Thursday, 30 September 2021

(10.00 am)

Presentation by Counsel to the Inquiry on the Pharmaceutical Companies (continued)

MS RICHARDS: Sir, yesterday I outlined the corporate structure, as we understand it to be, and the relationships between Bayer, Cutter and Miles. Most of the documents that we're going to look at will refer to Cutter rather than Bayer but, from time to time, we'll see Bayer documents.

In terms of the issues that we're going to look at today, I'm going to start looking at material relating to the licensing history for the factor concentrates manufactured by Cutter in the US, but the licensing history in the UK, in relation to Koate, in its various incarnations, which was the Factor VIII concentrate, and Konyne, which was the Factor IX concentrate.

It's right to note that Cutter also manufactured other products, including Gaminune, an immune globulin, there is quite a lot of interesting material relating to that but I'm not going to have time to touch on that or, still less, do it justice today, so it may be that that's something we can deal with by way of a written note in due course.

Having looked at the licensing history, I'm going to then look at some material which relates to the market share in the UK for the product and product usage in the UK of the Cutter manufactured concentrates. I'll then turn to look at issues relating to donor pools, plasma supply -- and there are some particularly interesting documents in relation to prison plasma as regards Cutter -- and donor screening and selection.

Again, that wouldn't be a comprehensive narrative because we're going to come back to a number of those issues in early November.

Then, lastly, I'll look at the data sheets, product labels and package inserts. Again, we don't have a complete picture but we can get a sense of how, in broad terms, warnings were expressed over the years, or indeed were not expressed.

As I hope will have been clear, both from what Mr Hill said last week and what I said before we started with Armour on Tuesday, this is not intended to be a comprehensive, still less an exhaustive, account of the activities of the pharmaceutical companies. The aim is to give an overview and to draw out some of the most interesting issues and some of the most interesting documents. Obviously, we're

coming back to knowledge of risk and response to risk of infection in November but, in the meantime, if there are documents or issues which Core Participants or the recognised legal representatives identify that we haven't referred to, we very much hope they'll flag them up to us so that we can incorporate them either in November or by way of a further written note in due course.

So against that background, I'll start, then -- against that introduction, I'll start by looking at some material relating to the licensing history, beginning with Koate, the Factor VIII concentrate. We don't have a complete set of licensing documents in relation to Koate, and we have a partial picture. But it's enough to tell us, I think, the basics. If we begin by looking at BAYP000001_098, please, Soumik -- sorry, BAYP0000001_098, my apologies.

So we can see this is a file containing supplementary particulars in support of the product licence application for Koate, and this is an application submitted in October 1975. If we go over the page and look at the index, we'll see the range of information that was submitted. So there are supplementary particulars, and then a number of attachments including the proposed package insert, and

then a second file, which I'm not going to be looking at, contains what's said to be scientific evidence, chemistry and pharmacy.

Then if we go to the next page, a third file with reports of clinical trials and studies.

So that's the kind of material that would be submitted in the 1970s in support of a product licence application.

If we go to the next page, please, just look at the basics of the application, we can see the product for which the licence was sought was anti-haemophilic factor Koate, and, at this point in time, the application was made by Bayer UK Limited. As we'll see, it was in due course, in fact, held by Speywood Limited for a period of time.

If we go to the bottom of the page we'll see the date of the application, 16 October 1975, then if we go to the next page we've got a description of the product and how it was supplied. We can see reference there to attached package inserts in relation to "Contra-indications, Precautions and Warnings".

"Method of retail sale or supply" is described as being "By direct government contract and private sale", and then we can see the manufacturers who were Cutter Laboratories Inc in California.

Then if we go to page 7, please. We'll see the information that was provided by the applicant included copies of labels, and then reference was made to applications in other countries, Koate has been passed by the FDA for marketing in the USA.

If we go to the next page -- sorry two pages further on, we can see here what was intended to be the draft package insert and you'll see the heading above "Description", "See sections entitled 'Indications' and 'Warning' for description of hepatitis risk".

If we go over the page, there's number of matters set out but, if we go towards the bottom of the page, the section in capitals above the heading "Action" reads:

"This product is prepared from units of human plasma which have been tested and found non-reactive for Hepatitis Associated (Australia) Antigen. Unfortunately this test does not with certainty preclude the presence of hepatitis virus. See warning."

If we go to the next page, under the heading "Indications", in the second paragraph, we have again in capitals, the word "CAUTION":

"Because of the possibility that any lot of Koate

might contain the causative agents of viral hepatitis, its use must be considered in light of this hazard, particularly in persons with few previous transfusions of blood and plasma products."

Then if we look at the next paragraph, it reads:

"Kasper and Kipnis have concluded that those who had little exposure to blood products had a high risk of developing hepatitis after introduction of clotting factor concentrates, such as this product. For those patients, especially those with mild haemophilia, they recommend single donor products. However, for patients with moderate or severe haemophilia who have received numerous infusions of blood and plasma products, they feel that the risk of hepatitis is small. They believe that the clotting factor concentrates have so greatly improved the management of severe haemophilia that these products should not be denied to appropriate patients."

Pausing there, this in contrast, I think, with what we've seen in relation to some of the other package inserts or leaflets, essentially contains a degree of guidance, addressed, I think, clearly to the clinician rather than to the patient, about the cohorts of patients for whom the product might or might not be appropriate.

Then if we go to the heading "Warning", it says:

"Koate concentrate is purified dried fraction of pooled plasma obtained from many donors. *SINCE THE PRESENCE OR ABSENCE OF HEPATITIS VIRUS IN KOATE CONCENTRATE CANNOT BE PROVEN WITH ABSOLUTE CERTAINTY, THE PRESENCE OF SUCH A VIRUS SHOULD BE ASSUMED* and the hazard of administering Koate concentrate should be weighed against the medical consequences of withholding it."

So, again, it could be said there's a direction to the clinician, or advice to the clinician, and then the last paragraph:

"Since there is this definite risk of hepatitis, we suggest that the physician give consideration to explaining to the patient (or the patient's family) the relative risks of giving or withholding this product. Then, should the patient develop hepatitis, as a result of the injection, it will not come as a surprise, and there is not nearly the likelihood of resentment, which will almost surely follow an unexplained and unexpected infection."

Then, in relation to this same document, if we go to page 16, we can see the heading "Warranty" and, in the second paragraph, you'll see there's an italicised section. I'll just read the sentences before that to

put them in context:

"A number of factors beyond our control could reduce the efficacy of this product or even result in an ill effect following its use. These include storage and handling of the product after it leaves our hands, diagnosis, dosage, method of administration, and biologic differences in individual patients. Because of these factors, *it is important that this product be stored properly and that the directions be followed carefully during use* ..."

Then this:

"... *and that the risk of transmitting hepatitis be carefully weighed before the product is prescribed*."

That's some of the material from the product licence application.

If we look next at MHRA0009277, we can see here some comments. There's a date, top right-hand corner, 3 November 1975. Reference is made to the manufacturer, Cutter Labs Inc, in California, and then we have a description of the product, Koate.

If we go down further, it's fairly faint but it looks as though there's a box identifying which committee should look at this, biological or -- I'm not entirely sure what those faded words say, but

I don't think it matters.

Then we can see the comment which suggests consideration by the medical assessor, Dr Andrews.

"It was agreed that after scrutiny by Dr Andrews, this application might be suitable for processing through the Licensing Authority. Should the application require to go to the Committees, it was noted that further copies would be required."

Then there's a note:

"9 Further copies required.

"Requested 10.11.75."

It's not entirely clear what that means. It seems there might have been a suggestion that it wouldn't need to be looked at by the Committee, but the request for further copies suggests that the intention then was that it would be looked at by the Committee.

In any event, we can pick up what subsequently happens starting at BAYP0000022_97. We've got it. Thank you.

This is dated 24 December 1975. It is, I think, an internal note, so internal to Bayer, but it's recording a telephone conversation with Dr Andrews of the DHSS:

"The product licence application for Koate appears to be 'going through the machinery' at the Ministry

and is being looked at by Dr Andrews on the medical side and Mrs Pratt on the chemistry and pharmacy side. During the course of conversation, Dr Andrews mentioned that the Minister is personally vetting all submissions on Factor VIII because there is a lot of publicity and emotional feeling about it at the moment."

Pausing there, this, of course, is the month in which the World in Action documentary had been broadcast, and we saw from the documents we looked at in relation to the Armour application, which was being considered at around the same time, the direct involvement of the Minister of Health, who was Dr David Owen at the time.

Then continuing with this:

"Apparently the price of our product will be important and will probably affect the success of our application. Dr Andrews suggested that as soon as we are granted a licence we resubmit a tender to the supplies division of the DHSS. He mentioned that the Cutter product 'looked good' because each plasma donation is tested by RIA for hepatitis and there have been no reported cases of hepatitis since it has been introduced into the USA.

"All being well, the submission will go before the

Biological Sub-Committee on 9 January 1976."

SIR BRIAN LANGSTAFF: The Kasper and Kipnis report, to which reference is made earlier, that -- I'd like to know whether that just deals with hepatitis B or with both B and non-A, non-B. I think it may do the latter, from memory, but this is working from memory.

MS RICHARDS: I'm just checking the date. I don't have a copy of the report and I don't think it's one I've read, so I'd need to do that, but it's a 1972 publication.

SIR BRIAN LANGSTAFF: Ah.

MS RICHARDS: I suspect it may be dealing with hepatitis B only, given the date. It's a publication, and I'm looking at the footnotes in the -- reference footnotes in the licensing application. To Kasper and Kipnis, it's hepatitis and clotting factor concentrates, it's published in JAMA221 --

SIR BRIAN LANGSTAFF: Yes, the reference is ARCH0002893_003, for those who want to find it.

MS RICHARDS: Thank you. And in any event it's -- the date is given as 1972, so I would anticipate hepatitis B as the subject matter of it, but we'll read and check that, sir.

SIR BRIAN LANGSTAFF: That was one in which they said in that article that for older children and adults who

had had a little exposure to blood products, especially those with mild haemophilia, single donor products were preferable. And I think that's partly reflected in the application.

MS RICHARDS: Yes. Yes, it sounds as though it is a not unfair account that is given in the application, but we will double check that.

Returning to the document onscreen, obviously it's the Bayer individual's account of the telephone conversation, and we don't know what Dr Andrews would say in relation to it. The interest of the minister is consistent with what we saw in relation to the Armour material. The suggestion that price will be important and will probably affect the success of the application is perhaps somewhat surprising, and concerning, in relation to the role of the Licensing Authority and the factors we would have expected them to be considering, as opposed to the kind of factors the Supplies Division of the Department might consider where price then might become an issue. But in any event it is what it is.

SIR BRIAN LANGSTAFF: It's -- what you showed me earlier or what I was shown earlier in the week or last week on the 1968 Act was that of the three main criteria, cost is not one of them. But they're not the only

criteria.

MS RICHARDS: They're not, no.

SIR BRIAN LANGSTAFF: So it was open, I suppose, to the Committee to consider cost, but it's not a primary consideration.

MS RICHARDS: No. And certainly not when one considers matters of relative weight. One would expect that for the Committee, issues such as safety and efficacy would be the kind of considerations that would carry the greatest weight or should carry the greatest weight.

