability of transferring that technology from Scotland to England. That's an example of saying the cooperation and collaboration wasn't all it could be.

I think in terms of the Factor VIII development, we were blessed with a colleague at BPL, in PFC, in the form of Jim Smith, and indeed people like Terry Snape, who were very, very good friends and close colleagues of ours. So I don't think these difficulties in any way affected, as I said before, the development of Z8, where we had excellent working relationships.

Q. Thank you, Dr Perry.

If we go back to your statement, please, at page 14,

we also have a full written reply from you as well, which we can take note of as well.

A. Yes.

Q. Dr Perry, that concludes this statement, but I think there are then two short supplementary statements we requested from you as well.

A. Yes.

Q. Could I, please, go to the first of those, which is [PEN0171864]? A one-page statement. In particular Professor Cash in his statement, which we looked at yesterday, had raised as a potential issue the question of whether any delay in carrying out in vitro virus inactivation validation studies at PFC, and particularly around 1986, may have contributed to any delay in the development and introduction of Z8, and we put that point to yourself and Dr Foster, together with Professor Cash's references, and I think your reply in short, Dr Perry, is that this issue raised by Professor Cash is a potential issue to be fair, but did not result in any delay in the development or introduction of Z8. Is that correct?

A. Yes, that's absolutely the case. This post-dated the development and introduction of Z8 as a routine --

Q. I wonder about that. If we could perhaps look at your written response, you say:

"I believe Professor Cash's comment refers specifically to the development of virus inactivation studies using live cultures of HIV. The planning of these studies commenced at the beginning of 1985 and these were subject to a number of delays, including the events referred to by Professor Cash concerning the intervention of SHHD".

We looked at one document with Professor Cash yesterday, which was dated early in 1986, where I think SHHD raised some concerns about that. So the time period does seem to be maybe late 1985/during 1986, about the time when Z8 is being developed but, if I may read on:

"However, the primary purpose of these HIV studies was to provide data in support of future Z8 product licence applications and the studies were not a prerequisite, either by SNBTS or the regulatory authorities, for its routine introduction into clinical use. At the time of its introduction, we were already confident that the severe heat treatment method would provide a high margin of safety with respect to HIV. Therefore, the availability of data from such studies was not on the critical path for introduction of Z8 and had no effect on the timing of its introduction, April 1987. The specific events to which I believe

Professor Cash refers, also post-date (August 1987 onward) the earlier introduction of Z8 in April/May 1987 ..."

I wonder if I have been confused Dr Perry. The issues arise in late 1985/1986 but studies are only required in relation to a future event, namely application for a product licence. Is that what you mean?

A. What I think I'm describing is although these were important studies, they were primarily required for the submission of a product licence to validate the process.

Q. So the studies were required for a future event?

A. A future event, yes, they were not -- as I have described it here -- they didn't have to be completed to permit us to introduce the product into routine use.

Q. I understand.

A. So although they were contemporaneous with the product development, they weren't on what I have described as the "critical path".

Q. Thank you.

The second supplementary statement, please, is [PEN0172201].

In short, this statement takes us to the clinical trial, the phase 1 clinical trial of Z8, including when the product actually became available for trial, and we

requested this supplementary statement from you because of certain points raised by Professor Ludlam in his statement, and this is all with an attempt really to try and clarify factually what happened at the time.

If I could, please, then go through your statement and refer to one or two documents which may help clarify things. So question 1. We looked at a memo from yourself yesterday, dated 22 December 1986 to Dr Cuthbertson, in which you ask that 200 vials of Z8 be sent to Dr Boulton, who will subsequently distribute it to participating centres. Professor Ludlam had noted that he could not find any evidence that the Z8 was dispatched from PFC or that any of it was forwarded to Glasgow or Belfast for assessment in patients. We asked you to look into that. And your response was you can:

"... confirm that 200 vials of Z8, batch 6-0110, were sent to Dr Boulton on 22 and 24 December 1986."

You say:

"This is recorded in the PFC batch issue sheet."

Which we looked at yesterday. I think that query has been resolved. The reference, without going to it, is [PEN0171437]. You then say you have been:

"... unable to locate any evidence or information concerning its onward distribution to other centres."

Is that a reference to, for example, Glasgow or

Northern Ireland?

A. Yes.

Q. But your recollection is that this particular batch of product was used only for clinical trials in Edinburgh Haemophilia Centre. You do then say:

"However, there is evidence that Z8 for clinical trial had been sent to Dr Forbes in Glasgow earlier in December 1986, although I have been unable to determine whether this was sent via the Edinburgh Regional Transfusion Centre, ie Dr Boulton, or directly from PFC".

We should, I think, go to the letter you refer to in December 1986. I think it's [SNB0076298]. It's a letter from Dr Crawford at Glasgow to yourself of 12 December 1986. Do you have any recollection of this letter, doctor?

A. Only when I have been reviewing it recently, but, yes, I understand it actually. And this is why I think I have submitted it as evidence that material did go to Glasgow because --

Q. I think we have looked for the letter of 9 December referred to but I don't think we have it in our database. It may be that may provide the clue to what this relates to, in that while the letter is headed "Clinical trial of new Factor VIII product Z8", I think

Dr Cuthbertson's position yesterday is that one can't necessarily assume that the whole content of this letter relates to clinical trial of Z8. One can't assume from this letter in itself that Z8 had been sent to Glasgow for clinical evaluation.

A. I think it falls very far short of proof that that happened but I think what I was looking for was some evidence that -- or evidence whether or not the Factor VIII that was sent to Edinburgh found its way into Glasgow. I can't think what else this would refer to at that point in time. I think for me it clearly points to product having been supplied as I say, either from the 200 vials that we sent to Edinburgh for clinical trial or directly from PFC, because our colleagues in Glasgow were very sensitive about the route with which we communicated with haemophilia doctors over there, and it was quite important that all these transactions were carried out through the regional transfusion centres. So this was an occasion of me bypassing a system and Dr Crawford indicating his displeasure, albeit in a very polite way.

Q. Certainly your inference from this letter is that it appears likely that Z8 had been sent to Glasgow for phase 1 evaluation?

A. I think so because it talks about the clinical trial of

new Factor VIII product and this is Dr Crawford indicating:

"I am well aware of the reasons why you found in necessary to issue the product directly and not via John Davidson's laboratory."

Which was the blood bank in Glasgow. So this to me was evidence, by one means or another, we had sent the product to Glasgow in anticipation of a phase 1 clinical trial being conducted there.

Q. In any event, I don't think we will resolve that today but we have asked Dr Cuthbertson to uses his best efforts to come back to us on that.

A. Sure.

Q. I think we will take a stage by stage approach in the first instance and wish him luck in that task.

Moving on to the next question and back to your supplementary statement, please. It's really the same point. The bullet point. We asked whether you could help us as to whether clinical trials of Z8 were in fact carried out in Belfast and Glasgow and if so, when, and if not, why not, and you say that your recollection is that clinical trials were conducted in Glasgow under the supervisions of Drs Lowe and Forbes. This recollection is supported by correspondence from yourself to Dr Lowe dated 30 March 1987.

We can perhaps just go to that, please. It's [PEN0172205]. We can see a letter from yourself to Dr Lowe of 30 March, headed "Clinical trial of Z9":

"I understand that you have now infused this material into patients and that these infusions were uneventful."

And you request a summary of the trial and you also say:

"This is now a matter of some urgency since stocks of the existing product are now almost exhausted."

Really as perhaps predicted back in June 1986.

A. Yes.

Q. Yes. Putting that letter to one side, please, going back to your supplementary statement, please, at the top of page 2 you say:

"However, I have been unable to locate a reply to this request, the date or dates when the trial took place or the results of any trials which may have taken place. It seems likely, given the date of my letter, that these trials took place after the trials which were eventually conducted by Dr Ludlam on 3 March 1987. However, I am unable to find evidence to confirm this. I have no recollection of clinical trials of Z8 being conducted in Belfast and can find no evidence of Z8 being supplied to Belfast for this purpose. I agree

with Professor Ludlam's interpretation of the available correspondence. Both Dr Forbes in Glasgow and Dr Mayne in Belfast had initially expressed a willingness to conduct trials of Z8, of which my recollection, and unfortunately no more than that, is that haemophilia centre directors in Scotland and Northern Ireland subsequently adopted a similar view to that of Dr Ludlam, concerning the requirement for indemnity assurances from SHHD prior to proceeding with clinical trials. In any event, it would appear that clinical trials in both Glasgow and Edinburgh were not conducted until early March 1987."

