THE TRIBUNAL RESUMED ON TUESDAY, JULY 10, 2001, AT
10:30 A.M. AS FOLLOWS:

MR. FINLAY: Dr. Snape, please.

THE CHAIRPERSON: Would you mind standing and taking the oath, or if you wish to affirm.

DR. TERENCE SNAPE, HAVING BEEN SWORN, WAS EXAMINED AS FOLLOWS BY MR. FINLAY :
A. My name is Terence Joseph Snape.

Q. Good morning, Dr. Snape. I think if we could first of all, just if you could tell us a little bit about yourself in summary. I think, first of all, do you have a degree in chemistry from Oxford University?
A. I do.

Q. And I think did you attain that in 1970?
A. Yes, in 1970 I finished that degree and went on then in employment at the Plasma Fractionation Laboratory. And during that employment, began and completed a PhD, a London PhD focussed around the work that I was doing at PFL.

Q. Yes. And I think, as you say, you commenced work in 1970 as a scientist at the Plasma Fractionation Laboratory in Oxford, isn't that correct?
A. That's correct.

Q. And just to take up the sequence of that, you worked at that until January of 1982?
A. That's correct.

Q. When you transferred from that to BPL at Elstree?
A. Which is part -- BPL was the mother organisation.

Q. Yes. We'll come back to that in a minute. And I think you had been employed with BPL since, is that correct?
A. Until last September.

Q. I see. Yes. Now, I think apart from that sort of basic facts of your employment, I think have you been a member of a number of committees, both national and international?
A. I have indeed.

Q. First of all, I think are you currently a member of the British Pharmacopoeia Committee H which deals, I think, with biologicals?
A. That's correct.

Q. And are you also the UK expert representative on the European Pharmacopoeia Group B dealing with blood products?
A. I am indeed.

Q. And have you served on a range of standing advisory committees in the UK health departments?
A. Yes, indeed.

Q. Including, in particular, the Biologicals Subcommittee?
A. That's correct.

Q. Yes. Now, in recent years, Dr. Snape, what has been the particular focus of your interest?
A. Very specifically, ways of improving the safety, safety in particular with respect to viruses and, more recently, prions, the cause of Creutzfeldt-Jakob disease; improving the safety of plasma products and improving ways of making plasma available for the manufacture of such products.

Q. Yes. Now, I think you mentioned that you started your employment in 1970 at the Plasma Fractionation Laboratory in Oxford?
A. Indeed.

Q. And can you just describe to us what that was?
A. Yes. PFL, if I may use that shortening, was a pilot plant laboratory. Its function was to develop processes and then operate those processes, but on a small scale - typically up to about 75 kilos of plasma. And then using those processes, both pass on the developed process to the mother organisation at Elstree, but also to make available clinical product from those processes. And for that reason, it was a great advantage that PFL was physically within the same building as a significant haemophilia centre in the UK.

Q. That would have been the Oxford Haemophilia Centre?
A. The Oxford Haemophilia Centre.

Q. Isn't that correct?
A. Yes.

Q. And would the PFL situated in the Oxford Haemophilia Centre, I think that was part of the organisation which ran the BPL, then the blood products laboratory at Elstree, is that correct?
A. BPL at that time was managed by an organisation called the Lister Institute of Preventative Medicine, and PFL was a subset of that. The haemophilia centre was an independent activity but we shared the building.

Q. I see. And ultimately would both Elstree and PFL at Oxford, would ultimately have they come under the control of the National Health Service?
A. Well, they were always funded by and under the control of the health service. More recently in 1978, they were -- began to be managed by the National Blood Service, so it's still part of the health service.

Q. Yes. And then just to complete the picture about this, in 1982 I think did you -- you transferred from PFL to BPL at Elstree?
A. I transferred at that time to assume responsibility for quality assurance and quality control for both laboratories.

Q. Yes. And I think the PFL, the Plasma Fractionation Laboratory, continued in existence until, I think, 1992, is that correct?
A. Yes, when I had the sad job of closing it.

Q. Yes. And was that intended as a centre for research and development which would then benefit the larger fractionation plant at Elstree?
A. Always, yes.

Q. Was that the role of it?
A. Indeed.

Q. And I think you refer to it -- from time to time you carried out pilot schemes?
A. Yes.

Q. Yes. Now, I think then, Dr. Snape, in your statement for the Tribunal at paragraph 7, you deal with the history of the production of coagulation factor concentrates in England and Wales, isn't that correct?
A. That's correct.

Q. And does that I think essentially start with the production of Factor VIII concentrate from about 1968?
A. Yes, from 1968 we were manufacturing a variety of Factor VIII concentrates.

Q. And I think was that using a method developed in Sweden by a gentleman called Blomback?
A. By a lady and gentleman called Blomback, husband and wife.

Q. Yes. And what kind of product was that, how would you characterise it or describe it?
A. It was a crude first concentrate. It was very impure. It contained a lot of protein, in particular a lot of fibrinogen, and, as such, was very difficult to dissolve.

Q. I think was that -- was the method used for fractionating that product an ethanol-based --
A. Yes, it used --

Q. -- fractionation?
A. It used ethanol to precipitate Factor VIII and other proteins. Ethanol precipitation performed in that way is not very discriminating, hence the high protein and the insolubility of the product.

Q. Yes. And from the point of view of its use in practice, in its therapeutic use, what sort of quantity would the patient have required to receive?
A. A dose of up to 250 units of Factor VIII would have been contained typically in about 50 to 100 ml of water. So by comparison with today's concentrates, this was a very inconvenient product. A large volume for a very small dose.

Q. And in practice, would it have involved being administered in hospital rather than at home?

A. Only in hospital or haemophilia centre. It was not suitable for home treatment.

Q. Yes. Now, I think in 1974, then, did you change your process for the fractionation of Factor VIII?
A. Yes. I'd been responsible for developing a modified preparation which we based on the method of an American worker, Alan Johnson, and the method was called the Johnson method.

Q. Yes. And did that involve the use of cryoprecipitation as the fractionation, as the essential fractionation?
A. It did. Cryoprecipitation had been developed in the meantime by Judith Poole and we used that principle to give us a first purification of Factor VIII.

Q. Yes. And would that essentially have involved the use of freezing and thawing plasma in order to refine the Factor VIII out of the plasma?
A. It did, all of the plasma came to the fractionation laboratories frozen and our job was to carry out a controlled thawing of that plasma during which thawing the cryoprecipitate came out of solution and we were able to recover it.

Q. Yes. And then what would have been the final form of the product; would it have been lyophilised?
A. It was lyophilised and it was -- most of the time it was lyophilised, but often, because of urgency of requirement and lack of inventory, sometimes the product would have been thawed and administered even before it could get lyophilised.

Q. Yes. And in respect of the lyophilised product, would it have been possible for that to be used for home administration?
A. It would, and it was, used for home therapy, yes.

Q. And as compared with the previous product, would it have had an improved solubility and an increased potency?
A. Both of those. And because there was less protein present, it was also better tolerated by patients.

Q. Yes. Now, in terms of the plasma pool size that would have been used, I think you deal with that at paragraph nine of your statement, Dr. Snape?
A. Indeed.

Q. I think you -- do you mention there that in 1975 the plasma pool size at BPL had increased to 160 litres?
A. Still a very small pool, yes.

Q. Less than a thousand donations?
A. Yes.

Q. Whereas at that time, commercial pools, the standard would have been a thousand litres?
A. Indeed; varying, but of that order.

Q. Yes. Now, did that batch size increase as time went on, Dr. Snape?

A. It increased progressively at BPL; at PFL the batch size always remained at around 75 litres. That was the maximum scale of the equipment. But at BPL the batch size increased progressively.

Q. Yes. And I think you mention here in this paragraph that it had increased by the early 1980s, it had increased to a situation where there were 5,000 donors?
A. Yes, indeed. We were very -- we tended to think of batch size in terms of numbers of donors, because we were conscious of donor exposure.

Q. Yes. And we'll deal with this in more detail later. You do, in your statement, Dr. Snape, I think you mention at paragraph 17 - and we'll be coming back to this - that in January of 1982, BPL increased maximum donor pool size to 7,500 donations?
A. That's correct.

Q. Yes. Now, I think you also mention, if we return to page nine, that the type of plasma which was primarily used had an impact on this question of the number of donors required?
A. Yes. We, in the UK, were using almost exclusively recovered plasma.

Q. And by this, do you mean plasma which has been extracted from a donation of whole blood?
A. That's correct. The blood would be separated by centrifugation and the plasma would be removed, but a donation in that case would be quite small. It would be typically 200, perhaps 250 millilitres of plasma.

Q. And this by way of contrast to plasmapheresis, where only the plasma is taken from the donor and the rest of the blood is returned to the donor?
A. And in that case a donation would be much closer to 800 millilitres of plasma.

Q. Yes. So that if one is getting plasma from whole blood donations, you require a greater number of donors than if you're getting the plasma from plasmapheresis, is that --
A. Indeed; both because of the size and also because the donors for whole blood, from which recovered plasma is made, can only donate the maximum of three times a year.

Q. Yes. Yes. Now, I think you mention at paragraph ten of your statement that the source of plasma traditionally in the United Kingdom would have been volunteer donors?
A. Indeed.

Q. As it is in this country?
A. Yes.

Q. And would that have continued to be the situation up until I think May of 1998?
A. That's correct.

Q. And was there a change then?
A. There was a change due to unfortunate circumstances at that time with the recognition of Creutzfeldt -- variant Creutzfeldt-Jakob disease in the UK population.

Q. What has occurred since then, what has occurred since 1998?
A. The Health Department took a decision in May of '98 to allow both BPL, the facility at Elstree, and the Protein Fractionation Centre in Edinburgh to import plasma for fractionation. And specifically disallowed the use of UK plasma as being unsuitable for fractionation.

Q. And so, since then, has the source of plasma, in fact, been from US paid donor plasma?
A. For England and Wales product manufactured by BPL, that is true. For Scotland and Northern Ireland, the plasma has been derived from some American plasma and some German plasma, but in that case from Red Cross organisations, not from paid donors.

Q. I see. Now, I think then you deal in your statement at paragraph 12 with virus safety considerations in the manufacture of fractionated plasma products?
A. Indeed.

Q. Is that correct?
A. Indeed.

Q. And I think you say there firstly that plasma fractionators have always been aware of the potential for the transmission of blood-borne virus infection agents by products manufactured from human blood plasma?
A. That's correct.

Q. And so that would go back right to the 1970s, that awareness of that risk?
A. The awareness certainly went back to the 1970s; perhaps the appreciation of the clinical significance has changed over the years.

Q. Yes. Now, I think you then make a comment, Dr. Snape, on the effectiveness of various strategies for dealing with that?
A. Yes, indeed.

Q. And in particular, on the question of whether or not one can find one single strategy for providing safety?
A. Yes. Experience has shown that a single strategy is very vulnerable, and by far the most effective approach is to build a battery of techniques, all of which make the product safer, starting with the plasma and working consistently then through the process.

Q. Yes. Is that something that you would have known in 1970 --
A. No.

Q. -- that particular observation?
A. No. Neither known nor have had the luxury to implement, even if one had imagined it, because the techniques, the possibilities simply weren't there.

Q. Yes. Now, I think you set out then, Dr. Snape, the present strategies for dealing with virus safety in blood products?

A. Indeed.

Q. Perhaps if we might just refer to your statement at paragraph 12, bottom of page four --
A. Yes, indeed.

Q. -- where I think you list these?
A. Yes.

Q. And the first of them would be, "donor selection to exclude donors in identified risk groups."
A. That's correct.

Q. Yes. Would that strategy have been available in the early 1980s?
A. Yes. Practiced in different ways. Certainly recognised in the -- in Europe, in the UK as being the basis; less well-recognised, perhaps, in North America in terms of paid donor collection.