If we then turn to MHRA -- no, sorry, can we go, first of all, to BAYP0000020_007. This is another internal note, the date is 7 January 1976. You just need to look at the first paragraph, which is headed "Koate":

"A Product Licence application was made in October 1975 and it is expected to go before the Biological Sub-Committee of the CSM this week. The Ministry have suggested that as soon as the Licence is granted we resubmit a tender to the Supplies Division of the DHSS. They say that the Cutter product 'looks good' because each plasma donation is tested for hepatitis and there have been no reported cases of hepatitis since its introduction in the USA."

Now whether that's just a regurgitation of the previous conversation or reflects some further dialogue is not clear from the material.

Then if we go to the documents we have relating to the Sub-Committee's consideration, it's at MHRA0009305. We can see here the date is January 1976, Sub-Committee on Biologicals, and we can see here the recommendation:

"On the evidence before them the Sub-Committee recommend the grant of a product licence for this preparation for the purposes indicated in the application on condition that ..."

Then there are number of conditions. The first is that:

"1) Satisfactory information is provided on

"a) the number of donations in each pool;

"b) the method of assay, the standard used and its calibration;

"c) batch to batch reproducibility."

Now, for our purposes, obviously, it's information about number of donations in each pool that is significant. I mention the reference to assay, the standard use and its calibration because there was then quite a lot of correspondence about those issues. I'm not going to go through all of that.

Then if we go further down, we can see (2) was about product labelling, (3) expiry date, and then (4):

"On-going information is provided on the reasons for, and the rate of, rejection of donors or donations, centre by centre."

So those are similar conditions to the conditions we saw in relation to the Armour application of Factor VIII.

And then (5) is:

"The applicant shall agree to the imposition of the batch release procedure ..."

And then we see the deliberation of the Main Committee:

"Advice

"On the evidence before them the Committee advise the grant of a product licence for this preparation for the purposes indicated in the application on condition that ..."

And we can see the same conditions. So the Committee effectively endorses the recommendation of the Sub-Committee on Biologicals. So we've got:

"Satisfactory information ... on

"a) ... number of donations in each pool ..."

And over the page, (4) is:

"On-going information is provided on the reasons for, and the rate of, rejection of donors or donations, centre by centre."

Then if we just look at the last two paragraphs on that page:

"It was decided that if the applicant did not agree to these conditions, a letter should be sent by the Secretary in accordance with Section 21(1) of the Medicines Act."

Then this:

"The Committee also advise that this product should be indicated as 'recently introduced' and should be the subject of a special directive for the reporting of adverse reactions."

It's not possible to tell from the recommendations themselves precisely what prompted that.

We've then got, on the next page, the assessor's report that presumably went before the Sub-Committee and the Committee. It's authored by Dr Andrews and dated 17 December 1975. That's on page 9 but we'll get to that in due course.

We saw a very similar report in relation to Armour's Factorate application, so we can see it begins with a summary of the application. We don't need to look any further at that.

If we go over the page, we can see, at paragraph 3.3, under the heading "Precaution and contra-indications", Dr Andrews report notes this:

"The company literature includes the usual warning about the presence of hepatitis B virus [so that's how he understands it, hepatitis B] and recommends restricting its use to Factor VIII deficiency only."

Then if we go to "Manufacture", we see the manufacturer identified as Cutter Laboratories Inc. And then there is a section on source material which I think is worth reading in full:

"Each plasma donation is currently tested by radioimmunoassay (RIA) for hepatitis B antigen according to the mandatory FDA requirement as of 15.9.75. No reports have been received attributing hepatitis to Koate since its introduction in February 1974."

Then this on source material:

"The raw material is supplied by no less than 54 different firms, which are classified in the submission according to whether the firm is owned and operated by others or Cutter owned, whether the plasma is collected by plasmapheresis or obtained from whole blood or whether the apparatus used is owned by Cutter or the firm concerned. The list includes a number of

American State Prisons."

So that fact was clearly known to the Licensing Authority at the point in time at which it considered the licence application in late 1975, early 1976. Then we are told:

"The following criteria are established according to the 'Cutter system of plasmapheresis' on file with BOB."

I think that says, which is presumably the Bureau of Biologics, or might be that.

"1. Suitability of the donor.

"2. Immunisation."

Top of the next page:

"Donor follow-up."

Then if we turn to page 8, we can pick it up -- sorry, if we go to page 7 just so we can see what sections we're dealing with.

So section 7 is headed "Evidence of Efficacy", then 7.5, "Summary of cumulative clinical experience". Again, this is Dr Andrews' summary of the application material.

If we go over the page, paragraph 8:

"Only two side effects were reported during the clinical evaluation of Koate."

Then those are then described.

Picking it up a few lines later:

"No cases of serum hepatitis were reported following treatment with Koate. In addition, no reports have been received attributing hepatitis to Koate since its introduction in the USA in February 1974. However, attached is a copy of a letter from Kasper and Kipnis ..."

Then we've got the reference in the American Journal.

"... regarding hepatitis and clotting factor concentrates, such as this product. It is one of the references used in the package insert."

If we go down towards the bottom of the page, paragraph 14:

"In conclusion, Koate has been demonstrated to be a safe and efficacious preparation for treating or preventing bleeding in haemophilic patients with factor VIII deficiency."

Then we get the "Medical Comment", so this is presumably Dr Andrews' comment:

"This Factor VIII preparation would appear to have been adequately appeared and to be efficacious in clinical usage. It suffers from being prepared from multi-centre donations which cannot be properly controlled by inspection. Nevertheless each

individual donation is said to be tested by radioimmunoassay and that the control of the blood donations is in accordance with the latest FDA regulations, copies of which are not included in the submission. The information set out is superior to that originally offered by Travenol but in fairness it is believed that Travenol have improved their method of manufacture in accordance with the new FDA regulations."

So Dr Andrews is there drawing attention, presumably because it is regarded as significant, to the fact that this is plasma derived from multi-centre donations, and it is presumably his own comment that those cannot be properly controlled by inspection.

He then continues:

"In the past the Committee have recommended that the following conditions are accepted ..."

We can see (1) is -- relates to the donations. So:

"Information is provided on:

"(a) The number of donations from which plasma is pooled for the manufacture of the product.

"(b) The reasons for, and rate of, rejection of donors or donations, centre by centre."

Then various other recommendations as to

conditions.

Then the "Recommendation" at 9:

"Subject to quality control being considered satisfactory and to confining the expiry date to storage at 5ºC the Committee might feel that a Product Licence could be granted."

And the date is 17 December 1975.

SIR BRIAN LANGSTAFF: Just going back to the top of that page, just as a matter of curiosity, possibly for later examination when we come to dealing with some of the blood services evidence more directly, is it to be inferred from what it says about the latest FDA regulations, that copies are not included in the submission, that the author did not know what those recommendations actually were? But he goes on to say:

"... in fairness it is believed that Travenol have improved their method of manufacture in accordance with the new FDA regulations."

Which is slightly odd if, indeed, there isn't a copy for him to check against. Why else mention that there's a copy missing?

MS RICHARDS: Yes. It's -- the most natural inference, I would suggest, is the inference you suggest, sir. And we can see, and it could -- is there a note of skepticism, one might ask, in the language:

"... each individual donation is said to be tested ..."

SIR BRIAN LANGSTAFF: Yes.

MS RICHARDS: "... by radioimmunoassay ..."

It's difficult. We obviously can't ask Dr Andrews and we don't have anything further which helps us unpick what was known to him or, indeed, to others within the Licensing Authority at the time.

SIR BRIAN LANGSTAFF: It would seem very odd if the FDA has issued regulations in this area and they weren't copied at least to the DHSS or they didn't have a copy, but it looks as though their medical assessor might not have had.

MS RICHARDS: It does look as though that's the case. We can obviously investigate what other material we have from the Licensing Authorities and the Department, from the MHRA --

SIR BRIAN LANGSTAFF: Yes.

MS RICHARDS: -- which might cast some light more generally on their state of --

SIR BRIAN LANGSTAFF: As I say, it's really a matter for later on.

MS RICHARDS: So that was the medical assessor's recommendation. We've seen what the Sub-Committee and the Committee decided. If we then pick the matter up

early in the following month at BAYP0000001_110, this is a letter dated 2 February 1976. It's from Dr Andrews, who is described there as Senior Medical Officer, and it's to the registration officer at Bayer UK. It relates to the product licence application. We can see that from the heading:

"You will be pleased to hear that the above licence application has now been considered and that the grant of a product licence has been advised for the purposes indicated in the application on condition that ..."

Then we can see the letter sets out the conditions that were identified by the Sub-Committee on Biologics and endorsed by the Committee on Safety of Medicines.

So, for our purposes, the relevant subparagraphs are 1(a), satisfactory information on number of donations in each pool -- it might beg the question what's meant by "satisfactory", the letter doesn't tell us, nor does the recommendation -- then paragraph 4:

"On-going information is provided on the reasons for, and the rate of, rejection of donors or donations, centre by centre."

So not just information, such as we saw in response to the similar recommendation in the Armour

application, where there was, as far as we could see, a one-off response, and nothing further. This seems to suggest there's an expectation of information being submitted on an ongoing basis.

There is then, if we go to BAYP0000020_008, a letter. It's from Mrs Boult, who was to the registration officer with Bayer in the UK, to Cutter Laboratories in California. It's dated 6 February 1976, and it says:

"Following my telex of to-day, I am sending you a copy of the letter from the DHSS, which I refer to in that telex, together with the comments on it."

So she is presumably sending the letter we've just looked at. We don't, I think, have, or at least I have not seen, what's said to be her comments on that. Again, I don't think that matters for present purposes.

She continues:

"The number of donations in each pool need only be given approximately, but they would like to have some idea of the size of it."

Then she goes on to set out what's required in relation to some of the other conditions, in particular the assay method and the standard used, and I draw attention to that simply because that becomes

the subject of some prolonged correspondence.

Then the next paragraph is about labelling. Then if we go to the third paragraph.

"Point 4 of the letter means that the future [I think that's probably 'in the future'], they will require records on this information from the Plasma Collection Centres. However, Dr Andrews mentioned to me on the telephone that if this information is provided on the Protocols which will be looked at by the NIB (National Institute for Biological Standards and Control), for each batch of the product which we propose to sell in the UK, this should be sufficient information."

SIR BRIAN LANGSTAFF: Does this suggest a process post-licensing of the control of distribution of a product in which the NIBSC take a look at what information has been given on pool size and decide whether it is, by whatever criteria, satisfactory?

MS RICHARDS: Well, I think in relation to "satisfactory", that is the adjective used at paragraph 1(a) of the DHSS letter --

SIR BRIAN LANGSTAFF: Yes.

MS RICHARDS: -- "number of donations in each pool" and that's what's being dealt with in the first paragraph.

SIR BRIAN LANGSTAFF: But it's "each pool", which means

referring to all the information that's been mentioned.

MS RICHARDS: I don't think so because I think the reference to point 4 -- if we go back to BAYP0000001_110, so paragraph 1(a) is satisfactory information about number of donations in each pool, then we've got other matters set out, and then point 4 is ongoing information on the reasons for, and rate of, rejection of donors or donations, centre by centre.

SIR BRIAN LANGSTAFF: So there's two bits of ongoing information, one is each pool, because the word is "each", and "ongoing information" identifies ongoing information as to the performance of each centre.