There is one further letter I would like to take you to, please, Dr Perry, simply while we have you here. It's an expression which has puzzled me from the outset. Can we go, please, to [SNB0076270]? It's a letter dated 1 December 1986. Unfortunately you are the recipient rather than author, in terms of whether you can assist, but we will see the letter is to do with Z8. It's this phrase:

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

What do you understand that to be a reference to?

A. That's a very simple reference. That's -- in the blood bank many of the products supplied by PFC were

temperature-sensitive. Their specified storage conditions were 4 degrees, so they would have held stocks of PFC Factor VIII, Factor IX, immunoglobulin products in their cold room, which was basically part of their blood bank stockholding arrangements. So that just specifies -- it's shorthand for "held in stock" by the Southeast Scotland Blood Transfusion Service. He is specifying the physical location in which he would expect to find them.

Q. It's not the reference to "cold room" which is puzzling, it's really the timing:

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

A. Sorry, the date of this letter is ...?

Q. Yes, if we scroll down a little.

A. Yes, 1 December 1986.

Q. Yes. So Dr Boulton seems to be suggesting that he is going to hold off contacting Dr Ludlam until the material is actually in the cold room. I just wondered why. If that was the inference in the letter, why?

A. I think, again -- sorry, I went down the wrong path about the cold room. I think that's a reference to being absolutely sure, following the delays earlier in the year. He is simply saying, "I want to see the stuff before I start -- before I start getting haemophilia

directors excited by the prospect of doing clinical trials".

Q. Yes, thank you.

THE CHAIRMAN: A cynic might read the first two sentences together, Dr Perry and perhaps wonder whether there isn't more to it than that.

A. "I have also received a letter ... "

THE CHAIRMAN: No:

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

And, "By the way, how on earth am I going to deal with Charles Forbes?"

The paragraph as a whole gives one the impression that there are factors below the surface that led to this letter being written. But that might just be an over-cynical view?

A. I don't know. I'm trying to provide some sort of interpretation of this -- of the third paragraph, which is: what is the best way of dealing with Dr Forbes. I think it is probably -- and it's no more than that -- this is speculation. I think it's probably describing how he actually supplies -- how the product is supplied to Dr Forbes and should it be sent directly to the cold room. These were matters of some sensitivity with hindsight, not much gravity but they were matters of

sensitivity, and it could be that Dr Boulton is simply describing that. I don't know.

MR MACKENZIE: We would ultimately have to ask Dr Boulton, perhaps?

A. If it becomes a significant issue, I think that's right. He would be delighted to hear from you.

Q. If I could perhaps move on, and just complete this statement, please. Question 3, we asked, Dr Perry, whether you had any comments on paragraphs 11 and 12 of Professor Ludlam's statement. We should, I think, go to Professor Ludlam's statement, which is [PEN0171620]. Could we, please, go to page 4 of the statement at 1623?

Paragraph 11 of the statement. Professor Ludlam states that, as well as undergoing the phase 1 clinical trials, it would also be necessary, before Z8 could be released for clinical use, for certain other things to have taken place: Batches would need to be finished, undergo standard quality control tests, which Dr Cuthbertson told us about yesterday, and labelling and packaging.

Then also in paragraph 12, while we are at this statement, Professor Ludlam states:

"In conclusion, his refusal to give test infusions delayed Z8's assessment in Edinburgh for about two months."

Then Professor Ludlam refers to the possibility of the phase 1 trial being conducted in Glasgow and Belfast. So that's the background to the question we asked you to comment on, Dr Perry.

A. Yes.

Q. Could we then go back to your statement, please? I apologise for all this jumping about.

A. That's okay.

Q. Thank you. Then your response to paragraph 11 of Professor Ludlam's statement is that:

"Professor Ludlam is correct in stating that adequate stocks of Z8 would have been a prerequisite for its introduction into routine use for all patients in Scotland."

To pause there, that wouldn't apply to previously untreated patients who would, I assume, have access to Z8 once it was available?

A. I think that would have been -- had that been requested by haemophilia doctors or it had come up from detailed discussion, that would certainly have been a mechanism that was put into place.

Q. One would certainly hope that would be the case.

A. Yes.

Q. You tell us again about events we have already looked at, the question of the timetable for the phasing out of

the old product and the phasing in of the new, all with references to the batch dedication system. Then at the bottom of the page, you say:

"My primary concern at the end of 1986 was, therefore, that PFC was building stocks of Z8 without evidence of its clinical efficacy or safety from patient trials. This raised the possibility of a Factor VIII supply failure in the event that clinical trials produced concerns over Z8 safety or efficacy when there remained only three to four months' stock of NY 68/24-hour product."

Professor Cash has told us how this was a concerning period for him and presumably for you as director of PFC, who was ultimately responsible for ensuring Factor VIII self-sufficiency, this must have been perhaps been a more concerning time?

A. I think the whole period was difficult. It was certainly stressful, as I think I have described here. I don't think we necessarily expected there to be clinical problems, we expected it to perform similarly to 8Y, but my concern as director was that you could go from a position of plentiful supply to a position of very, very strained supplies or failure to supply, if the clinical trial came up with evidence that the product was neither safe nor well tolerated. And that

is always a concern where you are moving from one product to other successive products; you always take the risk of that problem emerging.

And as I said -- I think I have said before, with three products being delivered over a period of two or three years, I think these risks were always present. I think at the end of the day we managed these risks fairly effectively but this was quite a close call, as it were, in terms of having the evidence that our Z8 process was actually a viable prospect for future supply.

Q. I understand.

A. Which is not to diminish the importance, I think, of Professor Ludlam's position in terms of having the need for compensation but I think those two events came together and, yes, you are absolutely right, it was fairly stressful.

Q. Yes. Thank you.

Then finally, please, on the last page of your statement, if I may, I think this brings some of your evidence together. You say:

"I believe Professor Ludlam's estimate of a two-month delay in conducting trials of Z8 in Edinburgh is correct. PFC records indicate that initial test infusions were carried out on 3 March 1987.

However ..."

Back to the point before:

"... the timing of introduction of Z8 ..."

For all patients:

"... was determined primarily by residual stocks of NY/68/24 which, with the agreement of haemophilia directors, would continue to be used until stocks were exhausted. This point was reached in April 1987. Therefore, whilst the conduct of clinical trials at an earlier date (whether in Edinburgh, Glasgow or Belfast) would have relieved some of the PFC concerns and anxieties concerning continuity of supply, the timescale for introduction of Z8 would have been unchanged."

I think we can insert the caveat, presumably with the exception of previously untreated patients?

A. Yes. Whenever I talk about "the introduction", I'm talking about Scotland-wide routine introduction. As I said before, I think the timescale for introduction of Z8 was determined by the point at which we discontinued manufacture of NY.

Q. Dr Perry, I'm almost finished. I have two documents I would like to take you to very much for completeness, to finish this chronology. Firstly, please, [SNB0040529].

Dr Perry, this document, I think, is undated. We

can see in the top right-hand corner, "Item 5 of 7/4/87". I assume it was a paper for a meeting on 7 April 1987?

A. Yes.

Q. Also I think we don't know the identity of the author. We can see the title is "Supply and demand 1987/88".

A. I think I would be the author of this.

Q. I'm grateful.

A. But we will see.

Q. Yes. I'm not sure we will. But you may recognise it. Looking on, perhaps to the next page, do you know what the purpose of this document would have been? Did you routinely report to somebody or a committee on these matters?