Q. Yes. And then the second matter was, "testing for virus markers and genomic material of known viruses." Would that strategy have been available in the late 1970s /early 1980s?
A. The only virus marker that was tested for in the early 1980s was Hepatitis B, Hepatitis B surface antigen.

Q. Yes.
A. The other virus markers for Hepatitis C; and of course neither Hepatitis C nor HIV were recognised as entities then.

Q. And then the third strategy that you refer to is, "plasma inventory hold based on knowledge of window period." And in brackets, "(the period of time which may elapse between a donor being infected and that infection being recognisable by available tests)."
A. No, that strategy could only be conceived of when the virus infection disease course was understood. So that came into play later.

Q. And testing for antibodies would have been available presumably, that would be implicit?
A. Depends on what is needed to be available in order to have --

Q. To have such a strategy?
A. To appreciate such a distinction.

Q. Then the fourth matter, "lookback, tracing and donation exclusion on the basis of post-donation information."
A. That was practiced, but perhaps not so consciously, because an organisation like BPL received plasma from a national blood service. Patients were treated with the red cells, the platelets from that blood. If a patient developed a viraemia as a result of that, then the transfusion centre would contact BPL and make that information available, and the plasma could be withdrawn. That option would not have been

available for pheresis plasma, for paid donor plasma used in other circumstances, because there are no cellular components transfused in that situation.

Q. Yes. And then the fifth matter was, "virus inactivation targeting known blood-borne viruses." Well, I mean, you discussed that in detail a little later on in your paper, isn't that correct?
A. Certainly not an option in the early days of fractionation. We treated Factor VIII with kid gloves and didn't defend it.

Q. Then the sixth matter, "process segregation downstream of virus inactivation (to avoid reinfecting the product)." Obviously that's something that goes with the viral inactivation. If you don't have viral inactivation that doesn't arise?
A. Absolutely.

Q. Now, you -- the risk factor, Dr. Snape, how would you characterise the risk factor in the early 1980s associated with different plasma products?
A. It differed, it differed by the -- by product type and it differed by method of manufacturing. Albumins, since the mid-'50s, have been heat-treated, pasteurised at 60 degrees for 10 hours and were fundamentally safe. Immunoglobulins were also fundamentally safe, but we didn't really know why. Clotting factors were the products that were known to transmit virus most often.

Q. Yes. Now, in terms of the level of risk associated with the concentrates, Dr. Snape, I think in paragraph 13 you deal with the level of risk which would have been associated in the 1970s with concentrate fractionated in England and Wales, isn't that correct?
A. Yeah, that's correct.

Q. And first of all, did you -- do you think that the origin of the donations was of significance?
A. Yes, it was. The donor pool, the donors contributing to the product were essentially altruistically motivated and the outcome was a plasma pool and then a product with reduced risk.

Q. As compared with paid donations?
A. Yes. Motivation was somewhat different.

Q. Yes. And then in relation to Hepatitis B, I think the implementation of testing from the early 1970s, did that reduce the risk of transmission of Hepatitis B?
A. It did indeed, it reduces the number of infected donors entering the pool and, therefore, the product is safer.

Q. Yes. I don't think it excluded the transmission of Hepatitis B?
A. No, because testing is always only as good as the sensitivity of the test in place at the time, and in the early 19 -- late 1970s /early 1980s, that testing was of limited sensitivity.

Q. It improved with time?
A. Yes.

Q. And what about, then, the question of the transmission of non-A non-B Hepatitis, as it would have been called at that time?
A. It was effectively recognised as a common sequitur to treatment, particularly of previously untreated haemophiliacs with large pooled concentrates.

Q. Yes. And when you say "large pooled concentrates," do you mean commercial concentrates or do you mean --
A. No, anything more than a few hundred donors. Given the incidence of non-A non-B Hepatitis, the plasma pools made at BPL and at PFL were perfectly capable and did transmit non-A non-B Hepatitis.

Q. Before there was any form of viral inactivation?
A. Indeed.

Q. Yes. And was that the experience found in relation to concentrates, the BPL and PFL concentrates?
A. It was.

Q. And I think you refer in particular, I think, at paragraph 14, to a study by Kernoff and others in 1984, which I think the Tribunal has already been referred to?
A. Yes. And was -- there had previously been some suggestion that there was less overt non-A non-B Hepatitis with NHS concentrates. In fact, by the time of the Kernoff study, it was becoming clear that they were universally capable of transmitting non-A non-B Hepatitis.

Q. Yes. You refer also to a previous study by -- I think by Dr. Craske in 1982 --
A. Mm-mm.

Q. -- which had shown that there was a higher degree of infectivity for non-A non-B from commercial concentrates, from paid donors?
A. That was certainly advanced by John Craske in late 1981 /early 1982. I think that by the end of 1982, we were not discriminating quite so confidently between commercial and NHS concentrates in that respect.

Q. Yes. And what would the position be in relation to cryoprecipitate; what was the risk of transmission of non-A non-B from cryoprecipitate?
A. Because cryoprecipitate is typically made from an individual plasma donation, and for administration will be pooled perhaps ten, a dozen cryos to the pool, then the patient is exposed to a much smaller number of donations. And the risk of the patient being infected is very much lower as a result. And a patient would have to be very unfortunate to receive the one infected donation in several hundred.

Q. And what about if the patient requires to receive a significant number of treatments of cryo?
A. Then it becomes almost unimportant because the lottery principle takes over and, over the course of a year, the patient will receive as many donations or be exposed to as many donations through cryo as they would be to a pooled concentrate. So regular treatment diminishes the benefit of cryoprecipitate.

Q. Yes. And would similar considerations apply to fresh frozen plasma used for patients with Haemophilia B?
A. Indeed, yes. Precisely similar.

Q. Yes. Now, in relation to the question of the size of pool, Dr. Snape, was that in itself regarded as an important consideration in terms of trying to produce a safe product?
A. It was. And certainly before the advent of virus inactivation, it was probably the only additional arrow in our quiver over and above donation screening.

Q. Yes. And did you attempt to keep down the size of your pools?
A. We did. And certainly in the design of the new factory at Elstree, we consciously designed in an area for producing small pool concentrates for that very reason.

Q. Yes. Were there constraints in attempting to achieve that aim of having small pooled concentrates?
A. There are significant constraints. It's not a very cost-effective way to work. It's also not easy to scale down good processes in such a way as to reap the benefit of those processes on the very small scale. And there are significant losses in terms of samples that have to be taken to prove the quality of the batch of product.

Q. So does it become more difficult to achieve regular and appropriate quality assurance if you're trying to make a small pooled product?
A. The -- very difficult, and the principles become quite different. You're not dealing with a large batch that you can study and put an imprimatur on. You're dealing with many small batches that all have to be characterised.

Q. Is there likely to be variation from batch to batch?
A. Yes, significant variation.

Q. In terms of activity and other elements?
A. Yes, reflecting the variation in the plasma donations themselves.

Q. Yes. And yet, Dr. Snape, you mention at paragraph 17 that in January 1982, BPL increased its maximum donor pool size to 7,500 donations.
A. Yes, and the logic for doing so was precisely the logic of patients who are exposed regularly to plasma products. In those circumstances, such patients have nothing to lose from being treated with a larger pooled concentrate.

Q. So would the -- I think previously you'd mentioned there had been a previous limit of 5,000 donations?
A. Yes.

Q. Would that have significantly increased the risk from the point of view of the patient, that increase from 5,000 to 7,500?
A. No, not at all. Typically a patient would be exposed to perhaps ten batches of concentrate in the course of a year. The increased risk is not statistically significant.

Q. Yes. And at this time, in January of 1982, the risk that would be considered was a risk of non-A non-B Hepatitis?
A. That's correct, and still a residual risk of Hepatitis B, but very much smaller.

Q. Yes. Now, I think you go on then, Dr. Snape, in your statement at paragraph 18, to deal with the question of viral inactivation of coagulation factor concentrates?
A. That's correct.

Q. And first of all to deal with heat treatment?
A. Yes.

Q. And I think you deal with the two fundamentally different approaches: One, heating in an aqueous solution; and two, heating the freeze-dried product?
A. That's correct.

Q. The first, heating in the aqueous solution, would I understand from that that this would be heating the concentrate before it has been dried, before it has been lyophilised, while it's still in a liquid state?
A. Yes. As a large processed bulk, before drying.

Q. And the second, heating the freeze-dried product, that's dry heat treatment or heating the lyophilised product --
A. In the container with its stopper so nothing can happen to it after that.

Q. Yes. Now, I think you mention at paragraph 20 that albumin had been heated since the 1950s?
A. Yes.

Q. Was that heated in a liquid state or a dried state?
A. That was heated in bulk, in solution at 60 degrees for 10 hours.

Q. And so that technology and the idea of sterilising a product in that way was something that was well-known?
A. It was, but I should qualify that and say that albumin products were then-- after filling, the albumin was also heated in the bottle closed. So in that sense it carries the characteristics of the freeze-dried concentrate in the sense that it's in a bottle, and nothing can reinfect it once it's been heated in that bottle.

Q. I see. And why wasn't that technique just simply applied to concentrates since it seemed to work for albumin?
A. We did try, but Factor VIII is very unstable and the result was loss of activity, and also, because of the fibrinogen in the Factor VIII, the product just became an offensive jelly. With Factor IX, the problems were activation of the Factor IX and the risk of generating thrombogenic materials.

Q. Yes. And was consideration given to trying to find some solution to those problems in attempting to heat concentrates?
A. Yes. It's always possible to consider stabilising the concentrates; stabilising them so that the virus is inactivated, but the protein that you're interested in, the

Factor VIII or the Factor IX, is not. But that discrimination is quite difficult to achieve.

Q. And by stabilisation, would that mean introducing another substance into the concentrate in order to protect the protein against being destroyed or interfered with by the heat?
A. That's correct. It might be an amino acid, like glycine, or might be a sugar or even albumin.

Q. Did that carry a risk that if you stabilised the protein and the coagulation factor, that you would also stabilise the virus and render the virus incapable of being destroyed by the heat?
A. Precisely so, yes.

Q. Now, I think did Behringwerke, a German manufacturer, use a Factor VIII product in 1980?
A. They did, and the process involved heat treatment in solution in the presence of a stabiliser. But in our experience, it was not an easy process to reproduce, and certainly the yield was very low.

Q. Yes. And at that time did that seem to provide a practical process for you in fractionating product?
A. It wasn't a practical process that we could implement and wasn't a practical process that most others could implement. But what it did was to cause us to rethink and believe that maybe more was possible.

Q. Yes. And then I think did you become aware of a report of, I think on this occasion, a dry heat-treating process?
A. Yes. This was the report generated by Rubinstein about dry heat treatment. And certainly that appeared to offer promise, but again, when we tried to reproduce it in our own facilities, we had problems both in terms of yield and the product that we produced simply wouldn't redissolve. So it was unusable. But again, the method -- the fact that the method had been tried and claimed by another worker persuaded us to think harder ourselves.

Q. Yes. And I think did that report appear at a Budapest meeting in August of 1982?
A. That's correct.

Q. You referred to that in your statement?
A. That's correct.

Q. Now, I think did you then commence development or examination of the possibilities of these two processes; the pasteurisation and the dry heat treatment?
A. We did.

Q. And when was that, Dr. Snape, can you recall?
A. It was in the early 1980s, in 1981 -- '81/'82.

Q. Yes.

A. And certainly following on from the Rubinstein patent, the work continued.

Q. Yes. And just the scale of that work, the scale of the research and development that would have been carried on, I mean approximately how many scientists or professionally qualified people would have been working on that at the time?
A. The whole of the activities of PFL in Oxford were dedicated to that activity. And typically, that would have been perhaps six scientists and ten technical staff in support.

Q. Yes.
A. So a considerable amount of activity at the time also producing clinical use of a product sometimes.

Q. Yes. Now, I think at this time, Dr. Snape, are we still thinking and -- primarily in terms of non-A non-B Hepatitis?
A. That was the thrust. That was the focus. In 1981/'82 we were conscious that there was an established risk of transmitting non-A non-B Hepatitis, yes.