MS RICHARDS: Yes. I mean, certainly "ongoing" is clear from the language used in 4. I take your point, sir, in relation to point 1 that, if you're talking about each pool, the natural expectation by the use of the word "each", because that's not going to be static, is that it is provided on an ongoing basis. That doesn't appear to be then how it was understood or applied because, if we go back to Mrs Boult's letter to Cutter Laboratories in the States, BAYP0000020_008, her understanding in the first paragraph, in relation to pool size in line 3:

pool by pool.

MS RICHARDS: Yes.

SIR BRIAN LANGSTAFF: So which means that every batch made from a different pool presumably is going to go to the NIBSC, if that's why -- where records go, and what then happens? Assume for a moment, without in any sense knowing, that, in the minds of those who are medical assessors, they put a limit of 10,000 donations to a pool, let's say. Beyond that, it's unreasonably unsafe, or something along those lines. What do they do about it?

MS RICHARDS: I don't know the answer to that, sir. It's a pertinent question to pose. We do hope to have, in due course, some witness evidence from or in relation to NIBSC. So it may be that, not necessarily by reference to this specific application but more generally, they can provide some information in relation to that.

I should just say that the reference in the third paragraph of this letter to "information being provided to Protocols that will be looked at by [NIBSC]" is in relation to point 4 of the letter, and that's not pool sizes; that's rejection of donors and donations.

SIR BRIAN LANGSTAFF: This information? I'd read that as

"The number of donations in each pool [again, we see the word 'each'] need only be given approximately, but they would like to have some idea of the size of it."

Well, it's a little unclear, I think, what was understood in relation to that. It's clear there's been some form of telephone discussion between Dr Andrews and Mrs Boult, because she refers to that in the third paragraph of this letter. But we don't have any records of that.

If we go over the page, we can see point 5 was about the batch release procedure, and then she asks Cutter Laboratories in the States:

"[We will] be pleased if you could send us your answer and comments to the five points raised in the letter as soon as possible so that there will be as little delay as necessary in us being granted a Product Licence."

That's the internal communication. There's a response then, and we don't, I'm afraid, have all the documents but there's a response in relation to some of this information at BAYP0000020_014. So this Cutter Laboratories Inc memorandum, so it's an internal communication, dated 23 February 1976, concerning Koate registration in the UK:

"The following is in response to Mrs Boult's telex of February 18, 1976."

So there's clearly been some further communications in the intervening period:

"Her requests are restated followed by our answers.

"1. Can you confirm that on-going information will be provided on the reasons for, and the rate of, rejection of donors or donations, centre by centre."

Then this is the response internally:

"We do not collect information of this nature. Such information would be of dubious value in evaluating a plasma derivative product's safety or efficacy. In the manufacture of Koate, all Source Plasma (Human) used as the starting material is collected and handled according to regulations described in Title 21 of the US Code of Federal Regulations. Similarly, all plasmapheresis donors must be acceptable according to the criteria described in these regulations. All plasmapheresis centers from which our source material is obtained are licensed by the US FDA. Thus, the FDA insures that all donors and units of Source Plasma (Human) are handled according to the relations. Copies of the specific US regulations covering Source Plasma (Human) and

plasmapheresis donors are attached for your reference. As can be seen only [hepatitis B surface antigen] negative units of Source Plasma (Human) from healthy donors can be used in the manufacture of licensed biological products such as Koate."

That's what's said internally in relation to that category of information. You'll see then, that the memorandum continues by dealing with a second aspect of the Committee's conditions, which was the batch release procedure. Again, I don't need to go to it, I think, in enormous detail, but we can see the response there is "We do not feel the batch release procedure should be applied to Koate", and reference is made to it having been licensed in the US for 10 years.

If we then pick matters up -- so that was 23 February, if we then pick matters up, BAYP0000001_111.

Oh, I'm sorry, that's wrong reference, MHRA0009298, I'm hoping you might have.

This is Mrs Boult's response to Dr Andrews, 27 February 1976:

"I am now able to supply you with the information requested under Section 44 of the Medicines Act in your letter of 2 February 1976 [the letter from Dr Andrews we looked at]. Our answers to question

numbers 1 to 3 are contained in the appendix attached to this letter. We have not yet had a confirmation from Cutter that they will provide an on-going information about the rejection of donors or donations, centre by centre. I cannot foresee that this will be a problem and will let you know further about this matter as soon as possible. In addition they have not yet formally agreed to the imposition of the batch release procedure if necessary, but they are aware that this procedure exists in the UK and they have already agreed in principle to it."

Now, the document we just looked at, which is dated four days previously to this, was an internal Cutter Laboratories Inc document, so internal within the US, between two employees of Cutter Laboratories Inc. It may be, then, that what was said in it had not yet reached Mrs Boult when she wrote this letter, or it may be it did, in which case what she writes in this letter is not consistent with it, and we've no particular way of knowing one way or another.

The appendix that she refers to then is at BAYP0000001_112. "Antihaemophilic Factor (Human) Koate", and we've got the reference there to the product licence number, "Answers to questions 1-3 of

your letter of 2 February 1976", and I think we need only concern ourselves with the answer to question 1(a):

"Number of donations in each pool.

"Each pool consists of 2500 litres of plasma. Each unit of Source Plasma (Human) is approximately 600 ml. Therefore, the pool would be comprised of approximately 4000 units or more. Generally, the plasma pool is such that it is comprised of approximately equal donations from at least 1000 individual donors."

Note there the words "at least", which may become significant when we look at some later material:

"A given lot of Koate is usually made up from material fractionated from 3 to 5 pools, ie the AHF suspension obtained from 3 to 5 separate plasma pools is combined to form the final product."

So, notwithstanding that your suggestion, sir, which may be right, at least as a matter of language, that this was information to be provided on an ongoing basis, the evidence we have suggests the answer was given on this occasion and on this occasion alone.

Then if we just go over the page --

SIR BRIAN LANGSTAFF: Just going back --

MS RICHARDS: Certainly.

SIR BRIAN LANGSTAFF: -- when it says that the plasma pool, as such, is comprised of approximately equal donations from at least 1,000 individual donors, that's a plasma pool. Is it then saying that the -- because a given lot of Koate, is a batch, if you like, is made up of material fractionated from three to five pools, that it would then be between 3,000 and 5,000 individual donors?

MS RICHARDS: At least, yes, that's how I understood it.

SIR BRIAN LANGSTAFF: So 3,000 to 5,000 donors is the range?

MS RICHARDS: Yes.

SIR BRIAN LANGSTAFF: Thank you.

MS RICHARDS: But I think as a minimum, we can probably read in, given the use of the phrase "at least". Then if we go over the page, we've got product labelling. I don't need to go through the detail of it. There's a very detailed response from Bayer UK on behalf of Cutter Inc.

If we go to the top of page 4, we'll see there at the top of the page reference, and this is in the context of the labelling:

"... package insert mentions 'obtained from many donors'. See also answer 1a to your letter above."

If we then turn to BAYP0000001_113, we see

There's some further information about that.

"I trust the Licensing Authority will now be able to continue the assessment of our application for a product licence."

Pausing there, we can see that, by the time we've got to early March, in response to those two conditions identified by the Committee, there's an answer given about pool size which was condition 1(a), which is a general one-off answer. Then, in relation to the request for ongoing information about reasons for, and rates of, rejection of donors, centre by centre, the information that's provided is, simply, "we don't collect that".

SIR BRIAN LANGSTAFF: "We can't comply with the condition".

MS RICHARDS: Yes, yes.

Now, what then happens, is that there's a series of further correspondence. I'm not going to go through all of it. I'll just start with one letter, BAYP0000001_114. It's another letter from Dr Andrews to Mrs Boult, but it's not dealing with either of the matters in relation to pool size or donor rejection. It's dealing with a number of the other issues that have been flagged up by the Committee, by way of proposed conditions.

Mrs Boult writing again to Dr Andrews, now on 4 March 1976. This, I think, explains what seemed curious in the earlier letter, given what we'd seen from the internal Cutter memorandum. She says:

"Further to my letter of 27 February and my telephone call to you last Monday, I am now enclosing the reply which we had from Cutter in answer to questions 4 & 5 of your Section 44 letter. I am afraid that I rather anticipated their answer in my previous letter. As you can see from the enclosed ..."

I don't think we've got the enclosed -- I'll check this, sir. I don't know at present whether she is simply forwarded the internal memorandum or whether that was reformulated into some other type of document. But she says:

"As you can see from the enclosed, they do not collect information about the rejection of donors, but the collection of plasma is carried out according to the US Code of Federal Regulations. With regard to the imposition on batch release procedure, they are not in complete agreement with it. However, as you can see from their comments, it is only certain aspects such as the provision of samples ... which they object to ..."

The correspondence continues with, ultimately, if we go to IPSN0000312_116. This is just -- again, by way of example, we can see there's then a response. There have been further telephone conversations. We can see that from the opening paragraph. This is Mrs Boult, 20 April. There's then further discussion about the issue of -- the use of the Cutter house standard, so relating to other aspects of the conditions.

If we go over the page, we can see that there is now agreement to the imposition of the batch release procedure. The correspondence that we have seen does not return to the question either of pool sizes or information about donor rejection. So there is no response, for example, from the Department saying, "Well, you can't comply with that condition", asking for more information about why, or saying, "Well, I'm sorry, we can't deal with the matter, we can't deal with your application any further".

SIR BRIAN LANGSTAFF: Was the licence ever varied?

MS RICHARDS: Well, the slightly complicated picture is Bayer withdraw their application for a licence and then Speywood get the licence and we don't have a complete set of documents. I'll show you what we do have. But the purpose, at the moment, of showing you

the correspondence is to indicate that the Licensing Authority did pick up on, and press, a number of matters in relation to the conditions. But the issue in relation to the pool sizes, that seems to have been accepted as satisfactory, and the explanation is that we don't have the information in relation to rates of rejection or reasons of rejections of donors. It appears no further in the correspondence or communications.

So it, effectively, appears to have been accepted. There's no evidence of the matter going back to the Subcommittee or the Committee, for further consideration of that issue. Now, that doesn't mean it didn't happen, but we've not seen any documentation to suggest that it did.

SIR BRIAN LANGSTAFF: So, as far as we know, there was a condition to which the licence was subject, which was never fulfilled?

MS RICHARDS: Yes. But, as I say, the position is complicated by the fact that Bayer UK withdraw their application, Speywood make a separate application, we don't have a complete set of documents but I'll show you in relation to that.

What I think we can say is, when we look at what seem to have concerned the Sub-Committee on Biologics

and the Committee on Safety of Medicines, such that they wanted these to be conditions on the licence, that there is nothing that addresses those concerns, other than the Bayer information about pool sizes, and a licence is granted, and Koate becomes a concentrate distributed in the UK.

So it's -- what you might think the unsatisfactory position that eventuates is that, for whatever reason, those conditions, other than the information about pool sizes, effectively fall away.

There is a letter from Dr Andrews at BAYP0000001_119, where he refers to a letter from Mrs Boult, 23 April. Again, this is dealing with the issue of calibration and use of house standard or international standard, and not dealing with issues relating to pool sizes or donations.

This shows that the Licensing Authority wasn't afraid to be robust when it wanted to, so on that separate issue, it's saying, "What you've told us is not an adequate reply":

"It will be necessary for this letter to be answered satisfactorily point by point in detail before the licence can be reconsidered. Cutter may not be aware of the extent to which control of Factor VIII products imported into this country has

had to be upgraded."