A. In 1987 the SNBTS had what came to be described as a "supply and demand meeting" for plasma products, and this was a point at which all SNBTS directors came together and the main topic on the agenda was supply and demand, which basically was supply of plasma and demand for plasma products, and it was a forward look over a period of at least 12 months to -- really quite detailed consideration for each individual product that was available because -- I think it's stating the obvious, but the demand for particular products had a direct impact on the activities of the regional

transfusion centres who were out there collecting the various different plasma types --

Q. I understand, yes.

A. So it was written for the 1987/88 supply and demand meeting.

Q. Yes, thank you.

Then Factor VIII. At the top we see, as we know, that:

"PFC discontinued the manufacture of NY/68/24 product in the summer of 1986 in order to reduce the national stockpile of NY material in preparation for the introduction of Z8 at 80 degrees for 72 hours. As an interim production development, Z8 at 75 degrees for 72 hours was manufactured for a short period. The stock position is now as follows."

One can see the stock position of the respective products. The NY/68/24, Z8 at 75 degrees for 72 hours and the Z8 at 80 degrees for 72 hours, and then:

"Thus, there exists the need to phase out old product and phase in the new Z8. The following proposal is presented for consideration. (a) Batch dedication is maintained. (b) Residual NY and Z8 at 75 degrees for 72 hours. Stocks are fed into the batch dedication system as normal. (c) An additional lane(s) is created at each RTC of Z8 at 80 degrees centigrade for 72 hours

to make available material for special patient cohorts (eg virgins, elective surgery, mild haemophiliacs) prior to consumption of existing stocks of old material."

I think that deals with the point that we have discussed.

A. Yes.

Q. "This will ensure equity of new product distribution whilst at the same time recognising the need to support special patient groups."

The final paragraph:

"Present stock levels (NY and Z8/75 degrees) are ..."

Set out, and:

"At present rates of demand, it is estimated that Z8 will become available for all patients by July 1987."

I think we had seen from batch issue records we have looked at previously that on 22 May 1987 Factor VIII at 80 degrees was distributed to haemophilia centres, I think, certainly Glasgow and possibly Edinburgh as well?

A. Yes.

Q. I'm just really trying to clarify when Z8, in particular heated at 80 degrees, was actually available for issue to all. Was it May 1987 or July 1987 or what?

A. Specifically the 80-degree material, I would really have

to do some detailed analysis of the issue. I suspect it's closer to July 1987 because there would have been -- although I think it would have begun around April/May time when some of these batch dedication lanes had been exhausted. The Z8 would have been put in place to replace them. I think the July date as an estimate is basically measuring the speed of the slowest ship in a convoy. This would have been the last remaining lanes of previous NY product to become exhausted. I think that's probably a best estimate of the point at which all product at issue would have been Z8.

Q. In the last paragraph, the reference to:

"It is estimated that Z8 will become available for all patients by July 1987."

Is the reference to Z8 a reference to Z8 heated at 80 degrees or do you think it's a reference to Z8 heated at either 75 or 80 degrees?

A. I don't know. I suspect it's both. I think it's probably the 75-degree and the 80-degree material but I can't be sure.

Q. Is that reference to that product, Z8, becoming available for all patients by July 1987. Is that really a reference to that's the month by which stocks of the old product will be exhausted?

A. The last remaining stocks in various lanes throughout Scotland would have become exhausted but I think, certainly from my knowledge around the period and certainly from stocks, the new Z8 product, whether it's 75-degree or 85-degree material, would have been introduced into some part for some patients prior to that date.

Q. Yes. Then finally, please, a letter [PEN0171267]. This is really to complete the record. It is a letter dated 10 April 1987 from Professor Cash to yourself, "Z8 phase 1 studies":

"Dr Cuthbertson and I have reviewed the raw data from the Edinburgh patients and I am satisfied that PFC may now move to issue Z8 for routine clinical use."

A. Yes.

Q. Presumably that statement is self-explanatory?

A. I think that's the system that we had in place, that Professor Cash was basically our medical adviser, de facto our medical adviser, as well as being the national medical director, and we would have done the studies and I think Dr Boulton would have presented a report to Professor Cash and he would have looked at it, he knew about these things, and he would have approved it.

Q. So Professor Cash is satisfied with the phase 1 clinical

trial of Z8?

A. Yes.

Q. And is authorising its issue for routine clinical use?

A. Yes.

Q. I think that's perhaps a suitable point for me to stop my questioning, Dr Perry, thank you.

THE CHAIRMAN: Mr Di Rollo do you have questions for Dr Perry on topic C3?

MR DI ROLLO: I don't have many questions in relation to C3 but what I would like to do is to ask some questions relating to C3A.

The situation is that there appears to be an overlap between the two, I think, because the material which I would like to refer to was actually in court book under C3 as opposed to C3A, and we can see from his C3 statement that there is mention of the obtaining of material from England. I would like to ask some questions principally in relation to the matters covered in Dr Perry's statement, which he gave under [PEN0171244], which is the statement on topic C3A.

Sir, I would like to refer to the material, some of which we have already seen.

THE CHAIRMAN: I can understand that you would want to do that. My concern is whether you should do it now. There are two aspects to that, Mr Di Rollo. One is the

time constraints on today, because we do have to hear from Dr Ludlam, and the other is whether Dr Perry has been advised that he is likely to be asked questions on that matter. I think that in fairness to him, he should be advised and consider whether he can do it fairly. But what about time? You know, we have a statement from Dr Ludlam that is not insignificant in its length and content. Are we going to get finished or is the introduction of C3A today going to frustrate the programme?

MR DI ROLLO: I reckon that I would be about 45 minutes to do --

THE CHAIRMAN: That worries me greatly. 45 minutes out of what's left of today with Dr Ludlam to come seems to me to raise a question. It might be better to do it some other time. I think what I should do is just rise briefly and let counsel have a chat about the feasibility of it.

MR DI ROLLO: Very well.

THE CHAIRMAN: And you have to include, of course, Mr Anderson and Mr Johnston for their interest in this too. I'm not anxious that we should split Dr Ludlam basically. So it's not a question of whether you should be allowed to do this at all; I can understand from questions you have already asked why you would want to

get into it, but I think we have to be very clear about the practicability of doing it today.

We will rise briefly.

(12.42 pm)

(Short adjournment)

(12.53 pm)

THE CHAIRMAN: I'm not quite sure whom I should ask first about developments that have taken place in the short interval. Do you have anything to help me with, Mr Mackenzie?

MR MACKENZIE: Yes, sir. I think the view here is that it's better to complete Dr Perry's evidence on this topic, C3, which will then allow us to start -- and I'm sure complete -- Professor Ludlam's evidence on this topic, and that Mr Di Rollo can perhaps address you on the question of his C3A questions.

THE CHAIRMAN: Yes.

Mr Di Rollo, C3A was to be dealt with on the basis of writing.

MR DI ROLLO: I'm not sure we actually had that conversation in fact, about whether it was to be dealt with in writing. I think what happened was at the end of the C3A section, Professor Colvin departed and I don't think my learned friend had the opportunity of going through the other statements that she normally would.

THE CHAIRMAN: That is correct.

MR DI ROLLO: I think if I had been given an opportunity to address the Inquiry at that stage, what I would have said is that I would like to ask these questions orally to Dr Perry at some stage.

THE CHAIRMAN: I can see that. I think that, given the constraints on time, I really don't want to get into this area today. I also think that it might be of advantage if you set out what it is you want to cover in a written application. Three quarters of an hour, I have to say, takes me a little bit aback on the basis of what I have read already.

MR DI ROLLO: Right.

THE CHAIRMAN: Knowing why it should take three quarters of a hour, rather than five minutes, for example, is sometimes a problem. So I think if you were to take the opportunity to give written intimation of what it is you want, that should cause us to bring Dr Perry back, we will find exactly how much time is required in discussion among the parties and fix a different time for it. But I really don't want to frustrate the programme for today and I very much suspect that that would happen. So if you could approach it that way, I would be obliged.

MR DI ROLLO: There is the one matter which is purely a C3

topic.

THE CHAIRMAN: I'm not asking you not to ask questions.

MR DI ROLLO: That's one question and I could do that now and let Dr Perry away, because I don't think anybody else will have any questions.