Q. Yes. Were there difficulties in attempting to ascertain whether or not any of these processes were of assistance in dealing with non-A non-B Hepatitis?
A. Yes, because we didn't have a marker of infection for the virus; we had a clinical outcome. So the -- the approach was much more pragmatic than would be the case now. We looked to see how -- just how much we could abuse the concentrate in terms of temperature, in terms of time, and still recover a clinically usable concentrate in terms of yield and solubility and acceptability to the patient. But in terms of outcome, we were then thrown back on clinical trial for safety and efficacy.

Q. Yes. I think in America some scientists have available to them colonies of chimpanzees or numbers of chimpanzees?
A. They did indeed, and chimpanzees were used for several years in that way, though I think the later studies were -- heat-treated concentrates in North America were tested in chimps considered to be virally safe, administered and then found to transmit -- still to transmit non-A non-B Hepatitis. One would have to conclude that they were not as effective as workers at the time might have liked to think.

Q. Yes. And was that a view that scientists in this part of the world would have had at the time of chimpanzees studies?
A. Chimpanzees -- first of all, there weren't the available colonies for testing. And I think the -- it was a much more rarified resource not available to people, typically to people in Europe. Certainly not to national fractionators.

Q. Yes. Now, I think you mention in your statement -- I think in 1984 was a protocol drawn up in relation to observing the clinical outcome?
A. Yes, indeed. This is the protocol drawn up by Pier Mannucci, the International Committee on Thrombosis and Haemostasis.

Q. I think the Tribunal has already -- other witnesses have referred us to that. And I think it was revised subsequently in 1988?
A. It was made more rigorous when it was revised, yes.

Q. Essentially that involves setting standards for how you would follow the result of the use of a product in order to establish whether or not it was clinically effective, isn't that correct?
A. The minimal number of batches, the minimal number of patients and follow-up, and so on.

Q. Yes. Now, at this stage, Dr. Snape, were you pursuing investigations in relation to both pasteurisation or wet heat treatment and dry heat treatment?
A. Most of the focus was on pasteurisation, but we had almost a sideline activity looking at dry heat.

Q. Yes. And were you doing this in conjunction with the Protein Fractionation Centre in Edinburgh?
A. We were, because that kind of work is labour-intensive and resource-intensive and it makes sense to share resource when you can.

Q. Yes. And the Protein Fractionation Centre in Edinburgh would have been your equivalent, if I put it that way, in Scotland; is that correct?
A. It was, and is.

Q. Yes. Now, I think you mention at paragraph 28 of your statement that the first report of AIDS-related symptoms associated with a person with haemophilia was published in July of 1982?
A. That's correct.

Q. And did that cause concern to you, as a fractionator?
A. Yes, indeed. Yes.

Q. And why was that?
A. Because it was a marker of a potential problem for all haemophiliacs treated with concentrates, not just in the particular locality in which that patient was diagnosed.

Q. Yes. And I mean, I think the Tribunal would be aware of this; that the causative agent wasn't identified or characterised in 1982?
A. No. And when you don't know what the causative agent is, with a protein preparation like Factor VIII concentrate, you really don't know how to go about eliminating it.

Q. Yes. And were there -- was there indeed debate as to whether or not the condition was a blood-borne or blood-transmitted condition for some time after July of 1982?
A. There was such debate, but I think it behooved fractionators to take the pessimistic view and to assume that they had a problem to deal with.

Q. And would that have been the view that you would have taken in --
A. It was.

Q. -- PFL?
A. It was.

Q. Now, were you aware then - I think you mention in paragraph 29 - were you aware of the development by Hyland or Travenol from mid-1983 onwards of methods of dry heat treatment of Factor VIII?
A. Yes. We had informal reports, and then more formal communications of that work. And of the conditions being used by Hyland, and then by other companies, to attempt heat inactivation.

Q. Yes. And what was claimed for that by the companies at the time?
A. The claims were based both on chimpanzee studies, where these were available, but also in terms of clinical trial, of reducing the risk of transmission of viruses that were susceptible to heat.

Q. Yes. And initially, what would have been the primary focus in those claims, what virus?
A. The focus would have been non-A non-B Hepatitis, because that's what was visible, that's what one could deal with. But that focus switched very rapidly from non-A non-B Hepatitis to HIV, or HTLV-III.

Q. Yes. And in respect of the non-A non-B Hepatitis virus first, what was the clinical outcome for the use of those products, the Travenol and similar dry heat-treated products?
A. The initial results were encouraging but then breakthrough of non-A non-B Hepatitis was observed with the less rigorous heat treatment protocols.

Q. Yes. And would that have been known in 1984, that that breakthrough was occurring.
A. It was.

Q. I think the results weren't published until later?
A. No, but --

Q. Until 1985?
A. No, but the outcomes were known in the community.

Q. Yes. When you say "in the community," Dr. Snape, are you referring to the community of scientists and doctors --
A. I am.

Q. -- who would have been interested in haemophilic --
A. I am.

Q. Would there have been international conferences and things of that kind?
A. Indeed. The International Committee on Thrombosis and Haemostasis and the International Society on Thrombosis and Haemostasis met annually, and that kind of work was reviewed.

Q. Yes. And therefore, would the results of those studies have been known before they were officially published?
A. Before they were published, yes.

Q. If we look at paragraph 30, Dr. Snape, you deal with the question of the mix of product which was in use in the United Kingdom at that time, isn't that correct?
A. Yes.

Q. And I think you supply us with some percentages and figures there?
A. Yes.

Q. Where were they drawn from?
A. They are drawn -- they have a common source. The common source was, in the case of the -- of those particular figures, the Haemophilia Centre Director Annual Reports.

Q. Yes. And I think have you supplied the Tribunal, in fact, with such an annual return for 1986?
A. That's correct.

Q. And one of the documents, one of the appendices attached to that is figures two and three of - I think it's towards the back of that document. It's in the form of a chart, is that correct?
A. Yes.

Q. And perhaps if we look at figure two, is that the -- is that the correct figure? It may not be so easy to see it on the screen. Do you have the paper in front of you?
A. I don't, but --

THE CHAIRPERSON: I can supply one for you.

(Document handed to witness.)
A. Thank you very much. Would you like me to help interpret it?

Q. MR. FINLAY: Yes, please. If you could just explain to us what this shows?
A. This is a graph showing the use, in million international units, of Factor VIII. That's the vertical axis. And over time, in years, that's the horizontal axis. And there, if you look at the curves, the curve with the open circles is the total Factor VIII used in the UK in each of those years.

Q. Yes. I think if you look at the top left-hand side of the diagram, the legend is there --
A. That's correct.

Q. -- that explains. So the line joined through circles is the total?
A. Correct.

Q. The next one, the commercial one?
A. The commercial concentrate usage is illustrated in the open triangles and the most significant feature there is the very rapid rise of use of commercial concentrate happening around 1973/'74. And the NHS concentrate, or concentrates - because there were several in use - is the curve traced by the crosses. And then finally, the other significant contributor for part of the time, the closed squares, is the use of cryoprecipitate to treat patients. And the -- certainly in the period of time represented

on the graph, the amount of Factor VIII concentrate prepared by -- available from NHS sources peaked at a little under 40 million international units in that year; about half of the total concentrate used in the UK.

Q. Yes. And even though it's Haemophilia A patients, plasma is also included as an indication. But obviously its use was negligible --
A. Yes.

Q. -- after, say, 1974?
A. That's correct.

Q. Would that be correct?
A. That's correct.

Q. And it's from this graph, and obviously the information which was used to prepare the graph, that you have supplied us with the figures which you refer to at paragraph 30?
A. Indeed.

Q. And I think, again, later on in your statement?
A. That's correct.

Q. So it -- the year that you look at is 1983, Dr. Snape, isn't that correct?
A. That's correct.

Q. And the total was -- the total amount of Factor VIII used in 1983 was 70 million, is that correct?
A. Indeed.

Q. And of that, BPL supplied 42 percent of the Factor VIII?
A. That's correct. The figures won't precisely translate to the graph because the graph shows all of the concentrate, NHS concentrate, supplied and used. That would include PFC. For my statement I used a broken down figure which was specifically BPL.

Q. I see. Then you say that the remaining supply was made up of 37 percent commercial concentrate and 21 percent cryoprecipitate?
A. That's correct.

Q. Now, were there concerns, Dr. Snape, about this -- the development of heat-treated product and the use of heat-treated product at that time?
A. There were different concerns. With Factor VIII, the concern, first of all, was that anything that you do to Factor VIII potentially inactivates it, causes loss in yield. And as you can see from the graph, for example, for the NHS concentrate, that fall from 1983 -- from 1984 to '83 was due almost entirely -- to '85 rather, was due almost entirely to the introduction of heat treatment. So reduction in yield reduces available product. That's one concern. Second concern is that when you heat-treat a protein, sometimes the protein bends a little, distorts a little, and becomes recognised in a different way by the body's immune system. And in the case of haemophiliacs, that could be responsible for the development of inhibitors to Factor VIII, a very serious

complication of Factor VIII. With Haemophilia B, different concerns would arise. The concern would be much more the generation of pharmacologically-active molecules that might cause thromboembolic sequelae indications.

Q. Now, was there an incident I think that you refer to in paragraph 32 of your statement, Dr. Snape, in October of 1984?
A. There was. We were advised of a situation in which a batch of product included plasma from an infected donor, and resulted in transmission or potential transmission. And therefore, we took a decision to recall that batch. Recall was very unusual in those days.

Q. And then was there also an incident in late 1984 in Scotland?
A. Yes. And there were more patients -- there were more patients -- more donors involved in that situation. It was a better characterised incident.

Q. And I think, again, the Tribunal has heard of this, Dr. Snape, I think from Dr. Tedder, apart from other witnesses. But what you're referring to there is I think what was known as the Edinburgh cohort of patients?
A. Yes.

Q. And these were patients who received only product produced by the Scottish fractionation plant, from Scottish donated plasma?
A. And so their disease could be associated causally with that treatment.

Q. So certainly from the combination of those two events, Dr. Snape, what would your view have been about the safety, from a HIV point of view, about the blood supply in the United Kingdom at that time, in late 1984?
A. That although the blood supply was generally regarded as being as clean as it was possible to achieve, there was still the risk of transmitting virus, specifically HIV, by pooled concentrates, and as a result of the inclusion of one or more infected donations in such a pool.

Q. Yes. Would the existence of that risk have come as any surprise to you at that time, Dr. Snape?
A. No. And it shouldn't have done because it was a repeat of what we already saw, with non-A non-B Hepatitis. But in the case of HIV, AIDS, the challenge to the donor pool was smaller. There were fewer infected donors.

Q. Yes. But nonetheless, they clearly -- their existence was demonstrated to you in this way --
A. Oh, yes; oh, yes.

Q. -- as a result of the combination of those two things?
A. Oh, yes.

Q. Now, I think you mention - again, I think the Tribunal will be familiar with this - that by mid-1984, a consensus had emerged about the causative agent for what later became known as AIDS, isn't that correct?
A. Yes, called, at the time, HTLV-III.

Q. Yes. And the work of Montaginier and Gallo identified the virus?
A. Yes.

Q. And did you become aware of a communication from the CDC in the autumn of 1984?
A. Yes. I don't believe what we received was a written communication; I think it was a verbal communication from the Centre for Disease Control, that we should presume that the virus was sensitive to heat and could be inactivated.

Q. Yes. And was that at an international conference, do you recall, or --
A. I don't recall, I'm sorry. I think probably not. I think it was as a result of a visit, but I don't have the date.

Q. I think there was a publication by the CDC --
A. Subsequently.

Q. -- and the MMWR in October of 1984?
A. That's right.

Q. Would you have been aware of that?
A. Yes, we were, as soon as it was published.

Q. Yes. And what was the effect of that, Dr. Snape?
A. Basically to focus all of our efforts to produce a heat-treated concentrate. And it became the single highest priority for the Oxford laboratory.