What that's a reference to, other than possibly the focus bought to bear on it by the World in Action documentary and the ministerial interest, is not clear.

If we then go to BAYP0000020_039, we're now at July 1976, and this is an internal Bayer/Cutter communication:

"Mrs Boult on holiday but have checked myself with Ministry. They intend issuing a licence to us as soon as possible. Any other minor difficulties they say can be settled after registration. Armour have received a licence and the product is therefore registered. I also confirmed this with Ministry."

Then if we -- then the documentation becomes a little confusing. If we go to MHRA0009276, this is a document from the Committee on Safety of Medicines to the Licensing Authority. It refers to Bayer UK's licence application. We've got the name of Bayer handwritten in there, and the product licence application, which was PL/0010/0061, which was the licence application in relation to which we've been looking at the material.

We then -- I have somewhere got written down somewhere what the translation is of the handwriting,

which I can provide in due course, but we won't go through that now.

We can then see the comment at the bottom which we saw from the document we looked at which set out the Committee's decision:

"The Committee also advised that this product (should be marked as 'recently introduced' in MIMS and) should be the subject of the special directive for the reporting of adverse reactions."

Then slightly curiously the date that's given, or the date upon which document is signed, is 29 July 1976. But that would fit with the understanding in the document many just looked at, the telex we just looked at, that there was an intention that a licence would be issued.

What then happened, if we go to BAYP0000020_040, is an issue arose -- if we just look at the second paragraph of that -- about the role of Speywood, and there was a request there that the licence would be in the name of Cutter Laboratories, the logo would read "Manufactured by Cutter Laboratories and distributed by Speywood". I won't go into some further material but it appears to have been determined that that wasn't possible.

If we turn to MHRA0009278, we can see then that

Mrs Boult of Bayer on 18 August 1976 wrote to the Medicines Division, so the Licensing Authority, saying:

"We confirm that when you receive an application for a Product Licence for Koate from:

"Speywood Laboratories ...

"we have no objection to your taking account of the data submitted to you by us in connection with our Product Licence application ... for Koate.

"At the same time, we wish to withdraw our application for a Product Licence for Koate as the importation and marketing of Koate in the UK will now be solely in the hands of Speywood Laboratories."

And there is then, if we look at BAYP0000020_048, a letter from Speywood, Mr Heath of Speywood, to Mrs Boult. He thanks her for her help. And he says:

"My visit to the Department of Health and Social Security was 'Plain Sailing' apart from the flap about the 'omnibus' undertaking signed by Cutter."

Then, it would appear, and it may be that we can cast some further light on this when we look at Speywood tomorrow, that Speywood have handed over the licence application that they are now making for Koate, and reference is made to some earlier correspondence.

Then we see the last paragraph Mr Heath says:

"Also I would like to see Dr Andrews reply to your letter of the 27th February 1976, in order to judge whether or not he accepted your comments re labelling, particularly how he want the pool size to be indicated."

And certainly, sir, I've not seen anything further from Dr Andrews in relation to that issue, pool size, either in terms of the substantive condition or in relation to the issue of labelling.

Then if we go to -- I hope this is the right reference, Soumik -- IPSN0000312_036.

So this is then the licence, the product licence in relation to Koate, which was granted to Speywood, so the product licence number is 3070/0004, because Bayer's application's been withdrawn. We can see the date of grant is 27 August 1976, although the product licence actually signed on 1 March 1977.

And if we go over the page, we can then see reference to the product, Koate.

If we go got the next page, we can see the manufacturer is, as we've already seen, Cutter Laboratories Inc.

At paragraph 7 we can see there what's said in this application:

"Koate concentrate is a purified dried fraction of pooled plasma obtained from many donors. Since the presence or absence of hepatitis virus in Koate concentrate cannot be proven with absolute certainty, the presence of such a virus should be assumed and the hazard of administering Koate concentrate should be weighed against the medical consequences of withholding it."

Then if we go over the page, we can see various provisions subject to which the licence has been granted. The first is compliance with various aspects of the relevant statutory regulations. (2) is about the number of the licence appearing on packages, package inserts and literature, et cetera. (3) is about usage. (4) is consistency between the specification and the finished product and the information in the application. (5) is about method of manufacture. (6) is essentially about the batch release procedure. And (7) is a further reflection of that. And then (8), again, is about withdrawal of batches if informed by the licensing authority that any particular batch doesn't conform with the relevant requirements.

So there's nothing further there in relation to the matters that we looked at in the context of

Bayer's application. We'll look tomorrow at such material as we have from Speywood but I'm concerned today with Bayer and Cutter, and Koate then becomes distributed in the UK by Speywood for a period of time. So you'll see licensed then by August of 1976, but with these various issues having been initially identified, at the beginning of 1976, as important, and then apparently seeming to fall away.

I am going to come later to some Cutter materials which show matters relating to the state of the market over a number of years in the UK in terms of sales of Koate, but before I do that, if we can just look at two of the tables we looked at in relation to Armour, because they also contain information at different points in time about Koate.

So if we start with PRSE0003437, this was a table showing quantities of Factor VIII concentrate used in UK haemophiliacs in the years 1980 and 1981.

And you'll see there -- we looked at the Armour figures earlier in the week, then we've got the Cutter figures for Koate, because, as we'll come on to, Cutter then come back into the scene by this time. And we can see the figures 4.935 million international units in 1980 and 3.823 million international units in 1981.

So not the same magnitude as, for example, the Armour product, but nonetheless a significant amount of the Koate concentrate being produced and distributed in the UK in 1980 and 1981. And then you'll see the reference there to Speywood's product, Humanate, which we'll hear more about tomorrow.

If we then, in terms of licensing, move forward to 1980, BAYP0000001_140. We can see this is a letter from the Licensing Authority now to Cutter Laboratories Limited, so Cutter's UK manifestation has now made an application for a product licence for Koate. We've got the licence number there: 1605/0004. The date of this letter is 10 June 1980. It says:

"I refer to your application dated 24 January 1980 as amended by your letter of 6 March 1980."

And unfortunately we don't seem to have those materials, in terms of the underlying application and correspondence.

"Authority has now been given for the grant of a product licence for ...Koate ..."

And there we've got the licence number.

Reference is made to the formal documents being enclosed. We don't, I think, need to look at all of those formal documents, but if we look at one part of the enclosures at BAYP0000001_142, we can see here the

licence itself, the product licence, 1605/0004, has been granted to Cutter, and then if we go to the next page, we can see the particulars there set out. We don't need to go to any particular part of that. We've got there the reference, just at 9, to manufacturer, Cutter Laboratories Inc. And you'll see there the reference to Cutter's facilities in Berkeley, California, and Clayton, North California.

I mention that only because there are a number of documents from Cutter in the States in which reference is made to those two facilities and, from time to time, to inspection of those facilities.

If we go to the next page, we then have "Further provisions subject to which the licence has been granted", and they are in the same familiar and what seems to be largely standard format.

So that's 1980. A licence for Koate is now held by Cutter Laboratories Limited. As I say, we don't, I'm afraid, have the licence application, so I can't assist with what information was provided.

We can see some of the difficulties that had arisen in relation to the relationship with Speywood. If we go to BAYP0000021_063, this is a board meeting of Cutter Laboratories Limited, so of the UK company, 16 December 1980, and under the heading "Koate" it

says:

"The whole situation regarding the present problems with sales of Koate was discussed extensively, including the fact that it had been impossible to sell Koate during the months of October and November, although it was hoped that following the reduction in price that it would be possible to make meaningful sales starting in December 1980 and going through January 1981 onwards at a price of approximately 7.2p per unit."

Next paragraph:

"It was agreed that the Managing Director ... would put together a full situation report regarding Koate and also the Speywood parallel product known as Humanate which was in fact Koate marketed under a different label."

Again, we'll come back to that tomorrow.

If we look at the bottom of the page, last paragraph, it says:

"As regards sales from January 1981 it was thought that at the reduced price and with shading on seven days settlement, there were good prospects for sales of fairly large lots. Whilst this situation [and this I think is the Speywood situation] had had an adverse effect on the 1980 figures it was hoped that by

producing a realistic sale price in the UK market that it would be possible to ensure that the Company had adequate sales and also that it should be possible to price Humanate out of the market coupled with the fact that NIBSAC and Dr Duncan Thomas were very concerned regarding Humanate and the impossibility of tracing its manufacture back to its source."

Then if we go to the third page, not on the theme of licensing, but so that we don't need to come back to this document, there's just a couple of paragraphs worth looking at.

Under the heading "Sales", it's said:

"It was confirmed that a number of credits were due from the [US] in respect of products which have had to be returned from both Oxford and St Thomas' Hospital due to adverse reactions having been obtained. At Oxford there had been 13 cases out of 20 patients using Koate and in the case of St Thomas' two patients had contracted hepatitis and Dr Richard Schwartz of Cutter Inc had authorised the immediate withdrawal of the batch."

Then there's a suggestion that there might have been some lack of proper storage by Speywood. But at any rate, it is the reference there to hepatitis that I wanted to flag up.

Then if you go to page 5 of this document, there's a reference there to Dr Aronstam and Treloar's:

"It was agreed that full investigation should go into the promises made by Carroll Jones and Sidney Pugh to the Alton Centre where Dr Aronstam had been promised some kind of financial support for a research fellowship and had put in a great deal of time and effort in putting forward a representation to the Company. However, nothing materialised and it seems that this was causing the Alton Centre to have nothing to do with Cutter whatsoever. It was agreed that this should now be looked into again with a view to the Company being in a position to offer some form of financial support for such a fellowship."

Again, clearly relevant when you come to consider matters such as relationships between pharmaceutical companies and Haemophilia Centre Directors.

Then we can just pick up the picture in terms of Cutter's marketing of Koate at BAYP00000019_080.

These are the minutes of a board meeting on 11 August 1981 of Cutter Laboratories Limited. There's a discussion recorded in paragraph 1 about prices.

Then at paragraph 3 we can see:

"Concern [being] expressed at the period which

existed in obtaining product licences due to some degree to DHSS staff shortages and possibly shortcomings in the form of presentation.

"It was agreed that all future Cutter submissions should go through the UK Company assisted by the experts at Bayer UK to see that future presentations complied fully with the UK requirements of the Licensing Authority both as to content and format."

It's not entirely clear what that's a reference to in terms of the particular licence application. As I say, there were other products. So whether it's factor concentrates or a different product that might have given rise to that concern is unclear.

Sir, I'm going to move next to a further product licence in 1983 for Koate, but I note the time so perhaps we could take a break at this stage.

SIR BRIAN LANGSTAFF: Yes, we'll take a break now until quarter to 12. Quarter to 12.

(11.15 am)

(A short break)

(11.45 am)

MS RICHARDS: Sir, in terms of the licensing history of Koate, we pick the matter up next in 1983. If we go to BAYP0000002_196, please, Soumik.

We can see here a product licence being granted

now to Miles Laboratories Limited, trading as Cutter Laboratories (Division of Miles Laboratories Limited). So we've got there the interrelationships which I referred to yesterday afternoon.