THE CHAIRMAN: That sounds fine.

Questions by MR DI ROLLO

MR DI ROLLO: The C3 question, Dr Perry, was in relation to clinical trials for Z8. We understand it to be the case that clinical trials were not carried out on pilot scale batches but it was dealt with by doing it after full production.

A. That's right, yes.

Q. I think previously it had been dealt with when previous products had come in, clinical trials had been done on pilot batches?

A. The pasteurisation product, the product that was pasteurised at 60 degrees for ten hours in process, that was indeed an initial clinical trial done on pilot scale. The reason why that was appropriate, that was not the definitive clinical trial, that was what I would describe as a proof of principle trial, ie, we developed quite a substantially different process and before we continued with that process, we wanted to establish whether or not the process that we had put together

would throw up any early clinical problems in use. So at that stage it would have been appropriate to do a clinical trial.

Had that project gone to completion, it would also have required a clinical trial at full-scale as well.

Q. Was there any reason why clinical trials were not carried out on pilot batches of Z8 then?

A. No, it was a simpler process. I think it was -- we had the benefit of 8Y and their experience, which was a closely similar product, to guide us. So there wouldn't have been any benefit in terms of timescale or introduction, had we carried out a clinical trial on a pilot scale batch because we would also have had to have done it on the full-scale batch as well, before we were to introduce a product into routine use. And my goodness, these trials are very, very small and very, very insubstantial compared with what's required nowadays, but to actually introduce a new product into routine use for the entire haemophilia population of Scotland without actually having tested one of the batches that has been manufactured in the routine production department would be completely unacceptable.

Q. Thank you for that.

MR ANDERSON: I have no questions.

THE CHAIRMAN: Are you content with that?

MR MACKENZIE: No further questions.

THE CHAIRMAN: Then we will rise with that.

(12.58 pm)

(The short adjournment)

(2.00 pm)

PROFESSOR CHRISTOPHER LUDLAM (continued)

Questions by MR MACKENZIE

THE CHAIRMAN: Yes, Mr Mackenzie?

MR MACKENZIE: Thank you, sir. The next witness is Professor Ludlam.

Professor Ludlam, good afternoon.

A. Good afternoon, Mr Mackenzie.

Q. Professor, we asked you to attend to give evidence on this topic C3 and you provided two documents for us, firstly an appendix, if we could go to that, please. It's [PEN0171625]. This is a quite lengthy, 23-page, really, chronology, I think, of events relating to compensation for clinical trials and other surrounding events as well, and it starts November 1983 and continues until November 1989.

What I intend doing, professor, is having this document taken as read. So it will form part of the Inquiry record. But rather than spending time going through it in detail, I propose just taking you to particular passages which I think are of particular

importance to us.

This is also against the background that I did spend some time, I think it was yesterday, taking Professor Cash through the relevant compensation documents.

If I may start with your appendix, please, in paragraph 2, we can see that you first faced the question of compensation and clinical trials at the meeting of haemophilia and SNBTS directors on 14 November 1983, and we have previously looked at the minute of that meeting. We can see you say here that:

"The catalyst to my raising this concern was the reaction that one of the patients experienced when given test doses of the heat-treated Factor VIII in September 1983."

Can you remember, professor, which product that was?

A. I think that was the pasteurised product that was under development and I gave it to one patient. I think I presented some of the details here in outline before, but the patient developed central chest pain and was quite unwell --

Q. We don't have to go back to that in detail but the product was from, I think, ZHT preparation?

A. Yes.

Q. And we can always refer back to your evidence on the

patient's symptoms, et cetera, if need be. It certainly is captured in the record from last time.

Just to pause here, what was the matter that concerned you?

A. The issue that concerned me was that we were asking individuals to volunteer to test new products that might have had adverse consequences, and it seemed only fair and appropriate and in keeping with what was becoming common policy in testing other pharmaceutical agents, that there should be a system in which the patient or the volunteer could be compensated without having to prove negligence.

Q. Thank you.

Next, please, if we could go to page 3. I do appreciate that the question of compensation was raised again in 1984 but I'm then going on, please, to page 3 and paragraph 9. This is to try and clarify a point regarding ethical approval which arose in the questioning of Professor Cash, and in paragraph 9 of this appendix you say that:

"In response to a request from Dr Boulton of 15 March 1985 to test the 68-degree/24-hour material, I replied on 19 March 1985, requesting details of the product. I sought compensation arrangements to be in place and indicated that the infusions would require

ethical approval (I might be prepared to forego if there were appropriate compensation proposals). The letter was copied to Dr Cash and Dr Perry."

Ethical approval from whom?

A. That would have been the Royal Infirmary of Edinburgh ethics committee.

Q. Why would ethical approval be required?

A. Because this was an experimental drug.

Q. And why might you have been prepared to forego such approval if there were appropriate compensation proposals?

A. I think I was wanting primarily to make sure that if anything did go wrong adversely for the patient, there would be reasonable arrangements by which they could be compensated.

Q. As I say, professor, I don't want to go into the whole question of ethics on this topic but it was simply to try and clarify a point which did arise yesterday.

Over the page, please, at page 4 and paragraph 11, you say:

"In my response to Dr Cash of 4 April 1985, I acknowledge his efforts to get compensation arrangements in place, point out that ethical approval has always previously been obtained."

And you insisted on having details of the product to

be infused. Et cetera. You point out that ethical approval had always previously been obtained; can you tell us a little about that? Did that just apply to Factor VIII clinical trials? Is that a wider point or what?

A. Any new blood product that I was being asked to test in volunteer patients I would have applied to the ethics committee of the Royal Infirmary, and to do that I would need to have some details of the product and anyway, I would require details for my own satisfaction to know exactly what it was that I was being asked to infuse.

Q. I understand. Could we then, please, go on to page 9, at paragraph 34. This then brings us into the Z8 period and paragraph 34 relates to a letter dated 5 January 1987. You write to Professor Cash -- and we have seen this letter earlier -- that:

"With great regret I am unwilling to test further blood products on patients until I receive written assurance that appropriate compensation will be available (possibly in a manner similar to the ABPI arrangements)."

Et cetera. Over the page at page 10, please. You say in the italic text:

"This should not have come as a surprise to Dr Cash as I first raised the matter in 1983 and I had made my

view clear in March and April 1985. I wrote in April 1985 that as soon as I received details of the present Factor VIII product that requires testing, I shall be delighted to arrange this. So far as the future is concerned, I shall be looking for a concrete guarantee (about indemnity) for my patients."

Then you say:

"Additionally he had been forewarned by Dr Boulton at the beginning of December 1986."

We have looked at that letter previously.

One point, professor: when you state here that, "I shall be looking for a concrete guarantee (about an indemnity)", what was your concern at this stage in December 1986? Was your concern the need for compensation arrangements for patients or the need for indemnity provisions for clinicians, or both?

A. Primarily for the patients. This was a patient safety issue and this Z8 was an entirely new product and hadn't been tested in humans before and therefore I felt it only fair to the patients that these arrangements should be in place.

Q. You said "primarily a concern related to compensation for patients". So to what extent, if at all, did any concern about requiring indemnity for clinicians influence your position on the clinical trials of Z8?

A. I don't think at all.
Q. I understand. It's simply that the use of the word "indemnity" triggered the thought in my head but we really mean compensation for patients?
A. Compensation for the patients not indemnity for myself.
Q. I understand. Sticking with page 10, please, at paragraph 35, Dr Cash copied your letter of 5 January 1987 to Dr McIntyre and wrote in a covering letter:

"You will wish to note that Dr Ludlam's letter is copied to Dr Rizza. It would seem clear to me that Dr Ludlam's actions are probably part of a carefully coordinated plan which was conceived at the October meeting of the UK haemophilia directors."

Out of fairness to you, I should read your response to that where you say:

"I can advise that there was no carefully coordinated plan which was conceived at the October meeting of the UK haemophilia centre directors. The minutes of the meeting are available."