Q. Yes. And the process of heat treatment that the CDC had referred to was I think a dry heat treatment or heat-treated in the lyophilised state, is that correct?
A. That's correct.

Q. And the indication was that that was effective against the HIV virus?
A. Yes.

Q. And so did that have consequences for your work?
A. It did, because what we then had to do was to evaluate the impact of heat on existing concentrates. We weren't at the stage of having created a concentrate specifically designed to be heat-treated at that stage.

Q. Yes.
A. So we had to evaluate the impact of heat on those concentrates.

Q. Yes. Prior to that, Dr. Snape, had there been any convincing evidence that the HIV virus was subject to destruction or inactivation by heat treatment?
A. I'm not aware of any reported data, but I'm sure at the time the heat treatment regimens described by Baxter Hyland and others were being observed in terms of post-treatment sequelae for observing freedom from transmission.

Q. Yes. Now, you mentioned previously the difficulty in evaluating the effectiveness of any heat treatment process because of the absence of a marker virus?
A. Yes.

Q. Did you -- did some of the HIV or HTLV-III virus, as it was then known, did that become available to you then for laboratory work?
A. Virus for spiking studies?

Q. Yes?
A. Not to BPL, no.

Q. I see. So you still would not have been in a position to examine in the laboratory the effectiveness of your heat treatment process --
A. Not directly.

Q. -- in that way?
A. No.

Q. And did you -- were you able to -- when you say "not directly," were you able to get somebody else to do that work for you?
A. The work was planned, but I'm not sure that for some years that that work then went on.

Q. So therefore, would I understand that the development of your heat treatment process of 80 degrees Centigrade for 72 hours, that was done without the benefit of the sort of log reduction studies, the measurement of spiked product and its reduction, the reduction of the virus by heat treatment?
A. That information came later. The development of the process was a much more pragmatic mechanism. We were looking to see just how much we could abuse the concentrate in terms of heating it; how high we could raise the temperature; how long we could heat it and still retain a product that was clinically acceptable, could be resolved and still had Factor VIII.

Q. And so, I mean, we'll be seeing in a moment -- you describe for us the product that you did make in 1985 and was released for use. Would there have been no viral inactivation studies, laboratory viral inactivation studies with spiked material in relation to that product in that particular form of heat treatment?
A. There were no viral inactivation studies at the time that product went to clinical trial --

Q. I see.
A. -- which was for safety and efficacy.

Q. Yes. I see. Now, you mention, Dr. Snape, at paragraph 35, that sort of with -- I think with some regret and reluctance, perhaps, that you, in effect, put the pasteurisation development, the investigation of pasteurisation, on the back burner or to one side in order to pursue dry heat treatment?
A. Yes. Regret because the programme was -- had involved a lot of work and certainly had it been -- had the work been more promising, then we would have found the completion of that project satisfying. But it was overtaken by the success of the dry heat treatment regimen.

Q. Yes. Would there have been a difficulty, a particular difficulty associated with using the pasteurisation system at Elstree?
A. The facilities at Elstree at the time were old. They -- we had planned, but not built, a new facility, and our concern was that any process that involved inactivation early in the life of a product would then be exposed to reinfection during the later life, in particular the formulation and then the filling and freeze-drying of that product. So we were concerned to avoid that.

Q. I see. Now, I think you did develop the dry heat-treated process, isn't that correct?
A. That's correct.

Q. Firstly for Factor VIII and then secondly for Factor IX?
A. Yes. The work was going on in parallel, but we took longer to satisfy ourselves with the safety of the Factor IX concentrate.

Q. Yes. Now, I think did you evaluate heating at 80 degrees Centigrade for 72 hours?
A. We did.

Q. Which was given a particular code of HT3?
A. Yes.

Q. Isn't that correct?
A. Yes.

Q. And did you, in fact, release a batch for clinical trial treated in that way in April of 1985?
A. We did.

Q. And what was the outcome of that?
A. That study, again, was a study of safety and efficacy, and the outcome was that the patients received the product well and proceeded uneventfully after treatment without development of infection.

Q. Yes. I think -- you mention in paragraph 37, Dr. Snape, were you simultaneously experimenting with other versions of heat treatment?
A. We were. And I ought to explain why, because we had an inventory of product already made. We knew that the HT3 conditions wouldn't be tolerated by most of that product. We were looking for conditions that could be applied to the existing product so that that product could be made available with some increased assurance of safety. Not as -- not the same as we were hoping to achieve with HT3, but still increased assurance.

Q. So that, do I understand you correctly, that in order to produce the product at 80 degrees Centigrade for 72 hours, that would involve not only heat-treating the final lyophilised product but some modifications in the manner in which you had produced that lyophilised product --
A. Quite significant modifications.

Q. -- to make it capable of being heated in that way?
A. Yes.

Q. Whereas the -- I think the lesser heat treatment that you used was 60 degrees Centigrade for 72 hours, and 70 degrees Centigrade for 24 hours?
A. Those were conditioned HT1 and HT2 respectively, yes.

Q. And was it possible to apply those to product which you had already made according to your then conventional means of fractionation?
A. It was possible to apply those processes to some batches. We found ourselves in the position of having to do a trial run on samples from every batch to determine whether they would withstand heat treatment. And we eventually determined that most product was susceptible to the HT2 conditions. So, in fact, the HT2 conditions were the ones that we used to heat most of the existing product.

Q. I see. And would that product have been issued then during 1985?
A. It was.

Q. I think do you mention at paragraph 37 that the first issues of this HT2 treated Factor VIII were made in February of 1985; and that after May of 1985, all Factor VIII issued would have been heated under at least the HT2 conditions?
A. That's correct.

Q. And then from what time in dealing with Factor VIII - I think it's from September of 1985 - would all issues of Factor VIII have been subjected to the HT3 treatment?
A. That's correct.

Q. And was that product then given the name 8Y?
A. It was, and that product continued to be issued until last year.

Q. Yes. And I think it was manufactured at both Oxford and Elstree?
A. That's correct.

Q. Yes. Now, how was the situation managed in relation to the transition in Factor VIII from unheated product to heat-treated product?
A. It wasn't a switch transition; it was a continuum. And in particular, we determined that we couldn't make a recall of product made before 8Y. So there was a continuous supply with overlap of use of unheated and then HT2; in a few cases HT1, a lot of HT2; and then the progression into 8Y, the HT3 product, but with no withdrawal of product during that time.

Q. And why was that, Dr. Snape, why wasn't it possible to withdraw the unheated product and replace it with at least the heated product; if not the 8Y, perhaps the HT2 or HT1?
A. To say that it wouldn't have been possible is probably -- would probably not be correct. I mean, if you set out to do something, you can do it. But first of all, it was not clear that it was appropriate, because withdrawal of any of those products would have deprived haemophilia treaters and haemophiliacs of a valuable therapeutic material. But also, the -- because the process was over such a long time and was such

a continuum, it would have been very difficult to define where the cut-off was; what was safe and what was unsafe.

Q. Would you have had stock of heat-treated product in, say, February of 1985 sufficient to replace the nonheat-treated product, which would then have been issued, if you had done a recall?
A. No, absolutely not. I mean, to have done a recall, we would have had to build up an inventory of 8Y, and that would probably have taken something like six months. So we would have delayed the availability of the HT3 product from -- by probably half a year.

Q. Yes. And if you did withdraw the nonheat-treated product, what option would have been available then to treating doctors?
A. Commercial concentrates or cryoprecipitate.

Q. Yes. And was cryoprecipitate in use at that time in the United Kingdom?
A. It's still in use in very small quantity.

Q. And who would have been producing that?
A. Produced at transfusion centres, locally from single donations of plasma; still produced as a frozen cryoprecipitate, not freeze-dried.

Q. Not freeze-dried. And would it have been produced by BPL or --
A. No.

Q. -- at Oxford or Elstree?
A. No, BPL's role was to manufacture freeze-dried concentrates.

Q. I see. Now, I think at paragraph 40, Dr. Snape, you mention that you think it was unlikely that any unheated BPL Factor VIII concentrates were administered after July of 1985?
A. That's simply because of the rapid utilisation of products and the rate at which one product supplanted the other.

Q. But that would be the date when you would assign as to when the last unheated BPL concentrate would have been administered?
A. Yes, because we would have been -- we had been supplying HT1 and HT2 concentrate for some time before that.

Q. Yes. Can I turn then to Factor IX concentrate --
A. Yes.

Q. -- Dr. Snape. I think you deal with that at paragraph 41 of your statement?
A. Yes.

Q. What was the history in relation to that in terms of the viral inactivation through heat treatment?
A. The product that we made prior to introducing virus inactivation was a product we coded 9D. It actually responded very well to heat treatment, surprisingly well, though there was some evidence of generation of thrombin in the product. We dealt

with that by adding a small amount of antithrombin during processing, which helped stabilise the product. And we -- the development of that product, really all of our focus was on avoidance of thromboembolic risk. So we resisted arguments for making that product available sooner until we had satisfied ourselves both with routine testing for safety in terms of thrombogenicity and also additional animal testing for safety conducted in conjunction with our colleagues in Edinburgh.

Q. Is that what I think is referred to sometimes as the dog study?
A. That's correct.

Q. Short of the dog study, when you say "routine testing," would that have involved testing in the laboratory for thrombo -- any sign of a thrombinogenic effect?
A. Both in the laboratory and in animals.

Q. Yes. And I think was the heat regime that was applied to Factor IX from the start, was that 80 degrees Centigrade for 72 hours?
A. It was.

Q. You didn't experiment with any lesser heat treatment?
A. We didn't, for several reasons: First of all, the 80 degrees, 72 hours was effective. And when you are managing that kind of process, there's a great deal of assurance; comes from not changing the equipment that you're using. By settling on the same heat treatment regimen for Factor VIII and for Factor IX, then we didn't have to manipulate dials, change controllers on ovens. We could simply use them interchangeably.

Q. I see. So would the application of the 80 degrees Centigrade for 72 hours, would that have been done to the Factor IX after the development in relation to Factor VIII?
A. Yes, it was.

Q. Now, when was the first Factor IX, heat-treated Factor IX made available for clinical trials?
A. That would have been July of '85. But that was just a -- again, a small trial of safety and efficacy.

Q. Yes.
A. The first issue -- serious issues were in October.

Q. Yes. Before we come to that, Dr. Snape, what was the position in relation to unheat-treated Factor IX --
A. It was --

Q. -- through 1985?
A. It was still being used. We discontinued release of unheated batches early in the year, but we I think were expecting to see unheated products still being used from stocks held in centres until July of that year.

Q. And can you just explain that to us, Dr. Snape: First of all, would you have been in contact with the haemophilia treaters, with the directors of treatment centres?

A. Much more closely for Factor IX than with Factor VIII. Because Factor IX had always been -- first of all, supplies of Factor IX had always been limited, so we managed the distribution of Factor IX directly from BPL. And we distributed directly to the hundred-plus haemophilia centres. Secondly, because the product had -- there was a significant concern in the late '70s /early '80s in terms of thromboembolic sequelae with Factor IX and we considered it appropriate to keep a tighter control over issue, and also to monitor feedback from haemophilia centre directors very closely. So yes, the communication was quite active on Factor IX.

Q. And I think, am I right, that up until 1985, the Factor IX, all of the requirement in the United Kingdom for Factor IX was supplied by yourselves?
A. Indeed.

Q. Yes. And so what happened during the course of 1985? I think you said that you stopped issuing new unheated Factor IX during the course of the year?
A. Yes. There was a period from July of '85 through to October when we made no issues.

Q. And why was that, Dr. Snape?
A. Because we had to make the break in terms of discontinuing supply of the unheated product. We were seeking to create sufficient inventory in -- for a concerted launch of the product, but only when we had satisfied ourselves of the safety in terms of potential thrombogenicity of the product.