We can see the date of grant is 16 August 1983. If we go over the page, we can see the detail of the product, so it's a licence for Koate. We haven't, I think, got the licence application documentation, I'm afraid, but if we go to the third page, we can see the "Warning", just over halfway down the page:

"Koate concentrate is a purified dried fraction of pooled plasma obtained from many paid donors. The presence of hepatitis viruses should be assumed and the hazard of administering Koate concentrate should be weighed against the medical consequence of withholding it, particularly in persons with few previous transfusions of blood or blood products."

I'll come back to the language of some of the warnings this afternoon, but that was the warning in relation to Koate as at the August 1983 licence grant. You'll note there no reference to AIDS at this stage.

If we look at BAYP0000028_038, and we'll come back to these issues later today, but we can see that back in February 1983, the manufacturer, Cutter Laboratories, is alert to the potential risk of AIDS

because it's beginning to take measures in relation to screening donors on the basis of it. We see from this announcement "Cutter Laboratories announces plasma donor screening programme", first paragraph, third line:

"... today announced it will screen plasma donors by using a confidential questionnaire designed to eliminate those in high-risk groups for [AIDS]."

We can see the second paragraph records:

"The initial investigations at [CDC] and at other research centers around the country have indicated that AIDS ... might be transmissible through blood and certain blood plasma products."

Then there's further details over the page -- we'll look at it now so we don't need necessarily to come back to it later -- about the questionnaire. We can see it is said, in the second paragraph, that:

"... all donors at Cutter-owned and affiliated plasma centres [and I'll be coming on to what we know about sources of plasma for Cutter later] will be asked to read and sign a confidential questionnaire which states they are not members of any of the three high-risk groups. In addition, the medical examination given to all donors will be expanded to include all questions specifically related to

AIDS-like symptoms, such as night sweats, drastic unexplained weight loss and recurrent fever."

Then there's reference in the next paragraph to an intention to:

"... initiate supplementary physical examinations of all ... donors ..."

Cutter, the next paragraph tells us:

"... is committed to taking whatever precautionary measures the company can to protect the haemophiliacs who depend on our products for their lives ..."

Then there's a reference to the development of heat treatment. So that's Cutter's position as manufacturer in February 1983 but, as I say, the licence granted to Miles Laboratories Limited, in August of that year, contains only the warning that we've seen by reference to hepatitis viruses.

Just sticking with 1983, for the moment, if we go to BAYP0000027_074, we can see a letter of 29 November 1983.

SIR BRIAN LANGSTAFF: 23.

MS RICHARDS: Sorry, 23 November 1983, from a sales manager, a Mr Barber, to Dr Wensley, who we know, obviously both in relation to the Blood Transfusion Service in Manchester and the Manchester Haemophilia Centre. We can see he is providing information

further to a meeting that he'd held with Dr Wensley about Koate batches. He refers to the copy of a May edition of ECHO magazine, devoted entirely to AIDS, and he talks about it containing a complete list of all plasma donor centres:

"... you will note that there are no centres in San Francisco or New York."

Again, I'll come on to this later. But then we can see, just interesting to note, the different lots of Koate being offered and the prices. So the first group is manufactured from plasma all collected after 1 March 1983, and that's described as the effective date when Cutter introduced the new regulations for donor acceptance at the donor centre, and the price that's there recorded is 6.75p per international unit. Mr Barber says this is going to increase to 8p per international unit from 1 January.

That's the post-March plasma.

The second group of lots, manufactured from Plasma collected before 1 March 1983, and we can see that's cheaper, 6.35p per international unit, "This price will remain firm to you", subject then to release by NIBSC and told the product could be available in early February.

Then there's a third lot described at the bottom

of the page, manufactured from plasma, so also manufactured from plasma collected before 1 March 1983, and the price of that is, if we look at the top of the next page, 5p per international unit.

So cheaper prices being offered in relation to Koate that is manufactured from plasma collected before 1 March 1983.

Returning, then, to the licensing process. If we go to BAYP0000003_230, we've got an application for a change to the licence. Again, we can see it's Miles Laboratories Limited, because they're the current licence holder for Koate, and then we've got the changes, which simply reflects HBc antibody tests now included in the Cutter system, and the date of this is 10 May 1984. I think, in fact, we don't have any further documentation in relation to that application.

If we then move to later in 1984, BAYP0000025_093, this is a letter addressed now to Bayer AG in Germany, 4 December 1984. We start to see at this point the transition to heat treated Koate, and I'll come on to the licensing process in relation to Koate-HT, but we can see reference in the second paragraph to a Koate-HT trial, and then the author of the letter Mr Marzouk says:

"... the situation has changed dramatically within

the last few days. A haemophiliac has died from AIDS and the death of this patient has developed into a big public and press campaign in favour of Heat Treated material. Because of this we are now selling Koate HT [that's a separate product for which there's a separate licensing process].

"It is apparent that all centres will be completely converted to Heat Treated material without the need for a study."

Then we can see discussion as at late 1984 within Cutter/Miles of the switch to heat-treated products at BAYP0000025_087, this is 30 November 1984, and we can see it says:

"Meetings were held with Cutter UK sales and marketing staff, as well as with Miles UK support personnel, to discuss results to date in 1984 and make strategic plans for 1985."

So that's what this document relates to.

If we go to the bottom of page 3 and pick up the heading "Koate HT", so the heat-treated product:

"AIDS has finally come to the United Kingdom with a force that has caused a virtual panic in the Department of Health. For one year this department has blocked every application for registration of heat-treated factor VIII products and now in the space

of one week they are in a panic responding to the newspaper demands for action concerning the AIDS risk to haemophiliacs. The action by the Department of Health comes after the announcement in the Sunday mail that 2 haemophiliacs have died from AIDS."

Then there's reference to a number of headlines.

"Following these headlines the Department of Health has advised Cutter that every action will be taken to grant us registration by early December. As we indicated in our last trip report ... on this subject, Marie Tatt is to make every effort to have them grant us a new registration, not a licence amendment.

"The Hemophilia Treatment Centers are now also responding to the newspaper stimulus and requesting heat-treated Koate on a name patient basis. Cutter UK had in inventory 1,000 vials of 500 IU Koate HT which has now been allocated and requests for other sizes have been received from the treatment centers."

Then, bottom of the page:

"The treatment centers are in some cases asking to return regular Koate [the untreated product] after they have received Koate HT. These requests are being dealt with on an account by account basis, but we intend to accept all returns where we perceive an

honest concern on the part of the transfusion center ."

Then we see can see the price of the heat-treated product at the top of the next page:

"We have established a selling price of 12 pence per unit on the Koate HT."

If we turn, then, to BAYP0000003_341, this is another application for a change of product licence, so this is still the original Koate product with the licence number 0055/0065 held by Miles Laboratories Limited. It's not the heat treated product, but if we see further down the page we can see what's said to be the reasons for change:

"The process changes were made in order to produce a product suitable for heat-treatment."

Then over the page we see the detail of that. So there's a change to the manufacturing process, the reason being it will enable production of the heat-treated product, and the date of this is 7 December 1984.

If we then go to BAYP0000024_047, we can see from an internal Miles/Cutter memo dated 30 January 1985, what we have is described as a "Key Indicator Report" for December 1984.

We needn't go through the details of the sales but

if we go to the bottom of the page we can see a summary of the position as between the two Koate products, the licensed product, which is the unheated product, and then the heat-treated, which is currently being dealt with on named-patient basis and is unlicensed.

"Koate Factor VIII Concentrate has successfully reached and exceeded the end of year budget by 4%. Koate HT was forced onto the UK market place by the market's demand for heat treated Factor VIII Concentrate. Some Koate regular material was returned during December ... However ... the sale of the Koate HT has compensated and exceeded the monthly budget ..."

So that's a snapshot of the picture as at the end of December 1984.

As we'll see shortly, there's then a licensing application process for the heat-treated product, but just to complete the picture in relation to what happened to the product licence for the unheated Koate, we can pick that up at BAYP0000011_090.

This is a later document, a Bayer document from 17 May 1988. It tells us that:

"A reminder has been received from the DHSS that the product licence of Koate [and we have the product

licence number there set out] expires on 15 August 1988 and a renewal application should, therefore, be submitted as soon as possible.

"However, I think I am correct in saying that this form of Koate is no longer produced since it has been superseded by Koate HT. If you are in agreement, I will inform the DHSS that the product licence holder, Miles, will allow the licence to lapse on expiry."

And that is what happened.

So effectively Koate remained licensed until 1988, the unheated product, but was not -- so the licence was not revoked, but it then lapsed in 1988, as we see here.

So that completes the overview, sir, of the licensing position in relation to the unheated Koate material.

If we can then just look a little more at the position in relation to Koate-HT, the heat-treated product, if we turn, first of all, to BAYP0000027_078. This is a document relating to the position in the US from Cutter Laboratories to the Office of Biologic Research and Review, November 21, 1983.

We don't need to go through the detail of it because it is dealing with the US licensing process

but we can see that, as at November 1983, Cutter was writing to the office of biologic research, and we need only look at the first paragraph, with a view to amending its product licence application to include the dry heat-treatment step. We don't need to follow through what happened in terms of US licensing.

In terms of the position then in relation to the heat-treated product in the UK, if we go to BAYP0000025_019, we can see a telex, the date of which is 3 September 1984 and we can see the position in the UK as at September of 1984 is that there had been an application under the CTX procedure in relation to a clinical trial of Koate-HT, and this confirms that approval had been received from the Department of Health for the clinical trial to commence on -- "which may commence on 12 September 1984".

If we then just -- I'm slightly dotting between the UK and the US here, but if we go to CGRA0000447, again, this is a document, I think, sent by the president of -- described as Cutter Biological in California, 26 October 1984, to haemophilia treaters, so haemophilia clinicians, in the States. I just draw your attention to the last paragraph on this page which explains that:

"... Cutter is immediately converting manufacture

of all Koate to Koate-HT."

So that was the plan in terms of manufacture as at the end of October 1984.

Then if we then move chronologically back to the UK to DHSC0002251_015, we can then pick the matter up at the end of November 1984. This is a communication from Dr ME Duncan to the Supplies Division, which records that:

"An abridged application has been received from Miles Laboratories to license dry heat-treated Factor VIII (... Koate-HT), and this will be handled as a matter of some urgency.

"NIBSC has been informed, and their expert advice has been sought".

So we've moved fairly quickly from the clinical trial process contemplated in September of 1984 to the abridged licence application for a product licence for heat-treated Koate by the end of November 1984.

In the meantime, if we look at BAYP0000025_081, we see -- and this happens to be a letter from the sales development manager Linda Frith to Professor Bloom, 29 November, but we can see that the heat-treated product was being offered for sale to Haemophilia Centres, and it was at that stage because it wasn't licensed on a named-patient basis. That's apparent

from various other documents as well.

If we then look at CRGA0000554, we've got a document headed "Cutter UK Year End Review and Reports", dated January 1985. And it gives us an overview of the position in relation to the introduction of heat-treated Koate in 1984. So if we pick it up at page 5, second paragraph begins:

"Koate HT was launched into the UK market at the end of November, 1984."

Then if we turn to page 8, we can see a little more about the background circumstances in that first paragraph.

"It was anticipated that Koate HT would be launched into the UK market during the second quarter of 1985. Its appearance at the end of November, 1984, replacing all non-treated material, was somewhat hasty."

And we've seen the other documents which explain the circumstances of that.