Your letter was copied to Dr Rizza because he was the chairman of UKHCDO and you thought he should be aware of the difficulties in Scotland in connection with testing new blood products. Just to pause there, professor, I appreciate your position about there being

no carefully coordinated plan conceived at that meeting. Am I right in thinking that you did relay your concerns about the lack of compensation for clinical trials to the other Scottish haemophilia directors?

A. I think I did and I think -- yes, my letter that was copied to Dr Rizza, I think was also copied to all the other haemophilia directors in Scotland.

Q. Yes.

A. So that alerted them.

Q. And I think -- sorry, I interrupted you.

A. No, I have finished.

Q. Thank you.

I think Professor Cash then wrote a letter to you in early January, which he copied to the other Scottish haemophilia doctors, where he asked them to respond to him, setting out their position, and we have seen before that the directors from Aberdeen and Dundee and Yorkhill replied to Professor Cash saying in short, they agreed with you and wouldn't undertake phase 1 clinical trials without compensation arrangements, and in fact Dr Hann at Yorkhill wouldn't undertake such trials on children at all.

Do you know, professor, as at the beginning of January 1987, what the position was of Drs Forbes and Lowe at Glasgow Royal Infirmary on whether they regarded

compensation as a requirement before they would undertake phase 1 trials of Z8?

A. I don't know.

Q. So you didn't discuss that matter with them at the time?

A. No.

Q. I understand.

Could I then, please, go on to page 12? At paragraph 41. I'm trying here to pick out the main events in the chronology. Paragraph 41:

"On 6 February 1987 Mr Murray, SHHD, wrote to Dr Cash in reply to his letter of 30 December about compensation arrangements."

Then further down there is the quote:

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

The position of Professor Cash and the SHHD was that the agreement to compensation related to phase 1 of the clinical trial and I know there is a later dispute about your understanding of the position, but certainly as far as Professor Cash and SHHD are concerned, that's their understanding of the position as at that time. Is that correct?

A. That is correct, yes.

Q. And you do refer in 42 of your appendix to the meeting on 9 February 1987 between haemophilia and SNBTS directors and you go on to narrate your concern that the draft minutes of the meeting didn't reflect your memory of what was discussed and agreed. That's all set out in your appendix. I don't propose to go back over that to try and resolve that today. I don't think that would be possible, but if I may then, please, go on to page 14, in paragraph 46, you will see:

"Assessment of Z8 was undertaken on patients in Edinburgh in March 1987 and on 31 March 1987, Dr Susan Howe wrote to Dr Perry giving the initial ... results in three patients ..."

We looked at that letter yesterday, I think. Then paragraph 47:

"On 3 June 1987 Dr Boulton wrote to Dr Perry with the results of infusions of batch 60270 in March and April in Edinburgh to four men with haemophilia ..."

Again, we looked at that letter yesterday. Over the page at page 15, a point of detail. In paragraph 49, line 6 you have pointed out to me that, in the sentence commencing:

"Treasury approval has not been received ..."

The word "not" should be deleted. So that should read:

"Treasury approval has been received."

A. That's correct, and I apologise for the typographical error.

Q. No need to apologise, professor.

Also lastly, please, paragraph 22. Paragraph 70, completes this chronology, I think, of the main events. Paragraph 70:

"On 9 November 1987 Mr Macniven wrote to Professor Cash in response to his letter of 8 July 1987 indicating that the SHHD would extend ABPI cover to the use of heat-treated Factor VIII for therapeutic use."

So that would then cover any phase 2 trial, for example?

A. I think right up until issuing of a product licence.

Q. And that met your concern in that regard?

A. It did.

Q. Thank you, professor.

We can now put the appendix to one side and go through your accompanying statement, please, which, if we now turn to that, is [PEN0171620]. Thank you. The single question, I think, we actually asked you is this:

"Does Professor Ludlam consider that the lack of appropriate compensation arrangements resulted in any delay in the introduction of Z8 and, if so, by how many weeks, months, et cetera, was the introduction of Z8

delayed because of the lack of such arrangements?"

In a way it's a simple question but there is perhaps a more complex answer, when one talks into account the batch dedication system, the needs of different patients and what have you but anyway, that was the question posed. You replied to this as follows:

"1. There was considerable uncertainty about when samples of Z8 would be available for clinical assessment in the second half of 1986."

And a:

"Although it was hoped to undertake test infusions in patients of Z8 in about September 1986, when it was anticipated that appropriate material might be available, difficulties were encountered with its freeze-drying. This led to a substantial delay and it appeared that the product might not be available until December 1986."

You then say in b:

"The initial Z8 product was heat-treated at 72 degrees in September 1986 ..."

To pause there, where did you get that reference from, professor?

A. I'm sorry, I can't remember. It was reviewing some of the documents, when I was preparing this. I don't think it's an important point but I'm sorry, I can't tell you

where that came from.

Q. That's okay. We can perhaps check our own records, if it's important, but it does seem to be the case that the product which was eventually made available for the phase 1 clinical evaluation and for the therapeutic treatment of patients was either the 75-degree product or the 80-degree product. I don't think there is any suggestion that a 72-degree Z8 was administered in patients?

A. That's correct.

Q. Yes. Then paragraph c:

"Although Dr Cuthbertson wrote on 26 November 1986 to Dr Boulton with a specification of the 75-degree/72-hour product, there is no evidence that this product was ever dispatched or received by Dr Boulton."

Et cetera. I think as a result of you making the point, professor, we then were provided by the SNBTS with the batch issue sheet we have looked at previously. I can perhaps bring it up quickly. It's [PEN0171437], which does state that the Z8 product was placed at issue on 2 December 1986 and 20 units were issued to Dr Boulton at Edinburgh Royal Infirmary on 22 December 1986 and then a further 180 units issued to Dr Boulton on 24 December 1986. I take it that now you

have seen this record, you are happy to accept that what is stated as having occurred in this record did in fact occur?

A. Yes, perfectly happy, thank you.

Q. I'm grateful. You won't, of course, have seen this document when producing your statement.

A. No.

Q. Then to continue with your statement, please, at page 2, paragraph 2:

"Dr Boulton had SNBTS responsibility for liaising with clinicians over arrangements for the test infusions of Z8 in patients."

You refer to a letter of 1 December 1986 from Dr Boulton to Dr Perry, indicating that:

"He had received a letter from Dr Mayne 'saying that she will be very pleased to enter into the trials as soon as the material is available.' His letter continues by stating 'I think it would be best if I wait until the material is actually in our cold room before I tell Dr Ludlam'."

Professor, what do you think was meant by that sentence, if you feel able to give an answer?

A. I think I had been anticipating a trial batch of Z8 for several months, during the latter part of 1986, and the rumours had come that there would be a batch coming

perhaps the following week, and my expectations were raised only to be dashed when it didn't arrive. So I think Dr Boulton was perhaps making the point it might be best to wait until he actually had the material in stock, because once it is in stock, I would invite patients to come up to have test infusions -- would be the normal arrangements, and I wouldn't want to inconvenience patients by inviting them up and there not being a product to give to them.

Q. Then in the last sentence of paragraph 2 you refer to a letter:

"Subsequently, Dr Cash wrote to me on 13 January 1987 reporting that Charles Forbes has agreed to look at the 75-degree/72-hour product."

We looked at that earlier and you say:

"It thus appears that both Dr Mayne and Dr Forbes were prepared to test the heat-treated Z8 by the beginning of January 1987."

I take it, professor, that is an inference you have drawn from these documents rather than a recollection you had at the time?

A. That is correct. There was no response from Dr Forbes or Dr Lowe or Dr Mayne that reached me to say that they had reservations about testing it.

Q. I understand. In paragraph 3 of your statement you

refer to a letter of 5 December 1986 from Dr Boulton to Professor Cash. We have looked at that. And the PS:

"I have heard from Dr Mayne that she is willing to participate in the trials of Z8."

Paragraph 4. This is a memorandum from Dr Perry, dated 22 December 1986, agreeing to the release of the 80-degree/72-hour material to Edinburgh BTS for clinical trial. You go on to say that:

"It was an unsigned memorandum and [you] couldn't find any evidence that the Z8 was dispatched from PFC or received at the blood bank at the Edinburgh Royal Infirmary."