Q. And so when you discontinued the supply of new issues of unheated product, I think you said in July of 1985 --
A. Mm-mm.

Q. -- would you have communicated to the treating directors that you were in the process of making a heat-treated product and that that product would be available in a specified period of time?
A. Yes, indeed we did.

Q. And I mean, what was your understanding as to what they were to do in the meantime, what therapeutic option was available for them and their patients in the meantime?
A. There were commercial concentrates available.

Q. And that would have been heat-treated commercial concentrates?
A. Some, but I'm not sure that I can tell you precisely which manufacturers had heated concentrates available at that time, or what regimens of heat treatment had been involved.

Q. But at that time, Dr. Snape, in terms of a commercial Factor IX, would the commercial Factor IX that would have been used, would that not have been heat-treated?
A. There would have been -- there were no licensed heat-treated concentrates available at that time in the UK, is my understanding.

Q. Yes, but in fact, the commercial concentrates that continued to be used, would they not, in fact, have been heat-treated, whether used on a named patient or whatever basis?
A. I can't recall.

Q. I'm just surprised at the suggestion that by this time, that by June or July of 1985, that a treating doctor in the UK would have contemplated using nonheat-treated commercial concentrate?
A. Well, certainly some of the concentrates, the commercial Factor IX concentrates, would have been heated. What I can't tell you is whether there -- I can't say categorically that there were no unheated concentrates, commercial concentrates in use.

Q. I see. I see. Now, I think in relation to the Factor IX, was there a difference in terms of -- I think it became available for general issue in October of 1985, is that correct?
A. That's correct.

Q. And I think you deal with this at paragraph 44 of your statement. Was there a difference in your approach to that, to the approach which had been adopted in relation to Factor VIII?
A. Specifically, in that we determined to make a recall of unheated concentrate.

Q. Yes. And I think that was done?
A. That was done and product was recovered, and it was feasible because, as I explained earlier, of this very direct link with the treatment centres, and the ability to approach them and provide them with heated concentrate as a substitute.

Q. Yes. And I think you mention at paragraph 44 of your statement that there was a single communication; in fact, you give us the date, the 7th of October, 1985?
A. That's correct.

Q. A letter from you to the --
A. To the directors.

Q. -- to the directors, informing them of the availability of the heated product, 9A, and instructing return of unheated product?
A. Yes.

Q. Presumably on the basis that that would be replaced with heated product?
A. Yes, indeed.

Q. Yes. And I think you refer, at paragraph 45, to the communication from Dr. Craske in June of 1985?
A. That's correct.

Q. Which was, I think, a letter in The Lancet, isn't that correct?
A. Yes, and reinforced the concern to have heated products available.

Q. Yes. Yes. But I think you draw attention that he -- that he recommend changing to heat-treated NHS Factor IX concentrate as soon as possible?
A. Yes.

Q. But his letter didn't make any specific reference to commercial concentrate, whether heated or untreated?
A. No.

Q. Yes. Now, I think, again, at paragraph six (sic), you return to the question of the usage for -- NHS Factor IX usage in 1985. Is that dealt with in this -- it's not dealt with in this --
A. There is a chart --

Q. Perhaps if you could identify that for us. Sorry, I beg your pardon.
A. -- which shows the same period, and the usage of NHS in commercial concentrates. So that's figure three.

Q. Yes. So if you could just look at that, Dr. Snape, and if you could explain to us: Again, it's a similar legend, the same symbols used to denote the various different forms of product, isn't that correct?
A. That's correct. So total is the open circles, crosses, the NHS concentrate; and the most significant feature is just the blip in '85, falling back in '86, of the use of commercial concentrate.

Q. Yes. And in fact, I mean, it illustrates very clearly, there was, in effect, no commercial concentrate used apart from that period, from between '84 and '86?
A. That's right.

Q. Other than that, doesn't appear on the graph?
A. That's right.

Q. And so there was a significant -- I mean, in terms of this, there was a significant amount of commercial product used in 1985?
A. That's correct.

Q. And there was a very significant drop, which one can see above that in the X, in the usage of your product during 1985?
A. Reflecting the fact that we weren't issuing between July and October.

Q. Yes. Yes. And the only matter of doubt which you've raised for us, Dr. Snape, is whether or not that was heated or unheated product that was in use in 1985?
A. Certainly I can't give -- I can't confirm at this stage that it was all heated.

Q. Some of the treating doctors from the United Kingdom who will be giving evidence will presumably be able to tell us that. Now, you make observations, Dr. Snape, at paragraph 47 and 48 of your statement about the status, the then status of the BPL as part of the National Health Service, and therefore, a Crown undertaking which enjoyed Crown immunity. Do I understand from your statement that that has created a situation in which it wasn't subjected to the licensing regime that commercial enterprises would have been subjected to?

A. It wasn't subjected to the formal licensing regimen in the sense of requiring submission of detailed dossiers for licensing of products. The organisation was subjected to the same inspection activity, so BPL and PFL were inspected by the same agency inspectors that inspected the commercial.

Q. But in terms of applying for a product authorisation, as it would now be known under the EEC code, there wasn't an obligation on -- do I understand, on BPL to apply for product authorisations?
A. We were advised to apply and did indeed make application for licenses in the mid -- late-1970s. But those dossiers were never, to my knowledge, formally reviewed and granted formal licenses. We had what was called a license of right under the Crown status provisions.

Q. Yes. And what impact do you think that had on the development of the heat-treated, the virally inactivated heat-treated product?
A. I think certainly it allowed progress to be made more quickly than had we at that time been subject to the formal rigors of licensing.

Q. So in that sense, you think it would have been a positive thing that you weren't subjected to that kind of regulatory control?
A. I'm not advocating it as a way to proceed, but I believe that was the outcome.

Q. Yes. I understand. I suppose that situation, though, would have some weaknesses, would you agree?
A. The weaknesses I think are self-evident, that the controls exist for a purpose.

Q. Yes?
A. And if controls are not in place, then it requires greater self-discipline from the organisation.

Q. And if there's any weakness, there's no independent outside audit to reveal that weakness?
A. Oh, no. The inspection provides the outside audit. What was not in place was the formal committee review of product licenses, but the audit was still there.

Q. And of course, while we're looking at this, an alternative solution which would produce the same effect would be for the regulatory authority to take a flexible approach to something that was obviously urgent, such as the heat treatment of product?
A. And effectively that's what the regulatory authorities did in general in terms of heat-treated product, in terms of supporting and encouraging clinical trial.

Q. Yes. So would that not seem to have been the case, for instance, in relation to the FDA --
A. Yes.

Q. -- which was -- I mean, the industry in America was highly regulated?
A. Yes.

Q. But they seem to have accepted unusual urgent applications and to have allowed progress to develop?
A. Indeed, yes.

Q. Now, at paragraph 49, Dr. Snape, you deal with the outcome in relation to the use of your product, the superheat-treated 8Y product, isn't that correct?
A. That's correct.

Q. And what was that situation? First of all, I think you refer to a product information sheet which you would have been able to issue by July of 1985. And what was the then state of knowledge about the clinical outcome?
A. The purpose of that information sheet was simply to bring haemophilia centre directors up to date on the number of patients treated and the period of time since treatment without development of evidence of virus infection.

Q. Yes. And I think that was the situation then, in July of 1985; that there had been no evidence of NANB viral transmission?
A. For about three months post-transmission in a number of patients, yes.

Q. Yes. What would be your reaction to that, Dr. Snape? I mean, what could one read into that?
A. It was promising, nothing more. Looked promising.

Q. And that communication I think was simply on the product information sheet --
A. Yes.

Q. -- that you refer to?
A. To haemophilia centre directors.

Q. And not in any form of public communication?
A. No. Formal publication was some time in being made.

Q. Now, you say that in May of 1986, BPL presented updated clinical trial data showing continued freedom from non-A non-B transmission. And what were you referring to there, Dr. Snape?
A. Again, this is information to haemophilia centre directors, and, as I state in my statement, followed up with a report to haemophilia centre directors. But the -- specifically I think in May '86 there was a presentation in abstract form to an international meeting.

Q. Yes. I think you have referred us to a reference, Dr. Smith (sic). If we look in the article, that I think again the Tribunal has seen, from 1988, the article that appeared in The Lancet of October the 8th, 1988, dealing with the safety of the 80 degrees Centigrade treating, there's a reference I think on the last page --
A. -- to a paper by Fletcher.

Q. Yes. Reference number 11, Dr. Snape.
A. That was to the World Federation of Haemophilia congress in Milan with Mary Fletcher as the prime author.

Q. So -- and that was -- was that the May 1986 that you referred to?
A. That's correct. But again, that was evidence of nondevelopment of virus infection after a period of time.

Q. Yes. This is obviously a significantly longer --
A. Yes.

Q. -- period of time?
A. Yes.

Q. For Factor VIII you have a year; and for Factor IX, something less than a year?
A. Yes. And more batches and more patients. So more robust evidence.

Q. Yes. Still, I think at this stage, not information in accordance with the protocol --
A. No.

Q. -- but the absence of any report of breakthrough of non-A non-B Hepatitis?
A. That's right.

Q. Is that correct?
A. Though the studies that were reported were modelled on the protocol. But as much information as possible was given in terms of patients treated.

Q. Yes. And then I think there was -- there was also, in September of 1986, there was an interim report to UK haemophilia directors?
A. That's correct.

Q. Which, again, reported the same thing, that the patients studied to date hadn't --
A. Had I think almost exactly the same information as was presented in Milan.

Q. Yes. And what was -- by that time, Dr. Snape, by, say, September of 1986, what could one say about the experience with the product?
A. By then we were very confident that we had a product, both Factor VIII, and, by analogy, Factor IX, that was robust in terms of the way it dealt with non-A non-B Hepatitis.

Q. Yes. And would you also, of course, have been confident that it didn't transmit HIV?
A. More so, because HIV is a less robust entity than non-A non-B.

Q. Yes. And would that knowledge about your product, would that have been general knowledge by the autumn of 1986 amongst UK -- the UK doctors and scientific community, persons who were concerned with haemophilia?
A. In the UK and increasingly internationally also.

Q. Yes. Now, I think then, just to complete this, there was the study in 1988, the -- which was published in The Lancet?
A. Yes. I mean, the study, of course, was ongoing, the publication.

Q. Was in 1988?

A. Was in '88.

Q. Yes. And I think there's a further study I think; was it perhaps in 1993?
A. That's correct.

Q. And the net result of all of these has been that there - is this correct - that there was no recorded instance of the transmission of either HIV or non-A non-B, subsequently Hepatitis C, from the use of these products?
A. To date, yes.

Q. Yes. Now, I think you deal then, Dr. Snape, in your statement, with contact, which there was between PFL or BPL and the BTSB, is that correct?
A. That's correct.

Q. And I think we've heard from Dr. Cunningham, and I think we may hear from Dr. Smith, about their contact about the question of heat treatment and safety of products. I think were you contacted by Dr. Cunningham in relation to -- were you contacted by Mrs. Cunningham in relation to the question of quality assurance and the testing of product?
A. Yes. Because at that time I had responsibility for quality assurance and quality control for the organisation.

Q. Yes. And I think, in fact, did you carry out quality assurance testing of some of the BTSB product?
A. We did. We were able to apply the tests that we used on our own products directly to the BTSB products.

Q. Yes. Can I ask you, Dr. Snape, how -- if I might put it: How transportable or transferrable was your heat treatment process of 80 degrees Centigrade for 72 hours, how easy would it have been for another body or fractionator to adopt that method?
A. It wouldn't, and it wasn't. There were other organisations who considered application of the 80 degrees heat treatment, but the process depends on a number of things: The nature of the proteins in the product; the moisture content of the product; how the -- whether the product is stoppered on the vacuum or under nitrogen; and the formulation in terms of any stabilisers. You can't typically just lift up one part of a process and superimpose it on another product.