"The fast response by Cutter UK and the availability of material ensured we retained all existing business and were able to supply additional sales where other commercial companies and the NHS were unable to supply heat-treated materials."

There's then a reference to overall market shares,

and you'll see there Cutter's market share is described as being approximately 22%, with Armour's being 56% -- this is during 1984 -- Alpha, 17; Immuno, 3; Travenol, 2%. Then there's a description of the offer of heat-treated material by some of the other commercial companies in the next paragraphs.

The bottom of the page just looks forward from Cutter's perspective to 1985.

"Cutter will remain one of the major suppliers in the UK for heat-treated Factor VIII concentrate during 1985.

"It is planned to make Cutter a household name, in the haemophilia field, promoting Koate HT's many significant advantages over the competition; improving and expanding our relationships with our users ..."

As you have previously observed, sir, that's effectively a reference to those who were purchasing the product as clinicians or Health Authority officials.

"... in person, by mailings and advertising literature.

"The US wall poster and 'slim Jim' information sheets along with the Home Treatment Therapy film will be useful tools. Product licence registration for Koate HT is expected during the first quarter of 1985

with product being supplied at present on a named patient basis."

Then if we go to page 10, this will save coming back to this document when we look shortly at Konyne, this is a reference here to Konyne HT, so the heat-treated Konyne product for the treatment of haemophilia B:

"Interest in Konyne HT has prompted a product licence submission to the DHSS with present supply again being maintained on a named patient basis.

"Adequate supply of Factor IX for the UK market had previously been supplied by Elstree, but heat-treated Factor IX is not expected to be available from this source until late 1985 or early 1986."

If we then go to CGRA0000559, this, again, is an internal Cutter document, Cutter or Miles document. If we go to the second page, we could again just pick up the picture during the bottom half of the page about the switchover from Koate to Koate-HT. So under the heading "Koate Returned Material", the document reports that:

"The December figures show returned Koate from only two centres, but the followed centres have subsequently returned or are in the process of returning material."

A list of haemophilia centres are there set out.

Then it is recorded that:

"All the centres which returned Koate in December and those subsequently have replaced with Koate-HT."

Then if we go to the next page, under the heading "The Current Factor VIII Market Environment, Koate heat-treated material", we see the observations from the Cutter perspective about a number of haemophilia clinician -- sorry, Haemophilia Centres and their response. So:

"The intention of the UK was to launch Koate HT into the market into the second quarter of 1985 with an organised entry ensuring product availability and a product licence.

"However on several occasions during November, 1984, the national papers flooded the media with shock announcements of the deaths and the contraction of AIDS through blood donations and the subsequent fractions of Factor VIII concentrate.

"Stories included ..."

Then we see a number of accounts there set out. We've seen reference, I think, to all of these in the evidence that the Inquiry has previously heard, so deaths in Australia; the death of a haemophiliac from AIDS, who was a patient at Newcastle; a Bournemouth

donor donating blood, and then having been diagnosed as an AIDS victim; and then the position in relation to Scotland.

"The response of the haemophilia centres covered the entire spectrum from panic to no action.

"The Wessex regional centre at Alton changed overnight from regular material to Armour heat-treated material.

"Newcastle's transition was slower but a definite replacement of regular stock to heat treated has occurred. No non heat treated material is now being used.

"Oxford, on the other hand, waited for a formal discussion between the haemophilia Directors before switching to heat-treated materials.

"Other centres like Saint George's, Birmingham, the Hammersmith, and the London are still using non-heat treatment material. The material may be commercial or NHS product."

Then over the page there's a discussion of Cutter Laboratories' role:

"We had the good fortune of 1000 vials of Koate HT 500 [international units] nominal potency for our inventory and the almost immediate availability and supply of other potencies from the US.

"This gave us, as we were to find out, a clear selling advantage over all our competitors."

Then objectives and tactics are then set out. Objectives:

"To retain all Cutter's existing Koate accounts ... by direct replacement with Koate HT.

"To increase Cutter's market share by whatever amount possible, given the situation and stocks available to us."

Then a number of tactics there set out:

"... inform all Koate users of the availability of Koate HT.

"To inform all Koate users we would be happy for them to return any Koate stock and credit their account.

"To inform all the other Factor VIII concentrate users to the availability of Koate HT.

"To organise sufficient stocks from the US to supply all current market needs ...

"Continual reappraisal of the situation, stocks, customers and competitor activity."

Then if we go to the bottom of the next page, we can see the licensing position is set out under the heading "Koate HT Licence":

"A submission has been made to the DHSS for the

registration of Koate HT. It is believed the licence will be granted at a meeting on 26th January. It will take possibly six weeks before paperwork is completed.

"Konyne HT

"A licence for Konyne HT has also been submitted."

Pausing there, we see from this series of internal documents a perspective we haven't perhaps seen before, the perspective of the pharmaceutical company in the UK as to its analysis of what happened in the latter part of 1984, in terms of what's described as the sudden response to media reports and a sudden demand for heat-treated material by some haemophilia centres, if not all, and then the impact that then had on the licensing process leading to the licensing process being compressed and a licence being submitted -- sorry, a licence application being submitted rather earlier than had otherwise been anticipated.

Before we leave this document we should perhaps look at paragraph 8 -- sorry, page 8, I'm sorry, Soumik -- page 8, which is a report of various meetings between Cutter representatives and haemophilia clinicians and other haemophilia staff. Again, it's perhaps just instructive in terms of what it reveals about relationships. So we've got, second

paragraph, Professor Bloom was contacted:

"... he assured me that they will stay with Cutter. He also informed me that they are switching completely to Koate HT from that day, (4th December)."

There's then -- next paragraph talks about a meeting with haemophilia staff at Lincoln, the Lincoln Haemophilia Centre:

"Koate HT was discussed, however no decisions have yet been made."

There's a reference to a visit from the Immuno rep.

"Dr Mitchell (DERBY) [a meeting] her decision to change to [heat-treated] material for their next order."

There's then -- we can skip over the next paragraph, because that deals with the blood bags that were sold by Cutter rather than Koate. Then there's a reference to a meeting at which it was learnt that:

"Sheffield, Nottingham and Leicester ... have decided to use heat treated material only on newly diagnosed severe haemophiliacs.

"The LEEDS region has made a decision to use only [heat-treated] material from the commercial companies and the likelihood of Cutter obtaining business in the region is fair. At the moment, however, they have

somewhere in the region of three months' supply of NHS material."

Then this:

"By far the most important happening this month is a very successful meeting with Dr Wensley (MANCHESTER), when he promised all of his business for the next contract. This is the period between January and April, 1985, depending on finances being available."

Then skipping over a line:

"Dr Wensley was promised a £10,000 sponsorship programme for research to be carried out over two years. In financial terms this contract will mean the sale of approximately 2.5 million [international units] of Koate HT during 1985 ..."

So interesting to see the range of interactions that were taking place between the pharmaceutical rep and the various treatment centres in that critical month of December 1984.

If we then go to BAYP0000024_034, we can pick up the picture in relation to the Licensing Authority's consideration of the product licence application for Koate-HT. So this is dated 17 January 1985:

"Re Koate-HT product licence. Informal telephone call received from Dr Duncan. Product licence will be

issued on receipt of written confirmation from us that we will include a statement in data sheet that product is 'heated at 68 degrees [centigrade] for 72 hours and this is done to reduce risk of infectivity'. No need to mention that dry heat is used. Please confirm that this is acceptable to Cutter."

Then the responses at BAYP0000003_301, 23 January 1985, to Dr Duncan at the DHSS, confirming that the data sheet for Koate-HT will include that statement about the heat treatment and that the step has been introduced in order to reduce the risk of transmission of infectious agents.

Then we can see the product licence being granted in relation to Koate-HT at BAYP0000003_309. So it's granted as a product licence 0055/0107 to Miles Laboratories Limited, trading as Cutter Laboratories Division of Miles Laboratories Limited. The date is 18 February 1985, we see that at the bottom of the page.

If we go over the page, we can see that the product is the Koate-HT product. Then if we go to the next page, we pick up the heading "Warnings", towards the bottom of the page. So there's reference to:

"Allergic reactions including chills, fever and hypersensitivity reactions ..."

Then there's an issue pertinent to certain blood groups.

Then if we go over the page -- so nothing else by way of warnings of relevance for present purposes, and then over the page we've got, under the heading "Contra-indications, Precautions and Warnings":

"Koate-HT concentrate is a purified dried fraction of pooled plasma obtained from many donors. The presence of hepatitis viruses should be assumed and the hazard of administering Koate-HT should be weighed against the medical consequence of withholding it, particularly in persons who have had few previous transfusions of blood or blood products."

So, again, the reference is to hepatitis viruses, no reference there in relation to HTLV-III or AIDS. But, in any event, that is the licence being granted for the heat-treated product on, as it were, an expedited basis in February 1985.

If we then go to BAYP0000008_069, we can see an application for a change to the licence, the date of the application is 30 May 1985, we see that from the bottom of the page. The top of the page tells us that it's an application in relation to the licence for Koate-HT, and then we see on the screen what the change is. The proposed additional words relate to:

"... including testing of samples from all donors for antibodies to HTLV III."

Then the reason that's given for that is that:

"The procedure for screening of donors has been updated in accordance with FDA requirements."

As far as we understand the position to be, that change was approved. If we just then look at BAYP0000009_030, this takes us forward now to October 1986, and this is information that's being given by Cutter through its sales team to haemophilia clinicians in relation to the Koate-HT product. This particular letter is being sent to Dr Prentice at Plymouth, Dr Lee, who was the Haemophilia Centre Director at Exeter, Dr Smith and Mr Gardiner at Bath.

We can see that there's been some form of meeting because Mrs Frith writes:

"It was a pleasure to speak with you last week about Koate HT. I've tried to answer your questions about the product as follows ..."

Then we can see the provision of some information as at October '86 about the product.

"Koate HT is prepared from pooled human plasma from at least 1000 healthy donors."

So we have that phraseology "at least 1000" again.

"All donors are required to read and sign

a confidential questionnaire which states that they are not members of any of the high risk groups for AIDS."

Then reference to the medical examination.

"No plasma is collected from the metropolitan areas of New York, San Francisco, Los Angeles or Miami ..."

That's plasma source, that's what's being said:

"Screening of Plasma.

"Prior to pooling, each individual unit of plasma is tested and found non-reactive for hepatitis B surface antigen and antibodies to HTLVIII."

So we've got the longstanding hepatitis B testing, the more recently introduced screening in relation to HTLV-III, and then we're told that:

"Cutter Laboratories is also screening individual donations for [ALT] levels."

Then that paragraph concludes:

"By the end of this year, all batches of Koate HT will have been prepared from plasma screened for ALT levels in addition to HTLVIII antibodies and hepatitis B surface antigen."

Then details are given about the heat treatment process. Over the page, under the heading "Virus Inactivation Studies: HIV", there's reference --

I don't need to go through the details of it -- to what's said to be a range of studies reporting the success of the heat treatment process in eliminating HTLV-III.

Then if we just look towards the bottom of the page, the paragraph above the heading "Product Integrity", it deals with non-A, non-B hepatitis, so:

"Further evidence of absence of non-A, non-B hepatitis and HTLVIII infectivity is obtained from clinical use of the product."