I take it that in the light of the batch issue sheet we have just looked at you are happy to accept that the records contained in the batch issue sheet are correct?

A. Yes, what is incorrect in my statement, in this paragraph 4, it should say "75-degree".

Q. I'm sorry, yes, thank you.

A. Which I didn't know at the time when I was writing this.

Q. So paragraph 4 of your statement should read:

"Documentation is available which indicates that Dr Perry agreed to the release of the 75-degree/72-hour material to Edinburgh BTS for clinical trial on 2 December 1986."

A. Yes, correct.

Q. You also in your answer go on to say that you cannot find any evidence that this material was forwarded to Glasgow or Belfast for assessment in patients. I think you are in the same position as the PFC witnesses who I think equally can find no evidence of that. You then say:

"I don't have any recollection of any communication from Dr Boulton to me that the material had arrived in the cold room at the Royal Infirmary ..."

We can only perhaps hazard a guess for that. It's possible, I suppose, Dr Boulton told you at the time and you have forgotten; it's perhaps equally possible that he didn't tell you because of ongoing concerns over compensation. We simply don't know. I'm not sure that point is important.

So we are then on page 3 of your statement, paragraph 5. You refer to:

"Dr Cash, in his report for the haemophilia/SNBTS meeting, which he compiled in January 1987 wrote (ii) 'We anticipate, having sufficient evidence, indicating acceptable recovery and t/2 within three weeks and that as a consequence it will be generally acceptable for routine use."

I should perhaps pause, professor, and ask the question. I'm not sure I'm 100 per cent sure what is

meant by the phase 1 half-life and tolerability studies. I think Dr Foster kindly simplified it for me by saying it just means the product works but as a haemophilia clinician can you perhaps explain to us what was involved in the phase 1 trial?

A. A phase 1 study in this context is giving a known amount of the Factor VIII, the new Factor VIII product, to a patient and measuring the level of Factor VIII in their blood before and after the infusion, not just immediately after the infusion but also over the succeeding 24 hours, to see how long it lasted in the circulation.

From those measurements of Factor VIII, you could get an estimate of how much was what we call "recovered" in the circulation; in other words, once you inject it, did it all sort of appear in the circulation. That's the immediate level following the infusion. And then how long would it last in the circulation, what was what we call its "half-life", the time for its concentration to fall by 50 per cent.

That's a -- what's called a pharmacokinetic study and that's usually carried out at this time in just four or five patients. Nowadays the European Medicines Agency regulations are, I think, it has to be something like 10 or 15 patients that you do this in. This time

it was just a small number.

Then phase 2 is looking at the clinical efficacy of the new Factor VIII; in other words, will it stop bleeding. It may give the right Factor VIII levels, as measured in the laboratory, but do the patients stop bleeding when they are treated with the product?

Coupled with that, part of the monitoring is to see whether they develop any other adverse reactions, for example either infections that might be transmitted or whether they developed antibodies to the new Factor VIII because the molecule might have been modified during the manufacturing process and the patients would recognise it as a foreign form of Factor VIII and develop antibodies, which would then neutralise it and make subsequent treatment ineffective.

Q. Just a small matter of terminology, I have continued to use the expression "phase 1" for meaning half-life and tolerability studies and to use the expresses "phase 2" for the wider, longer studies into freedom from infection, and adopting that terminology, I think everything you have just told us about would fall into what I have been calling "phase 1"?

A. No. The ability -- the assessment of the ability to stop bleeding and to not produce inhibitors and looking at its infective potential I think would all be

described as "phase 2".

Q. I see, including its ability to stop bleeding?

A. Yes.

THE CHAIRMAN: I think I would like to be clear about it too. At phase 1 would one ever expose a bleeding patient to the test?

A. No.

THE CHAIRMAN: No.

A. For two reasons. One, it's not an elective procedure and the other is the kinetics; the way in which Factor VIII is used up would probably be faster because the patient was bleeding.

THE CHAIRMAN: The other question I would like to ask in connection with this particular passage is the use of the expression "routine use". What do you understand Dr Cash to have meant by "routine use" in this connection?

A. I'm sorry, sir.

THE CHAIRMAN: Paragraph 5, the end of the quote:

"We anticipate having sufficient evidence ..."

A. The assumption was made -- and in fact has been borne out mostly -- that the level of Factor VIII that is measured after giving the new product, measured in the laboratory, in fact does equate with its haemostatic efficacy. But you can't make that assumption. And

that's that has come out more recently with new modified forms of Factor VIII. But it's part of the, if you like, the folklore of treatment of haemophilia that the level of Factor VIII as you measure it in the laboratory corresponds with the haemostatic efficacy at that particular level in the patient.

THE CHAIRMAN: All right. Really it's the expression "routine use". Does one have routine use of a product before it's licensed or is it all on a named-patient basis? Is that routine use? It's that sort of issue.

A. It's a difficult area actually from the point of view of clinical trial, and clinical trial, if you like, on a national basis. At this time -- and I think I'm right in saying that this product was probably issued under Crown immunity and it was, I think, unclear as to what clinical -- full clinical assessment would be, except that there was the anticipation that it would work effectively.

Nowadays the rules are much more stringent. There was the phase 1 study that I have described and then in the phase 2 study there would be a defined protocol for assessing the haemostatic efficacy of the Factor VIII. For example, there would have to be 10 major surgical procedures undertaken with the product to show that it did stop bleeding. It would be given to patients as

prophylactic Factor VIII therapy and the patients would have to demonstrate that they didn't bleed when getting the product.

This degree of proof was not the norm in 1986/87.

PROFESSOR JAMES: Can I try and exemplify this?

As a matter of fact, in this instance no proper phase 2 clinical trial was undertaken for at least a matter of months after the introduction of the Z8. So can you tell us, as a matter of fact, whether during that initial time of introduction in mid 1987 each patient actually did have to be given the Z8 on a named-patient basis or was there some kind of blanket arrangement whereby "everybody is in a clinical trial" and therefore it was given under a CTX, because it certainly wasn't licensed, indeed it wasn't licensed for a number of years afterwards, as I understand it, and I think we are trying to get at the sort of -- you know, all the witnesses in the last two days have used this phrase "routine use", but as a matter of fact, it really wasn't very routine as compared to if you were trying, at that time, a proton pump inhibitor from Glaxo. So could you perhaps try and help us a little bit with that.

A. I'll try but it's difficult.

PROFESSOR JAMES: It is sort of shark-infected custard this

area, isn't it?

A. It is difficult and it became much more an issue when we were testing Liberate in fact, and the difficulty here is that the patients who are receiving the product are all patients in Scotland. So there isn't -- in most clinical trials there is a defined group of 10 or 20 patients who are followed up in some detail but when you are introducing a product for treating all patients, we were left -- I was left with the difficulty, is this a clinical trial or is this SNBTS providing a new form of Factor VIII and we just get on and use it. That's why I was keen to issue a letter to the patients or an information sheet to let them know the situation, because I thought this was only fair because at one level there wasn't a choice; at another level you cannot force someone into a clinical trial. And you will have seen the correspondence about this and the advice that I took, including from the Medical Defence Union.

But I suppose, in specific answer to the question, it was probably given to the patients on a named-patient basis because there was no CTX. There was no clinical trial certificate.

PROFESSOR JAMES: Thank you.

MR MACKENZIE: Thank you very much, sir.

Professor, returning to your statement, please, at

page 3. I think we had got to paragraph 5 in Dr Cash's report of January 1987. I think, from looking at that document and perhaps the surrounding correspondence, your inference in writing this that Professor Cash was aware that you were not prepared to test the Z8 without indemnity and must have based his understanding on the fact this that it was being assessed in Belfast and Glasgow and no date for the introduction of material for therapeutic use is stated; from the last sentence and your comment, professor, does it follow that, at least when you wrote this statement, you understood when Professor Cash used the words "routine use", that referred to the phase 1 clinical trial rather than therapeutic use? Am I simply complicating matters again?