Q. Yes. And so in order to do the heat treatment at 80 degrees Centigrade for 72 hours, does that require a relatively sophisticated form of fractionation to get a product which is capable of withstanding that treatment?
A. It requires the ability - well, first of all, to evaluate the impact on the product and understand what you're seeing; and then if the impact is unattractive, then effectively to redesign your product to suit the heat treatment process. And that certainly would require experience, expertise, resource and time.

Q. Yes. Now, can I ask you, Dr. Snape, about the heat treatment of a Factor IX product at 60 degrees Centigrade for 144 hours. Do you have any view in relation to that as a method of viral inactivation?

A. It would be more effective than heat treatment for 60 degrees for 24 hours or 72 hours. The duration works in its favour. Beyond that, it would have -- the only judgment would be on how it performed with particular concentrates.

Q. Yes. I think are you aware, was it -- was that a regime that was used I think by Travenol?
A. By Baxter Hyland, yes, for the product Proplex. And to my knowledge, there were no recorded transmissions by product treated with that regimen.

Q. The Hyland product?
A. Yes.

Q. On the other side, was there any published study which would have conformed with the protocol showing it to be clinically safe from the point of view of non-A non-B Hepatitis?
A. I'm not aware of such a study.

Q. And again, Dr. Snape, would the application of that particular regime to a product which was fractionated not by Hyland but by some other method, would that create a difficulty?
A. It could only be evaluated -- evaluated in practice in the same way that when we were looking to deal with our heat-treated -- our unheated HCRV and HL products in late '84 /early '85, we evaluated the HT1 and the HT2 regimen to see how the product would survive. In exactly the same way, a third party product could be evaluated in the Hyland, Baxter Hyland protocol.

Q. Yes. But I think is it clear from the evidence that you've given that one couldn't assume, because the heat treatment regime was satisfactory for Hyland with their product, and the product fractionated according to their method, one couldn't assume that that would necessarily be a satisfactory heat treatment to be applied to some other product fractionated in a different way?
A. You certainly couldn't assume that. But on applying the heat treatment, it would become immediately apparent whether the product had been adversely affected by the heat treatment. What wouldn't be apparent is how effective the virus inactivation was.

Q. Yes. Now, I think at paragraph 54 of your statement, you deal with the question of the solvent/detergent method of viral inactivation.
A. That's correct.

Q. And I think was that adopted by or introduced by BPL, a solvent/detergent treated Factor VIII, under license from Baxter in March of 1990?
A. That's correct.

Q. Now, in relation to the introduction of individual HIV screening of donors, that was introduced I think in the United Kingdom in October of 1985 --
A. Correct.

Q. -- is that correct? So that from then on, donations would have been screened individually for HIV antibodies?
A. They would.

Q. Yes. And when was the last Factor VIII manufactured from unscreened donations issued? Do you follow?
A. I do. I mean, very much later than that might suggest. I think in my statement I quote a date of November '86.

Q. For Factor VIII?
A. For Factor VIII, and later still for Factor IX, April '87 for factor -- that's a mistake by the way. That is --

Q. '86, I presume?
A. '86.

Q. Yes.
A. Threw me for a minute.

Q. So it's November 1986 for Factor VIII and April 1987 for Factor IX?
A. That's correct.

Q. Why would there have been such a prolonged time lag?
A. Several things contribute to that: First of all, the implementation of screening at centres led to plasma being received at BPL over a long period, which was a mix of screened and unscreened. We also had a large inventory of unscreened plasma. By then we had an effective virus inactivation mechanism, we believed, in our processes, so that the -- it wasn't considered necessary to discard unscreened plasma, but we continued to process that. And what I've quoted there is, if you like, just a snapshot in time of when the last donation from unscreened plasma was processed. There wasn't a concerted attempt to say, after November 1986, we won't process any more unscreened plasma. It was simply a snapshot of when it happened.

Q. I see. And so you considered it safe to proceed with the fractionation of the unscreened plasma?
A. It was as safe in November '86 as it was in October '86 or September '86. It's very difficult, under those circumstances, when you've made another change, an effective change in the form of introduction of a virus inactivation step, to implement a cut-off just on the basis of the introduction of screening. For a concentrate, it's not at all clear that that's an appropriate thing to do. Very different for red cells or platelets where the testing is the only assurance of the safety of the product.

Q. Yes. Now, you finally deal then, Dr. Snape, with the question of self-sufficiency?
A. That's correct.

Q. And perhaps it's -- it can be very graphically seen if one looks back to your chart for Factor VIII.
A. So figure two?

Q. Yes. I mean, if one looks at the total usage of Factor VIII, which is the top line, and the quantity produced of National Health Service Factor VIII concentrate, which are the Xs, it's very clear that there was always a very major gap between the two?

A. That's correct.

Q. So that at no stage in the period we're looking at did the NHS ever achieve a situation in which you were supplying all of the product which was being used?
A. Except for Factor IX.

Q. Except for Factor IX?
A. But not for Factor VIII.

Q. Not for Factor VIII. Why was that, Dr. Snape?
A. Because clinicians have freedom of choice, and that freedom of choice means that they can either choose to use, in the case of Factor VIII, the BPL product, 8Y; or an alternative commercial product. When we first -- when the definition of self-sufficiency was first coined, self-sufficiency meant precisely that; that the target would be the BPL produced all of the Factor VIII that was going to be used in England and Wales. It then became -- the definition became adjusted to mean all of the Factor VIII or Factor IX that clinicians in England and Wales chose to prescribe.

Q. Yes. And was even that situation achieved?
A. In the time here, no, because clearly, in the second half of the -- from '84 through '87, haemophilia centre directors in the UK would have preferred to have more UK-derived Factor VIII available to them.

Q. And I think then you mention in your statement that by 1988, the new factor -- manufacturing unit at BPL was fully operational?
A. Yes.

Q. And still, in fact, your product would only have accounted for approximately 50 percent of the national requirement?
A. That's right. That's correct.

Q. So by that stage, by 1988, was there sufficient capacity there in BPL to produce product?
A. There would have been sufficient capacity had that capacity been called on. What we did was to commission the facility and then operate it at a level sufficient to maintain supply against demand.

Q. So by 1988, it's a situation in which the treating doctors are able to get as much as they want to of your product, would that be fair?
A. Yes. Yes. That's not to say that, had we chosen to produce more and to adopt different strategies in terms of presenting it to a marketplace, perhaps maybe the outcome would have been different. But that's the situation certainly by '88.

Q. Yes. Now, would it have been possible, Dr. Snape, for your organisation to carry out, in effect, custom fractionation of Irish plasma at the request of the BTSB; would that have been a feasible thing?
A. Feasible, possibly, but with some significant constraints. What we would not have been able to do would be to maintain two fractionation streams and process Irish plasma and UK plasma, maintain them separate and maintain the two product lines independent.

Q. And why is that, Dr. Snape?
A. The difficulties -- I mean, we effectively have -- had only one fractionation stream that was committed to -- I should explain that when a batch of plasma is processed, that plasma produces typically five or six products. And those products occupy several process lines in the factory. Those process lines aren't duplicated. To have accommodated another plasma source would have meant dedicating those process lines for a period of time to that other plasma source and controlling the change between the two. That would not have been practicable and would certainly have imposed constraints on how much UK plasma could have been processed.

Q. I see. And would there have been capacity -- so, what you're saying is I think between Northern Ireland and Scotland I think was there a system of sending plasma from Northern Ireland over to Scotland and they got back an equivalent quantity of product from Scotland; would you be aware of that situation?
A. I'm certainly aware of that, but, to my knowledge, there was never any attempt to maintain the plasma separate.

Q. No. No. I mean, what happened was that plasma from the North of Ireland was sent over, used by the Scottish fractionating plant --
A. Treated interchangeably.

Q. Yes, and an approximately equivalent quantity of product returned to Ireland?
A. Yes.

Q. So are you saying that that would have been feasible?
A. I'm sure it would have been feasible, but would have required agreement.

Q. Would it have been feasible prior to 1988?
A. Absolutely not. The -- we were capacity-limited prior to that time by the old factory; and by the time the new facility was commissioned, we had a stockpile of some 250 tons of plasma, half a year's processing, that we simply hadn't been able to deal with.

Q. Yes. Now, on a separate matter then, just moving away from that for a moment: If you had received a request for your product from treating doctors in Ireland, would it have been possible for you to meet such a request during the period, in particular perhaps from, say, 1986 onwards, if you had been -- if a request had been placed with you for a limited quantity of either Factor VIII or Factor IX?
A. Factor VIII, no. The arrangements for supply of Factor VIII in the UK were on what's called a pro rata basis, and that meant that haemophilia centres received back an amount of Factor VIII that was equivalent to the amount of plasma that their regional transfusion centre supplied to BPL. That arrangement was monitored very closely and the return to Factor VIII very zealously guarded. So we could not have supplied Factor VIII to any other agency. Factor IX, it would have been possible on a one-off basis to deal with a particular request, but to have accepted a larger commitment would have meant redesign -- reprogramming processing through the plant in such a way as to accommodate a greater demand for Factor IX.

Q. I mean, I wasn't talking about a large commitment; I'm asking you about whether it would have been possible to meet a request for - possibly on a regular basis, but for a small quantity?
A. I don't see why not.

Q. I see. And when you say that there would have been a problem about supply in relation to Factor VIII, do I take it that means up until the commission of the new fractionation plant in 1988?
A. Even beyond that.

Q. Even beyond that?
A. Even beyond that.

Q. I see. Now, just one final thing, Dr. Snape. I think perhaps just to refer to it more than anything else: At table one of your statement, you set out in a very convenient tabular form the products which were made over the years by BPL and PFL, isn't that correct?
A. That's correct.

Q. And I mean, I think you have described for us the various products that we would be concerned with. But just to identify, you have here a summary of the products, the dates when they were made and their various characteristics, isn't that correct?
A. That's correct.

MR. FINLAY: Thanks very much, Dr. Snape.

THE TRIBUNAL THEN ADJOURNED FOR LUNCH.

THE TRIBUNAL RESUMED AFTER LUNCH AS FOLLOWS:

THE CHAIRPERSON: Good afternoon, Doctor.

MR. BRADLEY: Good afternoon, Madam Chairperson.

THE WITNESS WAS THEN EXAMINED AS FOLLOWS BY MR. BRADLEY:

Q. I appear on behalf of the Irish Haemophilia Society and my name is Raymond Bradley. I have a number of questions for you arising out of your evidence this morning. From the time of commencement or usage of the new BPL plant in 1988, what was the capacity of that plant to produce Factor VIII concentrate?
A. The operational capacity of the plant varied between 500 tonnes of plasma - five-hundred thousand litres and six-hundred-and-fifty litres, at different stages since 1998 -- 1988.

Q. And in terms of availability of plasma for usage at that plant, what was the availability?
A. To begin with, we began with a significant stockpile of plasma, more than half a year's supply. That was consumed, and then any subsequent stockpile negated with the introduction of Hepatitis C screening. So we progressively, by 1990 /'91, were

using plasma as it came in, and typically, might have had between a month and 13 weeks of inventory at any one time.

Q. Okay. If we look at the year 1988, what was the annual usage of plasma at the BPL plant in Oxford, in 1988?
A. PFL. I don't have the precise figures to hand. It's unlikely that PFL would have processed more than 75 or -- more than 75 tonnes in that year, or since.

Q. And the capacity of the plant was 500 tonnes?
A. No, the capacity of BPL at Elstree was 500 tonnes. You just asked me about the PFL at Oxford.

Q. Okay. In relation to the overall capacity of both PFL and BPL, what was that capacity for the year 1988?
A. Probably 550, between 550, 600 tonnes.

Q. And for that year, what was the actual usage of plasma in both plants?
A. I can't give you that figure precisely but my estimate would be something in excess of 500 tonnes.

Q. Is that an estimate based upon actual figures, or have you any basis for that estimate?
A. I don't have data with me; it's based on my memory of how the plant was commissioned and at what rate we filled the capacity. The data are available, but not with me.