Then it's said that:

"Since it was first marketed in the USA in February 1984 and in the UK since February 1985, no reports of hepatitis non-A, non-B or HTLVIII antibodies seroconversion in patients treated with Koate-HT have been received from these or other markets worldwide."

So that's the information that's being provided to, it would appear, a number of clinicians who have sought specific answers to -- or sought further information about the safety of the product, and then, if we go to the next page, we can just see, in terms of the marketing of and sales of the product, last two paragraphs, Mrs Frith is saying that they can deliver Koate-HT and all Cutter products the next day on

receipt of a phoned order; in an emergency, same day courier service and we can provide free home treatment packs and carrier bags if required.

If I just then move forward in relation to Koate-HT to 1988.

I am hoping this is the right reference, Soumik, BAYP0000015_101.

If we go to the next page -- that's fine. I've got the document in a slightly different format but this is what we need:

"July 1 ... Visit to Bayer UK."

So it's an account from someone from, I think, Cutter in the US to a visit to Bayer UK dealing with a number of matters, most of which I don't need to trouble you with. But if we go to -- it's probably page 5, Soumik, we can see, bottom of the page -- there's an issue there where it says:

"We returned Dr Thomas' call ... about the hepatitis reports with [a particular lot of] Koate HT ..."

It's said that all records have been reviewed:

"Every unit was tested and negative for HBsAg as was the plasma pool. He asked whether we could rule out human error. Of course, we could not."

Then there's a further discussion in relation to

this issue in relation to hepatitis B. I'm not going to go through all of it.

If you go to the next page, we can see there's then a discussion in the second paragraph about whether the product would be taken off the market. The response is:

"... no, because there are patients to whom this product represents no additional risk."

Then it's said that the lot, the particular lot, will be withdrawn, and it will be called a withdrawal rather than a recall and that the lot would probably be destroyed. Then there's a request for samples. Then we can see it says:

"Dr Thomas called back later to say he is releasing the lot of Koate HT being held up. For future lots, he wants a sample of plasma pool ..."

We will be coming back I think at a later stage of hearings to look in more detail about what the processes were at NIBSC in terms of both batch release stop orders, recall and so on, but we can just see there an example of interactions between Cutter and Dr Thomas at the National Institute looking at issues relating to hepatitis in particular lots.

Then, if we go to BAYP0000005_143, we're now in November of 1989, and we can see, just to complete the

licensing picture, this is an application to renew the product licence for the heat-treated Koate product due to expire on 17 February 1990. You will recall it had been granted in February 1985. And there's an application to renew the licence.

If we just go to page 4, we can see there again the terminology that's used:

"The source material is pooled plasma obtained from at least 1,000 healthy donors."

So that same term that we saw back from 1976, at least 1,000 is used.

"It is collected by plasmapheresis at centres in the USA, licensed by the FDA and inspected by both the FDA and Cutter Laboratories ...

"The plasma is collected according to the Cutter System of Plasmapheresis which incorporates all the current FDA requirements for Source Plasma ... including testing for Hepatitis B Surface Antigen and antibodies for HIV. In addition, Cutter test samples from all new donors for Antibody to Hepatitis B Core Antigen."

So that the basic information in terms of the screening and testing of the donations.

SIR BRIAN LANGSTAFF: It doesn't say anything there about ALT tests.

MS RICHARDS: It doesn't, no.

SIR BRIAN LANGSTAFF: Despite that being part of the licence.

MS RICHARDS: Yes. You're right, it doesn't. Whether there's a reason for that, sir, I don't currently know. But we can ascertain that.

Then BAYP0000033_012, this is a memorandum, 25 February 1992, and it's just an update about the current status of Cutter products in the UK. If we go to the bottom of the page it deals with the Factor VIII products. It says:

"We currently hold a product licence for the dry heat-treated product, Koate HT. This was withdrawn from the market a couple of years ago for two reasons, namely, the availability of safer products and the fact that it is no longer manufactured by Cutter. The licence will be allowed to lapse."

So that was the end of the licensing history in relation to the heat-treated Koate -- or the product, sorry, Koate-HT.

"Owing to inadequate resources from Cutter, the additional work required to register the next generation wet heat-treated product, Koate HS, was not performed and our licence application was withdrawn."

Top of the next page:

"All effort has since been put into Cutter's current product, Koate HP, a solvent detergent-treated product."

Although it is then said that "there are no current plans to market this in the UK".

So there is quite a lot of material relating to the licensing application process in relation to Koate-HS. I'm not going to spend any time on that today, because there are quite a lot of documents relating to other aspects of Koate, particularly in the 1970s and the early 1980s that I want to concentrate on. But at some point, perhaps when we come back to evidence relating to licensing, from the perspective of looking at what was actually done by the Licensing Authority, we might want to come back to it because it may be thought that the approach taken by the Licensing Authority in the second half of the 1980s was more rigorous than the approach taken at an earlier stage, and the way in which, for example, the application for Koate-HS was dealt with might provide some form of a mini case study in relation to that so I'm not going to deal with it today, but there is an issue for potential exploration about whether it shows a more robust approach on the part of the Licensing Authority by the second half of the eighties.

I'm going to turn, therefore, briefly to Koate -- sorry, to Konyne.

If we start with BAYP0000004_285. We can see, top of the page, "Konyne, Factor IX Complex" and the licence holder is Cutter Laboratories, and the date of the application, bottom of the page, is 3 July 1980.

We don't, I'm afraid, have either a complete set of documents in relation to the licensing application for Konyne or a complete set of documents which tells us what happened to the licence. So at the moment I can tell you based upon this that an application was made in July of 1980.

If we go to BAYP0000008_071, there's a little bit of a background here in -- I'm not sure what the authorship of this document is. But in any event, it purports to set out a potted history, as it were, in relation to Konyne.

"As early as 1968 Cutter Biological introduced Konyne, a preparation of factor IX complex, on to the market in the USA and in many other countries around the world.

"An application for a UK product licence for Konyne was submitted by Cutter in 1982 [we've seen an application from 1980] but as the format was not in compliance with the DHSS guidelines, the application

was unacceptable and subsequently withdrawn. For commercial reasons a re-submission of the data in the correct format was not pursued."

Just pausing there, we do see some evidence potentially of Konyne being used on a named-patient basis, but we know from other material that most Haemophilia Centres had NHS Factor IX available to them.

So that may be why it refers to commercial reasons, I don't know.

Then it's said:

"In 1984, following intensive work on methods designed to reduce the risk of transmission of potential infectious viruses in their coagulation products, Cutter completed the development of a heat-treated preparation of Konyne, Konyne-HT.

"As the clinical use of Konyne was then well established worldwide and the heat-treated product had been shown to be equivalent in terms of in-vivo biological activity and half-life to the non-heated product, no additional clinical trials were conducted with Konyne-HT."

It then refers to the heat treatment process for Konyne-HT being the same as that for Koate-HT, for which there was a licence.

If we then go down a couple of further paragraphs to the paragraph beginning:

"On the 8th May, 1985, Miles Laboratories submitted an application for a product licence for heat-treated Factor IX Complex, Konyne-HT ... manufactured by Cutter Biological, Division of Miles Laboratories Inc, USA."

So we can see then -- and this is really a convenient shorthand rather than going to all the underlying documents -- we see that an application for a product licence for Konyne-HT was submitted in the course of '85. And then, we're told:

"In October 1985, the company received a Section 21 letter from the Committee on Safety of Medicines informing them that, on grounds relating to safety, quality and efficacy, they might be unable to recommend the grant of a Product Licence."

And we can see that it appears that the Committee on Safety of Medicines had a number of concerns about the provision of inadequate evidence or information.

If we go over to the top of the next page, it said:

"Inadequate evidence had been provided of virus inactivation."

So that was one of the concerns. Then we can see

in fact the origin of this document below paragraph 5:

"This representation is Miles' response to the points raised by the Committee and includes additional information relevant to the grounds referred to above.

"The Committee is asked to consider these documents in the knowledge that Miles Laboratories has requested a hearing."

Then I don't think I need to go through the detail of it, but there's various pieces of information then provided in support of Miles's application for a product licence for the Konyne-HT.

If we go to page 7, we can see that this addresses -- and we can see it from the heading -- the suggestion that had emanated from the Committee on Safety of Medicines that insufficient evidence had been provided of the clinical safety and efficacy of the product.

Then there's a description, amongst other things, of matters relating to transmission of viral hepatitis. If we pick it up three paragraphs from the bottom we can see it's said that:

"The transmission of viral hepatitis has always been of concern in clinical use of antihaemophilic factor VIII or IX, and the evidence to date suggests that the heating process employed in production of

Konyne-HT reduces this risk."

There's then reference to a study on chimpanzees. Then, if we go over the page, top paragraph refers to there being:

"No evidence of non-A, non-B hepatitis or hepatitis B ... observed in animals administered with heated Konyne ..."

Then it says:

"Clinical studies designed to investigate the possibility of transmission of non-A, non-B hepatitis have to be performed in patients who have not previously received blood products, that is, virgin haemophiliacs with haemophilia B. Quite apart from the ethics of conducting trials in these patients, the number of available patients is very small.

"Cutter is currently monitoring the use of Konyne-HT in such patients but, so far, only two patients have become available for inclusion in the study and the study is not yet complete.

"Although, as yet, we have no absolute evidence that the heat-treated Konyne does not transmit non-A, non-B hepatitis in haemophiliacs, we have had no reports of non-A, non-B hepatitis in haemophiliacs receiving our dry heat-treated factor VIII preparation ... which has been in clinical use for several years."

Then the conclusion in that final paragraph:

"... although all possible steps have been and are being taken by Cutter to reduce the risk of transmission of infectious viruses, the technology presently available does not allow us to claim with certainty that the product is completely free of infectious virus. The risk to the patient must be considered carefully in each individual case and balanced against the risk of depriving the patient of treatment with the product."

So that is part of the information that we can see being submitted in response to the provisional conclusions of the Committee on Safety of Medicines that there was insufficient evidence to reassure them.

I don't think we have a specific date for that document, but we do know from other documents which I don't need to take you to that Konyne-HT was being supplied on a named-patient basis, to a limited extent at least. I don't think we know the full extent of it.

Then we can see BAYP -- sorry, I'm going to take you to a different document. BAYP0000004_326.

We can see here this is some of the underlying documents to which that background summary referred. So this is October 1985. This is a communication from

the Committee on Safety of Medicines to Miles Laboratories in relation to the Konyne-HT product. And we can see here set out the provisional conclusions of the Committee to which that other document was responding, including, at 4:

"Inadequate evidence ... provided of virus inactivation."

And then at 5:

"Insufficient evidence had been provided of the clinical safety and efficacy of the product or of the product on which it is based."

Again, it may be that looking at how the Committee on Safety of Medicines dealt in the mid and latter part of the 1980s with applications such as this, may provide a degree of contrast with the approach taken by the Licensing Authority or Committee on Safety of Medicines in the 1970s and in the early part of the 1980s.

There are a range of communications then between the Licensing Authority and Miles Laboratories. I don't think we need to look at them in any great detail, but if we just pick up the picture at BAYP0000007_161, we perhaps get some insight into the approach of the Licensing Authority.

So this document is dated 2 December 1985, and

it's a note of a meeting held at NIBSC on 28 November 1985 to discuss the Committee on Safety of Medicines' decision on Konyne-HT. We can see there's also a discussion about Gaminune.