A. No, I think "routine use" would be for -- would be after phase 1.

Q. Yes.

A. Yes.

Q. Then paragraph 6. We have seen this indemnity by SHHD was offered in this letter from Mr Murray of 6 February 1987 to Dr Cash. We have looked at that and also the question of the meeting on 9 February 1987 of the SNBTS and haemophilia directors and the subsequent difference of opinion and we can see all that. Then

paragraph 7:

"The 80-degree, 72-hour Z8 was tested in three patients at Edinburgh, probably in March 1987."

I would have to check this myself. Was it 80 degrees or 75 degrees?

A. No, it was 80-degree. This was one of the slight advantages in fact of having delayed the testing because if we had tested the material delivered on 22 December 1986, that was 75-degree material, and we would have then had to have tested the 80-degree material subsequently. This material, the 80-degree material, was delivered on 11 -- I think it was 11 or 13 February 1987 to Edinburgh.

Q. I understand. In paragraph 8:

"My understanding is that it was proposed to phase in Z8 as the stocks of 68-degree/24-hour material NY ran down."

Over the page:

"My understanding of events is that manufacture of 68/72 ceased in February 1987 and that there was only a small amount of stock."

I think that sentence is wrong, isn't it?

A. Subsequently I have looked at documents and it's clear that it was July 1986.

Q. And related to the 68 degrees/24 hours product?

A. Yes, that's correct, yes.

Q. Thank you. In paragraph 9 you say:

"If indemnity arrangements, for test infusions, had been in place by 1 January 1987, it seems likely that I would have been able to arrange such infusions in January 1987 ..."

Paragraph 10, the reference to Dr Mayne in Belfast and also Dr Forbes in Glasgow. I am afraid the position there remains a little unclear and we are trying to clarify it, to the extent we can.

Paragraph 11, you then say:

"As well as undergoing satisfactory test infusions prior to Z8 being released for clinical use, it would have been necessary for PFC to manufacture several batches to demonstrate that the production process could be replicated and was stable. These batches would need to be finished, ie undergo standard quality control tests ... [packaging]."

And then:

"Furthermore, before releasing any for clinical use, it would be necessary to have a stock of several batches, at least enough for 1 to 3 months' supply."

Paragraph 12:

"In conclusion, my refusal to give test infusions delayed Z8's assessment in Edinburgh for about two

months."

And your interpretation of the correspondence was that both Glasgow and Belfast were prepared to test Z8 without indemnity arrangements being in place. Although we don't know as a matter of fact whether that is true or not:

"Furthermore, without knowing more about the production, schedules of batches and stock at PFC, it is not possible for me to draw a valid conclusion as to whether the lack of indemnity delayed introduction of Z8 for clinical use."

Finally in your statement:

"If there was a delay of approximately three months (Z8 introduced for clinical use in May rather than February 1987), untransfused patients (PUPs), who would have been at risk of non-A non-B Hepatitis, could have had access to 8Y (a small stock of which had been acquired in August 1986). Thus patients, therefore, should not have been disadvantaged if there was any delay in the introduction of Z8."

I would like, professor, to look briefly at the question of batch dedication. I think you were present this morning when I went over this with Dr Perry. So I think you are up to speed on the points that were discussed. But could I perhaps look at Dr Perry's

statement again, please, which is [PEN0171219]. We can go straight to page 7. In question 5 we asked Dr Perry -- and can I perhaps put this to you, professor, for your response. Dr Perry's position is that:

"For the reasons described above ... "

This is to do with, I think, stockpiling NY, stopping production of that and then producing and stockpiling Z8 but not releasing that for general use until the existing stock of the existing product had ceased, all in keeping with the batch dedication system, he says:

"It is unlikely that any delay in subjecting Z8 to clinical evaluation resulted in a delay in the phased introduction of the product for all patients in Scotland. Earlier completion of the clinical evaluation would have made the product available for specific patients, identified by haemophilia directors, eg those with little or no previous exposure to coagulation factor products."

Do you agree with what's said in that paragraph? Do you disagree? Do you wish to add to it?

A. No, I think that's probably reasonable. Yes.

Q. A reasonable summary of the position?

A. I think so, yes.

Q. Thank you.

I think I can then move away from batch dedication and refer to two final documents. Firstly, please, go to [LIT0010868]. This is a paper published in Transfusion Medicine in 1993 by the haemophilia directors for Scotland and Northern Ireland, including yourself, professor:

"The study of viral safety of SNBTS Factor VIII/IX concentrate."

Before we look at the summary, am I right in thinking, professor, that at some stage a phase 2 clinical trial of Z8 took place?

A. In previously untransfused patients, yes. I have made available to the Inquiry the protocol for that, including the patient information sheet and the consent form, and that was a national study to monitor patients who received Z8 for the first time under the protocol laid down by the ISTH, which was a very rigorous protocol -- fortnightly blood samples for, I think, the first 16 weeks and then monthly for two monthly, looking at ALT levels. That protocol was first devised, I think, in 1984, published in 1987.

Q. Yes.

A. With the Behringwerke product in the New England Journal and was subsequently revised by Professor Mannucci and

Dr Colombo in, I think, 1989. It was a little bit overtaken by events because in 1989 Hepatitis C was identified and there were then specific tests. So it was so much easier then to see whether patients developed infection as a result of blood products, just by measuring the antibody and later on the virus. So our study, which we set up in about 1987 or 1988, was to look prospectively, with fortnightly blood samples by the ISTH, the original ISTH protocol, and then subsequently these patients were tested for HIV and Hepatitis C and almost certainly Hepatitis B, if that was appropriate.

Q. There is then a report of this study and I simply propose reading the summary which states:

"To assess the viral safety of the Scottish National Blood Transfusion Service intermediate purity Factor VIII and IX concentrates, the liver function and viral status were assessed prospectively in 13 recipients. None developed hepatitis or seroconverted to HIV or HCV. This study provides additional evidence for the efficacy of dry heat treatment at 80 degrees centigrade for 72 hours in preventing virus transmission by coagulation factor concentrates."

Then moving on, doctor, the final paper I would like

to put to you, please, is [SGF0011758]. This is the Mannucci paper setting out the ICTH guidelines and talking about the rule of three, and I have been searching for a witness to put this paper to and I think you have kindly agreed to take us through it. I don't think we have to know it in too much detail but we should know a little about it.

It may actually be helpful, professor, to start at the end, particularly if we could go, please, to page 533 of the paper, just the second page actually. In the bottom right-hand column under "recommendations" -- actually I should pause and ask, the International Society on Thrombosis and Haemostasis, what is that organisation and what did it do in the 1980s?

A. The International Society on Thrombosis and Haemostasis is the principal international organisation for blood coagulation and it has a number of subcommittees, scientific and standardisation subcommittees comprising international experts on the particular topic. And there was one in relation to Factor VIII and Factor IX, particularly Factor IX concentrates.

This committee meets in open session every year, either at the ISTH biennial meetings or they have meetings in the years between also. So there is

an annual meeting to discuss topics in relation to Factor VIII and Factor IX, particularly quantitation and quality aspects.

Q. Thank you. Returning to the paper, please, we can see that:

"The Factor VIII and IX Subcommittee of the Scientific and Standardisation Committee of the ISTH gives the following recommendations for conducting clinical studies of the safety from hepatitis of clotting factors concentrates:

"1. Inclusion criteria and the follow-up protocol recommended in 1984 are still valid. In particular, the need to enrol only patients previously untreated with any blood or blood product and to test them for aminotransferase values at 15-day intervals for at least four months is reinforced by the accumulating experience, at least until specific diagnostic markers for NANB hepatitis become largely available.

"2. Patients missing two consecutive aminotransferase values in the first four months and one value in the next two months should be excluded from final analysis.

"3. Studies should include at least 20 analysable patients treated with at least 10 batches of the concentrate, setting the residual hepatitis risk

arbitrarily at a compromise value of 15 per cent when no case of hepatitis occurs.

"4. Studies should be stopped when among 20 patients, at least two cases of hepatitis are detected."

That's for safety reasons.