Q. Okay. In relation to the 250 tonnes that were stockpiled, were there any concerns in relation to the usage of that particular 250 tonnes?
A. No.

Q. Was it not stored separately in sealed saline containers for a period of time?
A. No.

Q. Did BPL or PFL export plasma-derived products to other countries outside the United Kingdom?
A. We didn't export products at that time. We sometimes responded to requests for supplies of products like Factor VII or Factor XIII or Factor XI that were manufactured by BPL and not manufactured by other organisations.

Q. Did you export Factor VIII to countries like Egypt?
A. We began to export Factor VIII, but again, you are testing my memory now. My belief is that that didn't begin significantly until 1990, and -thereafter.

Q. So BPL or PFL had the capacity to export plasma-derived products to countries outside the United Kingdom?
A. Physical capacity, yes, but we (mark) were not an organisation -- we weren't a commercial trading organisation at the time, and our purpose wasn't to raise money by exports.

Q. I appreciate that. But in circumstances where there was a request or there was an order placed, product had been provided outside the United Kingdom?
A. Yes, but be careful. What I was talking about would be either specific supplies of a therapeutic material for compassionate use - if the other country didn't have the ability to make Factor XIII or Factor XI or Factor VII - and in some instances, beginning a little later, the supply of surplus, surplus Factor VIII or albumin not made under contract, not made to order, but supply of a surplus.

Q. In relation to the 80 degrees Centigrade by 72 hours heat treatment method, do you know whether that particular method was used elsewhere other than the UK?
A. It was subsequently -- other than the UK?

Q. Other than the UK.
A. I don't believe it was. Certainly not in the -- in that timeframe. Subsequently I know it's been evaluated in other countries, but --

Q. More specifically, was it used in South Africa and was it used in New Zealand?
A. The process was adopted by the South African Blood Transfusion Service. Not just the heat treatment but actually the Factor VIII manufacturing method was also adopted; and was also adopted by the Australian fractionators, the Commonwealth Serum Laboratory.

Q. Therefore, it was a method that had been evaluated and introduced into other countries?
A. It was subsequently adopted in other countries, yes.

Q. And did those countries have much difficulty in relation to introduction of that particular method?
A. They did in different ways. Certainly the Commonwealth Serum Laboratories in Australia were not able to achieve the yield with the 8Y process that we did. The Scots of course evaluated the process and were not able to achieve the yields that we did, hence they went on to develop their own process. And the South Africans I think adopted it pretty much unchanged.

Q. Okay. In relation to the genesis of the 80 degrees Centigrade by 72 hours method, it was a higher heat treatment protocol than other manufacturers were using. What was the purposes -- purpose of introducing such a high heat treatment to plasma?
A. It was as extreme conditions as the product was capable of tolerating. If it would have tolerated 90 degrees for 72 hours, or even perhaps 90 degrees for a shorter period, we would have considered that rather than the 80 degrees.

Q. And why were you pushing so far to the extreme of the -- the level of heat treatment that would be tolerated? What was the purpose of doing that?
A. To be sure.

Q. To be sure in relation to the elimination of viruses?
A. Of viruses, yes.

Q. And was that -- when other companies such as Baxter-Travenol, Armour were using lower heat treatment protocols, why did you opt for the higher heat treatment option?
A. Why wouldn't we?

Q. What particular virus were you trying to eliminate?
A. We weren't trying to eliminate any particular virus. We began with a concern for non-A non-B Hepatitis. By 1985, the focus -- the immediate focus had become HIV, but fractionators are always aware and, quite properly, reminded by clinical colleagues of the concept of the unknown virus, the next one just around the corner. So, for me, it was quite natural to chase the most extreme conditions consistent with the product retaining its characteristics.

Q. When did it become apparent in terms of initial clinical data coming back to you that this particular heat treatment process could eliminate Hepatitis non-A non-B?
A. That was within three, four months of the introduction of the product on safety and efficacy trials.

Q. And how many centres were involved in those safety and efficacy trials at that time?
A. A very small number. I think --

Q. Would it have been in the region of six centres?
A. Five or six. Not the thirty-two that was eventually quoted in the Fletcher paper certainly.

Q. So therefore would it -- would it be reasonable to assume that the initial data would be relatively well-known among the haemophilia treater community in the UK?
A. Certainly within the -- in the UK, haemophilia centre directors were kept fully abreast of the information that was available to us.

Q. You mentioned in your evidence this morning that the donor selection requirements were well recognised by voluntary blood banks, but less recognised in America. What did you mean by "less recognised in America"?
A. I don't think I said the donor selection requirements. I mean, I think --

Q. Donor selection?
A. Yeah. The issues are lifestyle risks. In national blood services, such as the one in the UK, with voluntary donation, donors self-defer, if they are unwell. When a donor is entering into a commercial contract for sale of his plasma, and that contract is a significant, or maybe the significant, part of their income, then there is not the same commitment to self-defer if their income is dependent on the donating plasma. That was I think not properly recognised in the '70s and early '80s. I think now there is no question that in that respect, commercial plasma sources are as committed, if not maybe even more extremely regulated, than national blood services.

Q. Would it not have been something that would have been appreciated in the mid-1970s after the Hepatitis B outbreak in the commercial concentrates?

A. There was awareness of those risks, but equally, commercial plasmapheresis plasma was not a replaceable resource. At any time during the manufacture of plasma products, plasma has been a strictly limiting raw material. It would not have been possible simply to discontinue use of apheresis plasma from paid donors. Certainly wouldn't be possible now.

Q. And why do you say that?
A. Well -- that it wouldn't be possible now?

Q. Why would it not have been possible in the past?
A. Because that would have immediately reduced by up to a half the amount of available Factor VIII at a time when there was already considerable pressure to bring about process changes for safety, virus inactivation that were also reducing the amount of available Factor VIII.

Q. But in terms of self-sufficiency, certain countries in Europe did achieve self-sufficiency and they managed, without the necessity of having -- close to managing, without the necessity of having concentrates imported from commercial donors?
A. Yes. You can achieve self-sufficiency in a number of ways: One of them is to make -- reduce the clinical freedoms; another is to make the continued availability of a domestic concentrate on a no-charge basis so attractive that by comparison, people simply choose not to or can't afford to purchase the commercial concentrates.

Q. You indicated this morning that the clinicians didn't allow a facility or facilitate self-sufficiency, is that correct?
A. Sorry, could you --

Q. You indicated this morning that the clinicians didn't allow or facilitate self-sufficiency. I might be paraphrasing what you said.
A. I think you probably are. I hope that what I said was that the clinicians simply didn't go down that route; they went down a route of choosing to prescribe concentrates other than the ones supplied by BPL.

Q. Then you subsequently said that the availability of concentrates, BPL concentrates, was dependent upon the plasma collection from the regional centres.
A. That's right.

Q. So therefore, the choice of the clinicians was somewhat limited?
A. Yes, indeed it was. And up to 1988, the constraints were one of two things: They were either the availability of plasma, or the capacity of the BPL plant to process that plasma.

Q. You subsequently did have the -- did have the capacity?
A. We then had the capacity.

Q. And that's a matter of minimising yield from plasma in those circumstances, where you have a plant that has the capacity and you have patients who require the product yield or collection?
A. Or satisfying demand. At the end of the day, a plant like BPL is an extremely expensive plant to run. The amount of plasma that the plant processes increases that

cost. It was never our practice to fractionate more plasma than was necessary to meet demand.

Q. But the organisational structure of BPL and PFL would be radically different to the structure associated with a voluntary blood bank that was endeavouring to fractionate its own products?
A. No, it was -- that's exactly what BPL was.

Q. But in terms of scale and size and economics, you had different considerations to a smaller-scale operation?
A. Oh, yes, but that was a decision that was taken and had to be funded.

Q. And in terms of -- I don't know whether you have heard the evidence of -- seen the evidence of Professor Leikola?
A. I have.

Q. The donor pools used in relation to the manufacture of the intermediate concentrates in 1984 were in the region of 800 people. How did the Finnish manage to manufacture a concentrate with such a limited number of people and donors as in comparison to your product? What were the different considerations that resulted in that particular situation?
A. I can't speak specifically for Finland.

Q. Okay.
A. But in those circumstances, first of all, the plant would be scaled for the amount of plasma that was available, which would presumably reflect the demand. They would have to accept lower yields; they would have to accept lower reduced cost-effectiveness of processing. It's an acknowledged fact within the industry that plants less than about 300 tonnes per annum are simply not cost-effective. And the Fins and others have acknowledged that by contracting out the fractionation of their plasma.

Q. But the situation that pertains in relation to the Finnish situation would be in the region of 800 to 900 donors, whereas the situation that pertains in the UK situation from BPL to PFL would be in the region of five to seven-and-a-half donors, depending upon the period?
A. Yes.

Q. So, the number of donors that you were required to use for manufacture of your products was dependent upon the requirements particular to the population that you had to address in respect of needs --
A. I wonder if we are at cross-purposes. The seven-and-a-half thousand in the case of BPL was the donor pool size.

Q. Yes.
A. That was the number of donations pooled in any one batch.

Q. Yes.
A. I presume that the 800 that you are quoting is similarly donor pool size.

Q. That's correct.

A. That doesn't relate to the number of donors making plasma available to either the Finnish blood service or the UK blood service.

Q. I accept that. But what I'm saying is that the methodology that is used in relation to the delivery of the quantity of product that is required at your plant is appropriate for a situation where you are meeting the needs of a very large scale -- large population?
A. That's right. And it's -- a country that is in such a position is fortunate. Countries with lesser population, lesser demand have to adapt either by contracting out the fractionation, buying in product or operating with very low cost-effectiveness in a smaller plant.

Q. So it's an entirely different perspective on life in terms of providing the same products?
A. Yes, it is.

Q. Okay. You mentioned this morning about the Scottish cohort that unfortunately became infected with HIV?
A. Yes.

Q. Was that widely known at the time in the haemophilia community?
A. I don't know. It was certainly discussed between BPL and PFL as fractionators, and it was discussed within haemophilia centre directors in the UK. I can't comment beyond that.

Q. In relation to the manufacture of Factor IX concentrates, is that a complicated process?
A. Yes.

Q. Is it a process that would be normally undertaken in a large blood bank with the appropriate facilities?
A. There is no reason why not. Complicated processes are capable of being reduced to steps that could be documented, and the effectiveness of which can be challenged.

Q. In the United Kingdom, besides BPL and PFL, are there any other institutions that manufacture Factor IX?
A. Absolutely not.

Q. In terms of the rest of Europe, besides organisations of a similar size to BPL and PFL, are there any other institutions that manufacture Factor IX?
A. Yes. Let me just qualify what you have just said: First of all, BPL and PFC are very different in size. BPL processes about 500 tonnes; PFC in Edinburgh about 100 tonnes. The other fractionators in Europe -- in Germany made Factor IX concentrates; the Netherlands, Red Cross, a smaller organisation, certainly, than BPL, made Factor IX concentrates; the -- at least the Finnish Red Cross and the Danish State Serum Institute made Factor IX concentrates. So, yes, there were other fractionate -- smaller fractionators making the product.

Q. You are familiar with the Blood Transfusion Service Board and you have mentioned those particular other institutions. Would both have similar resources available in terms of support scientific, personnel available to them?
A. My perception was not.

Q. So therefore, the Blood Transfusion Service Board would be unique in terms of manufacturing Factor IX?
A. I don't know if it would be unique, but certainly it was, from my perception, not as well resourced as others fractionating similar products.

Q. In terms of when one wishes to change a heat treatment protocol for a product, does that result in the necessity for major changes in processes or changes in requirements for licensing, or what is the impact in that situation?
A. Then we have to put it in a time frame.

Q. In the period 1985 to 1987.
A. In the period 1985 to 1987, the approaches would have been one of measured pragmatism - evaluate the impact of the particular regime on the product at hand, undertake such laboratory evaluation as was possible, undertake such testing, possibly including some animal test. If the product responded to the heat treatment regime, then, for example, as with the BPL 9D product, we found we had to make very little changes. The addition of antithrombin was a change, but not as complicated a change as it might have been. So it really does depend on the product and how it responds.

Q. Talking about measured pragmatism, does measured pragmatism includes assessment of inhibitor levels?
A. Not for Factor IX.

Q. Factor VIII?
A. Measurement of --

Q. Assay studies.
A. Assay studies would be done to determine whether proteins were being generated that might stimulate formation of inhibitors. The only way of actually determining in reality whether -- is clinical trial and post-surveillance.

Q. I was interested to note this morning that you indicated in relation to assessment of the heat-treated product before it went on the market, that there was no assessment done in respect of HTLV-III kill; there was no assessment in relation to log kill. Would there be normally viral studies or log kill quantums done prior to release of a product on the market?
A. In 1985, no; in 2000 and 2001, yes.

Q. So your evidence to this Tribunal is that it would be unusual for log kill to -- assessments to be undertaken in respect of the heat treatment process for a product being released on to the markets for use by people with haemophilia?
A. In 1985, yes.

Q. And would you be familiar with the work of people like Dr. Alfred Prince, Dr. McDougal?

A. Yes.

Q. Dr. Tedder?
A. Yes.

Q. At that time?
A. I'm not aware of those. I'm familiar with Prince's work on virus inactivation, but not in the context of HTLV-III.

Q. Would you have been aware that CDC in late 1984 would have done -- undertaken an assessment of the commercial products available on the market in the United States in respect of log kill?
A. You are not talking about a manufacturer's evaluation of a product there. What you are talking about is a national institution undertaking an evaluation of a range of products that are being presented for supply into the US market. BPL, and I can only speak for BPL, did not have access to those resources in 1985.

Q. So, if you had of had access to those resources in 1985, it would have been a test that you might have considered undertaking if you changed your heat treatment process?
A. Oh, it's possible with hindsight, you know, if you turn the clock back like that, to do lots of things, yeah.

Q. Would you consider that in terms of safety, and considering the evolution of knowledge at that time, that it would have been a preferable option in terms of safety?
A. How could it be preferable when what BPL did was make available to the marketplace, in the shortest time possible, a product that remains the most effective terminally-heated product to this day? I mean, what you are saying is that, yes, had we had the resources, we would almost certainly have delayed release in order to make that product available.

Q. So in essence -- I want to paraphrase, to some extent. In essence what you saying, you use the maximum heat treatment process in order to achieve the maximum amount of safety?
A. That's right.

Q. And therefore, that obviated the necessity for checking the log kill in respect of HTLV-III viruses?
A. It didn't obviate the necessity. I mean, it was simply not an option that we believed we had at the time.

Q. But if you weren't using the maximum heat treatment process of 80 degrees Centigrade, then in such circumstances would it be preferable to assess the log kill in respect of such a product?
A. When I talked about the maximum heat treatment process, I was talking about the maximum heat treatment process for our product. It's possible that another organisation would find a different set of conditions obtained for their products. Whether or not they would have access to resources for testing is a separate issue.

Q. Would it be normal to vary heat treatment processes in respect of one particular product?
A. Within an organisation?

Q. Within an organisation, within a short time span.
A. Well, we did, because we found that we -- progressively, we found, for example, that we were able to heat-treat the new product more rigorously than the inventory of product that we had on the shelf. For two different products, I think one would still choose -- under those circumstances, one would still have chosen the most rigorous heat treatment cycle consistent with retaining the product characteristics.

Q. When you say you varied the heat treatment process, do you release products with two heat treatment processes; one in respect of a product that had already been manufactured?
A. Yes.

Q. And that was a particular instance. And in relation to newly-manufactured products, you only ever used one heat treatment process?
A. This is true, because that's what they would tolerate.

Q. Therefore you didn't require to vary it. Okay. In terms of -- you mention in your statement about the heat treatment process of 60 degrees for 144 hours?
A. That's correct.

Q. And that in relation to Factor IX or -- do you know whether any assessments were done in respect of the elimination of non-A non-B, in respect of ALT testing, in respect of such a method of heat treatment?
A. I don't know whether any assessment was undertaken. It presumably wouldn't have been ALT testing if it had been.

Q. But surely in 1986 in terms of assessing the effect of non-A non-B Hepatitis, the only manner in which it can be done in respect of a recipient was to look for abnormal ALT levels?
A. My apologies. I misunderstood you. I thought you were talking about a test applied to the product.

MR. BRADLEY: Thank you very much, Dr. Snape.

THE CHAIRPERSON: Mr. McGovern, please.

THE WITNESS WAS THEN EXAMINED AS FOLLOWS BY MR. McGOVERN:

Q. MR. McGOVERN: Dr. Snape, my name is Brian McGovern and I have just a just questions for you. I act on behalf Professor Temperley and Dr. Helena Daly and Dr. Jackson, who are haematologists. The first matter I want to ask you about is just in relation to the relationship between the BPL and the treating clinicians in the UK. As I understand your evidence, the position seems to be that you were relying on the clinicians or treating doctors to clinically assess products which you were supplying, is that right?
A. That's correct.

Q. And you were getting feedback from them on any benefits and/or problems they might be having?
A. That's correct.

Q. And to that extent it was a symbiotic relationship and it was helpful for you obviously to know what the treating clinicians thought of a product and what problems they may have with it?
A. That was always the way BPL worked, yes.

Q. And would it be fair to say that that was the extent of it, the relationship between the BPL and the treating clinicians?
A. It was slightly different for Factor VIII and Factor IX. For Factor VIII because the product was distributed remotely via the transfusion services, our relationship was a little more distant. For Factor IX, the distribution was directly from BPL to the physician, and in fact the physician had to make application to BPL for supply of product on a named patient basis for Factor IX. Over and above that, though, the only other relationship with BPL was that BPL at that time had a standing invitation to the annual meetings of haemophilia centre directors in the UK and BPL. Also made input to several of the haemophilia centre directors' working parties: The Hepatitis Working Party, the Inhibitor Working Party.

Q. Yes. Now, can I ask you about the period 1986 to 1990: Can you recall if BPL were asked by any blood transfusion service or treating doctor outside the UK to supply small quantities or any quantities of Factor IX concentrate?
A. To the best of my recollection, not Factor IX. We were asked to supply and did supply Factor VII, Factor XIII, Factor XI.

Q. Yes.
A. But I have no recollection of supplying Factor IX outside the UK.

Q. And you have no recollection of ever being asked by any blood transfusion organisation or treating doctor outside the UK for Factor IX?
A. To the best of my recollection, no.

Q. I see. Just the -- the other matter I want to ask you about relates to paragraph 23 of your statement, Dr. Snape. In the course of that, you say that "it was always important to strike a balance between process yield to meet the demand for concentrates and expectations of reduced risk of virus transmission." What did you mean by that?
A. I meant that certainly in the supply of fractionated plasma products, it's always been necessary to recognise that pursuing the ultimate in product safety, product characteristics, wasn't necessarily consistent with the best interests of patients. And that in particular, where a process will reduce the yield, that -- to put it crudely: There is no point having the ultimate process in terms of a safe product but no product to supply.

Q. I see.

MR. McGOVERN: Thank you very much, Dr. Snape.

THE CHAIRPERSON: Thank you, Mr. McGovern. Mr. O'Brolchain.

MR. O'BROLCHAIN: I have no further questions, Madam Chairperson.

THE CHAIRPERSON: Mr. Murphy, any questions?

MR. MURPHY: No questions.

THE CHAIRPERSON: Mr. McGrath?

MR. McGRATH: Just one or two very short matters.

THE WITNESS WAS THEN EXAMINED AS FOLLOWS BY MR. McGRATH:

Q. Dr. Snape, in relation to the question I think you were asked by Mr. Bradley concerning the protocol which was referred to at paragraph -- or at page 16, paragraph 53 of your statement, which was I think 60 degrees for 144 hours, and I think Mr. Finlay touched on this this morning also, do you have any comment to make in relation to the lengthier period; in other words, the 144 hours or indeed the 152 hours, do you have any comment to make in relation to the lengthier period in respect of the effectiveness of the lengths in heat treatment?
A. Only to say that it would follow almost inevitably that a longer heat treatment period would achieve greater virus kill.

Q. Now, again, just dealing with the viral inactivation by solvent/detergent technology. I think that you clearly would have been familiar with the introduction of that technology in America and its introduction to Europe in the early -- in fact, I think in the late 1980s /early 1990?
A. Indeed.

Q. Now, are you aware of when solvent/detergent was introduced in Ireland?
A. I'm not.

Q. Right. Well, if I was to tell you that it was in early 1990, how would you -- how would you -- or would you have any comment to make in relation to the consistency of the introduction of solvent/detergent treatment here with other countries in Europe at that time?
A. I compare it immediately with our own use in the UK, which was in the middle of 1990. So in that sense, it seems quite timely.

Q. Yes. Now, again, in relation to the - just going back slightly to the heat treatment that was applied by your good selves, that 80 degrees for 72 hours, and I think that you spoke to Mr. Finlay this morning about difficulties that might be encountered by other bodies in terms of applying that particular heat treatment protocol. I'm just wondering do you have any comments to make to the state of knowledge you would have had of the BTSB, whether it would have been --

MR. FINLAY: I think that is going beyond what Dr. Snape --

THE CHAIRPERSON: We have had this last week as well. Really, what Dr. Snape is giving is his expertise about his country and his state of knowledge pertaining to that. We have had evidence in relation to what the BTSB did and I can draw my own conclusions on the evidence.

MR. McGRATH: Very well, Madam Chairperson.

THE CHAIRPERSON: Thank you.

MR. McGRATH: Thanks, Dr. Snape. Thank you.

THE CHAIRPERSON: Mr. Finlay?

THE WITNESS WAS FURTHER EXAMINED BY MR. FINLAY AS FOLLOWS:

Q. Yes, just really two things: First of all, Mr. Bradley asked you about the introduction of a superheat-treatment process in, I think, Australia and South Africa. And I'm wondering two things: First of all, when did that take place in either of the countries; I mean approximately, if you know, Dr. Snape?
A. I was hoping you weren't going to ask that. I was hoping nobody would ask that. I can't remember.

Q. All right. And secondly, just the scale of the plant which would have been involved in either country, would you be aware of that?
A. Okay, the South African plant was very much smaller. I think they were processing typically around 100 tonnes, 150 tonnes.

Q. Yes.
A. The Commonwealth Serum Laboratories in Melbourne is a very different organisation, processing around 350, 400 tonnes per annum, and a very technologically, scientifically-aware organisation.

Q. Yes. And just one other thing, Dr. Snape: When you said to us, commenting generally on heat treatment for 144 or 150 hours, that the longer you treat, the longer period, the greater the virus inactivation?
A. Mm-mm.

Q. We had evidence I think from Dr. Prince to the effect that that progression is not a simple matter; in other words, as time goes on, you get less result?
A. There would inevitably be a diminishing returns situation.

Q. Yes.
A. I think it would be impossible to predict when that would start to prevail.

Q. I see. But you would agree it's not a simple thing, that the longer it goes the better the viral inactivation; that the process, as you say, diminishes over time?
A. I'd agree with that, but if I were presented with two processes --

Q. Yes.

A. -- with the same temperature and a short time and a long time, and if the product would tolerate the longer time, I would use the longer time.

Q. Very good.

MR. FINLAY: Thank you very much?

THE CHAIRPERSON: Thank you, Mr. Finlay. Thank you, Dr. Snape.

THE WITNESS THEN WITHDREW.

THE CHAIRPERSON: We will resume tomorrow at 10:30.

THE TRIBUNAL THEN ADJOURNED TO WEDNESDAY, 11TH OF JULY, 2001, AT 10:30 A.M..