Professor, are you able to take us through the paper and perhaps briefly indicate to us how the recommendations changed between the original recommendations in 1984 and these revised recommendations, the main points of change. Is that possible? It may be I could perhaps try and help a little. Could we go back to page 1 of the paper, please?

We can see in the introduction that:

"In 1984 the ICTH, concerned about the lack of a uniform protocol for clinical studies of the safety from hepatitis of clotting factor concentrates treated with viricidal methods, appointed the subcommittees ... to jointly draw up and recommend uniform criteria for the design and conduction of such safety studies ..."

I think the difficulty, professor, we have is that nowhere in this paper, I think, does it state what the 1984 recommendations were. It rather comments on them and comments that these recommendations should stay for these reasons. I think we have asked for a copy of the

1984 recommendations but I think that has proved difficult to get.

Under "inclusion criteria", the left-hand column on page 1 of this report, under the second paragraph:

"The criterion that has been the most controversial was that of including only patients who had received no previous transfusions of blood or any blood products."

Then if we go to the right-hand column, a little bit up, about ten lines roughly from the top. It says:

"Despite this, the subcommittee still maintains that the inclusion in the safety studies of previously treated patients should not be recommended, for at least four reasons."

So as far as one can tell, I think the inclusion criteria remained the same between the original recommendations in 1984 and the revised guidance.

The next matter at the bottom of the right-hand column, "follow-up protocol". Then over the page, in the left-hand column, about ten lines up from "exclusion criteria", again we see the words:

"That the stringent 1984 ICTH criteria for blood sampling should be retained is clearly indicated ..."

Et cetera. So again, it seems to be that the follow-up protocol in the original 1984 recommendations appear to have been retained.

Looking next at "exclusion criteria", it states:

"In 1984 the ICTH recommended to exclude from final analysis patients who during the follow-up period received transfusions with any blood product, other than the concentrate being studied. This basic recommendation is obviously still valid. A previously unaddressed point is that of how many aminotransferase values can be missed during follow-up without jeopardising the accuracy of the study."

If we go to the recommendations in 1989, is that a point that has then been addressed? Can we see? Yes, I think we can.

A. Yes, it has in the recommendations.

Q. Yes, recommendation 2. So after all that preamble, I think I have identified a change. There is a new recommendation, number 2. I think it perhaps involves a bit of detective work in just trying to see the changes.

A. Perhaps I can help you out.

Q. Yes, please.

A. I think there is very little change from the original 1984 protocol, which is published in Klaus Schimpf's paper in the New England Journal in 1987. It's set out there in several paragraphs and it's almost identical to this. What is emphasised in this publication, the

Mannucci publication, is that these studies should only be done in patients who had never been transfused with any blood product or -- at all.

As you say, correctly, it defines how patients should be excluded if they miss follow-up blood samples because certainly in, for example, the 8Y study, the original one, published in 1988 by Colvin, that was considered here at the Inquiry a few weeks ago, there were a number of patients who had missed values, missed blood samples, and some of those patients would have been excluded from the analysis if they had been subject to this protocol.

Q. Thank you, professor.

Now, finally, I think we can't leave this paper -- keeping the best until last -- without looking at the rule of three, which had arisen, I think, during Dr Foster's evidence. Scroll up the page again, please. We see "Size of the study". I'll just read this out, if I may:

"Even though the number of patients enrolled in a safety study is critical for the reliability of the estimation of the hepatitis risk after treated concentrates, no recommendation was given by the ICTH in 1984 as to the number of patients who should be included and analysed before stopping the study. For this

problem, studies recognising cases of hepatitis differ from those with no recognised case of hepatitis.

"Even studies with no case of hepatitis obviously do not exclude that those concentrates might transmit hepatitis. The one-sided 95 per cent confidence intervals around the true risk of hepatitis can be calculated simply by the 'rule of three', dividing 3 by the number of analysable patients, ie those who completed the recommended protocol and follow-up. Hence in a study of 10 patients with no cases of hepatitis, the interval around the true risk of hepatitis would vary from 0 up to 30 per cent; for 15 patients, to 20 per cent; for 20 patients, to 15 per cent, for 25 patients, to 12 per cent; for 30 patients, to 10 per cent and so on. Obviously, the 'acceptable' upper limit of the hepatitis risk can only be set arbitrarily. Since increasing the number of these rare patients from 20 to more than 20 (for instance, 25) only modestly decreases the hepatitis risk (from 15 to 12 per cent), the subcommittee proposes to set the risk at 15 per cent as an acceptable compromise. Hence, studies should include 20 patients but need not include more for a concentrate to attain a verdict of 'low infectivity', the only reasonable goal to be pursued in safety studies in view of the futility of pursuing a policy of zero

risk."

Which in a way brings me back to the question I posed all those months ago on the accumulating data for the safety of 8Y. I used the word "likely" but this is another way, I think, of looking at it. Is there anything you want to add to that explanation of the rule of three or to explain how that worked in practice?

A. No, I think that's a very fair description of it and I know the paper on which it was based, "If nothing goes wrong, is everything all right?" intrigued us when it was first published in 1983 or 1984. What has changed, as I mentioned a moment ago, very markedly, immediately following the publication of this paper, is anti-HCV testing. That made it much easier to test, for example, small babies who were given Factor VIII for the first time. You didn't have to bring them back at fortnightly intervals for blood tests to be able to assess the infectivity of the Factor VIII that they were given.

So this outlines why a compromise had to be made of the 15 per cent and I think this is a fair assessment. It was accepted internationally as the way to proceed.

Q. Thank you, professor. Sir, I have no further questions.

THE CHAIRMAN: Mr Di Rollo?

Questions by MR DI ROLLO

MR DI ROLLO: Professor Ludlam, what I wondered in relation to the compensation issue which arose with Z8 -- I think it's fair to say that you and thereafter your colleagues -- I think I used the phrase yesterday with Professor Cash -- "dug their heels in" in relation to resolving that compensation issue before clinical trials took place.

You had perhaps raised the issue previously with previous products but perhaps not been so insistent. Can you explain why there was a contrast in relation to the Z8, as opposed to the NY, in terms of digging your heels in? Are you able to help me with that?

A. I think it's a very good question. In testing the NY/68 degrees/two hours material in December 1984, there was really a need to get on and test it because we had found HIV in the patients a month or two previously. The patients didn't react adversely to that. I was then invited to test the material that had been heat-treated at 68 degrees for 24 hours and I raised the issue at that time about compensation for the patients. Perhaps I should have insisted at that point and that would have brought things forward.

I think it was an evolving situation about compensation for patients. Even two years later my hospital's ethics committee was prepared to give

approval without compensation arrangements being in place, which rather surprised me.

This was only going to be infusions into four people in the spring of 1985. It wasn't at that stage going to be immediately rolled out to a lot of patients, so we had time to assess the response in the patients. It was a very similar product to the one that had been given in December. Perhaps I should have insisted; it would certainly have saved a lot of difficulties later on.

I dug my heels in, to use your phrase, in December 1986 because I thought I had given a lot of notice that this was an important issue and, frankly, I felt I wasn't being taken seriously by the people who were able to provide the compensation system.

So I had one of two options. One was to roll over and say, "There shouldn't be compensation arrangements," and get on and test the product or I should say, "I won't test it".

I'm there as a patient's advocate in this instance and it seemed to me that if I didn't draw a line at this point, there might never be arrangements and there might be some terrible consequence of one of these test infusions and then one would be dependent on the CSA's goodwill. I felt it only fair to the patients that there was something a bit more explicitly available than

just the hope that there would be goodwill.

Q. Thank you for that. I have no further questions, sir.

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

THE CHAIRMAN: Mr Johnston?

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

MR MACKENZIE: I have no further questions, thank you.

THE CHAIRMAN: Thank you very much, professor.

MR MACKENZIE: Sir, we have no further witnesses today. Dr Smith will attend on Tuesday to speak to topic B3 and we will return on Wednesday to come back to C3.

THE CHAIRMAN: We look forward to seeing whether he lives up to the expectations that the use of his name throughout has generated.

(3.17 pm)

(The Inquiry adjourned until 9.30 am on Tuesday. 1 November 2011)

I N D E X