Then if we look at the second paragraph:

"GS said ..."

I think that's someone from NIBSC:

"... that they were tightening up on blood products and required more detailed information concerning screening of donors for HTLV-III ..." et cetera, et cetera.

Towards the end of that paragraph:

"... wished to see results of viral inactivation studies ..."

And, bottom of the page, we can see they also want to know about elimination of viruses during purification. So again, there's an insight there perhaps into a more robust approach being taken from a licensing perspective.

If we move then on to a document in 1987, BAYP0000010_170, this is dated 29 September 1987. It's an internal Miles and Cutter document headed "Konyne-HT - Expert Report". It explains as follows:

"Our Konyne HT PLA [product licence application] was submitted two years ago but the CSM required

further information on safety and efficacy before recommending the grant of a product licence. After discussion with the licensing authority it was agreed that we would have to provide some long term evidence of safety in clinical use with special reference to the transmission of infectious viruses."

Then, next paragraph:

"After further discussion with the licensing authority on the problems of generating the safety data we decided to approach a haemophilia centre director in the UK to obtain support for our submission to the CSM. Unfortunately, we have not yet been able to find anyone willing to do this, although Professor Temperley [he was Irish, based in Dublin, I think] had indicated to me that he would be prepared to assist us.

"The CSM is now pressing us for a response to their request ...

"We still wish to register Konyne HT in the UK and I feel that we should be able to provide a satisfactory response to the CSM with or without the support of UK clinician. At least we could make a stab at it."

Again, I'm not going to go through the full picture, but -- I don't think we have all the

documents. I think it's 1988, I'll check, and confirm if I've got that wrong after lunch, but the licence application for Konyne-HT was withdrawn, and so it didn't proceed to the grant of a licence.

So that's the picture in relation to licensing for the factor concentrate products.

I just then want to turn to a handful of internal documents from Cutter which show changing market shares and product usage in the early part of the 1980s.

So if we start with BAYP0000021_016, this is a document described as "1981 Koate Marketing Notes". If we turn to page 3, there's a "Market Overview". The first paragraph refers to strict control of health services finances.

If we go to the bottom of the page we can see it's said:

"At present, none of the three leaving suppliers appears to have a dominant image with Haemophilia Centre staff. Cutter has an opportunity to become the market leader and company identifiable with the treatment of Haemophilia."

There's then, if we go to page 5, identification of key Reference Centres and allied major users.

Then if we go over the page, we can see, at the

bottom half of the page, what's said to be the "Estimated Current Market", and it's not quite clear what that's based on. Again, we see Armour, although not by a huge margin, being identified as having the largest share of the market and Cutter's as being relatively modest in comparison, 7.5%.

We then see a list on the next page of existing contracts with competitors, I don't need to go through the detail there, but you'll see a list of who's got contracts with Travenol, Armour, and Immuno.

Then if we go to page 9, we can see Cutter's marketing objectives in 1981, which include establishing Cutter "as a major supplier with a good definable market image", whatever precisely that means.

Then over the page we can see there what's going to be the focus, it would appear, from a marketing perspective:

"Penetration of major accounts.

"Nine major accounts/buying groups have been selected where the objectives are to gain major volume sales."

We can see the number of leading reference centres there set out and then we're told that:

"Oxford have been buying Koate ... until recent

product problems appeared."

Thank you. The next paragraph deals with tenders for the Royal Free, to be issued in January 1981, and then expectations of an order from Cardiff and Leeds and efforts being made to repair previous damage done to business relations at Alton. So that's Treloar's.

Then if we go to page 13, we can see what's said to be supporting activities. So these are some of the ancillary services or facilities being offered, it would appear, by Cutter. So "Education Programme": booklets, leaflets, posters, magazines and the like. "Service Programme", which includes home care packs, for example. And then "Meetings": hospital meetings, Haemophilia Society meetings, national and international meetings, Haemophilia Nurses Association.

So an insight into the marketing strategy of Cutter in relation to Koate in 1981.

I'm not going to go through all of the documents, but we can just then see to some extent whether those objectives were realised in the following years, BAYP0000019_073. This is a 1982 marketing plan. If we go to the third page, it's said that:

"1981 has proved to be a difficult year for Cutter Laboratories, largely due to factors outside our

control ..."

1.3 refers to:

"Koate quality problems, coupled with adverse publicity concerning quality problems with Humanate, the pirate Koate product sold by Speywood Laboratories [again, we'll come back to that tomorrow].

"Continuing difficulties in obtaining sufficient Koate in required potencies ..."

But it's then said:

"Nevertheless, we feel that we have established the Company very firmly in the eyes of both customers and competitors and that we are now well placed to achieve our ambitious plan for 1982."

Then if we go to page 18, under the heading "Market Information", there's then a table of estimated total usage of concentrate, as at July 1981, with the estimated shares being there set out: so Armour significantly increased, 41%; and Cutter there at 13.2%; and we can see the figures for the other companies, as well.

So that's 1982.

1983, CGRA -- sorry, that's a 1982 plan looking at the situation in 1981. If we go to CGRA0000586, this is described as a 1983 preliminary marketing plan. If we go to page 3, we can see the "Overview", 1982 is

described as having been:

"... a year of major difficulties in all product areas ...

"The major difficulties have been ..."

Then point two is a 20% fall in prices for Factor VIII concentrate. Then below that it's said:

"Our successes in 1982 have been to firmly establish Koate in the Factor VIII market ..."

Towards the bottom of the page, the perspective is offered that:

"The National Health Service continues to be under-funded and we can foresee no fundamental changes in purchasing philosophy in 1983. Price is likely to remain the most dominant influencing factor in our market areas."

Then if we just go to page 9, under the heading "Market Information", this perspective is offered:

"The market is extremely competitive. Prices have fallen by 20% over the last 12 months."

Then if we go to the next paragraph:

"50% of the commercial market is contracted on an annual basis with most contracts being awarded during the first few months of the UK financial year. Our share of this market sector is 20%.

"The market continues to demand cheap factor VIII

with little consideration given to purity [et cetera].

"Nevertheless, we have continued to emphasise the quality of Koate compared with competitive products, and this has gained us substantial business in two major accounts, Cardiff and Liverpool."

Bottom of the page:

"In some major centres, eg Alton, St Thomas' and Belfast a major reason for not obtaining business has been ongoing trials with Autoplex and Feiba. Our failure to again a share of the North West Thames Regional Contract ... was due to a combination of price and doubt concerning our labelled potencies."

Next page, second paragraph:

"Low prices have been the major difficulty in the last 12 months. The average selling price in large centres is now below 5.5p."

Then we can see a table with the market shares set out. Again, we see the figure in relation to Armour, although that's estimated to have dropped between 1981 and 1982, and Cutter's market share to have increased from 13% to 20% from 1981 to 1982.

I'm not going to go to it but the following two pages set out in some further detail some of the particular centres or regions that were going to be targeted by Cutter.

Then if we turn to BAYP0000028_071, if we go to page 7, we can see a description of the position in 1983. Under the heading "Koate", it's said that:

"1983 opened quietly for Koate, due partly to good supplies of NHS product to the centres. However, a good of the sales shortfall is being clawed back in March due to good sales to a major new centre -- Alton. Encouragingly, prices are now hardening fairly rapidly and have risen back above the 6 pence mark."

If we go on a further two pages, please, Soumik to page 9, again it is said that the market is fairly quiet, it is anticipated that 1983 will be a good year for Koate, and I'm, again, not going to go through the detail of that, but the anticipation in that final paragraph is:

"These developments should enable us both to gain market share and to command higher prices for Koate in 1983."

Then the last document I think that we need to look at in this category of documents is at BAYP0000028_134.

This is an internal memorandum described as a key indicator report. It's dated 11 July 1983, and it's in respect of June 1983. We can see bottom of the page, under the heading "Koate", there's a paragraph

at the end that says:

"This result was the second best ever with unit sales ... and the best ever with sales revenue. Good sales to all major accounts including a very large order to the Royal Free Hospital achieved this result."

Then if we go to the third page, "Record sales of Koate demonstrate that no changes in treatment levels because of AIDS have occurred in the UK. Information required by the DHSS concerning checks on plasma collection etc, was supplied with the assistance of Cutter International."

That second sentence, sir, I think is a reference to the steps we know were taken by the Department of Health in around June 1983, to find out what, if anything, was being done in relation to the FDA recommendations and products made from plasma collected before March 1983.

So, we do have other such documents from Cutter, but don't want to go through all of them. That gives, I hope, a flavour of the position in relation to the first part of the 1980s.

What I'm going to do after lunch, then, is to turn to a range of documents which look at issues of plasma supply, so where Cutter Laboratories in the States was

getting its plasma from, collection from prisons, pool sizes, and various documents relating to issues about donor screening in the 1970s and 1980s.

SIR BRIAN LANGSTAFF: Thank you very much. Well, we'll take a break, then, until two o'clock. Two o'clock.

(1.00 pm)

(The luncheon adjournment)

(2.00 pm)

MS RICHARDS: Sir, I'm going to move on to look at various matters relating to the sources of plasma and to issues relating to donor selection and screening. I hope to do it thematically and then chronologically within themes but, in fact, there are documents which pertain to all three, and rather than go back to the same documents, what we might end up doing is looking at them in an order that isn't necessarily completely chronological. So I hope that's okay.

I want to start, however, with some documents which are from the first part of the 1970s and which look at Cutter obtaining supplies of plasma for fractionation from outside the US. So we can start with BAYP0003693. This is Cutter Laboratories, the date at the top is 3 December 1971, writing to the Division of Biologics Standards at the National Institutes of Health, referring to a purchase order

for human plasma for fractionation from Mexico and we can see reference to inspection of the facility taking place in September 1971, and the request is made for a permit for importation of products in short supply.

If we go over the page, we can see a little more information given:

"This our purchase order contract for Plasma (Human) for fractionation ... collected by plasmapheresis as 'Products in short supply' ... at Banco de Sangre Biologico, Mexicano ..."

Next paragraph explains that they're authorised by the terms of this order to ship up to 2,000 litres per month through March 1972. If we go to the next page, it records that the centre:

"Banco de Sangre agrees to permit inspection of any facilities used in the collection of plasma under this contract by Director of Control, Cutter, his designee, or the Division of Biologics Standards."

If we then go to BAYP0003700_005, we can see from this letter dated 20 March 1972, from Cutter Laboratories, that the permit for importation of products from Mexico was issued, and the request is being made for the permit to be extended to December 1972.

If we go to BAYP0003700_006, we can see there the

permit that was indeed extended. The date of this is 29 March 1972, and it's permission to import human plasma from Banco de Sangre Biologico Mexicano, and the date is 1 April 1972 ending 31 December 1972.

If we then look at BAYP0003700_001, this is 3 March 1972, and we can see here reference to a purchase order for human plasma for fractionation from Hemo Caribbean in Haiti:

"This to serve as your notification of this source of plasma ..."

Then the information is there given. Reference is made to the facility in Port-au-Prince having been inspected on 24 February 1972.

We can see that permission was given at BAYP0003700_004. This is the permission to import from Haiti human plasma for fractionation for a period beginning 5 March 1972 and ending 1 September 1972.

If we then go to BAYP0003748, this is now February 1974, and we're back to purchasing plasma from Mexico. A request is being made to the FDA for a permit for importation of products in short supply from Plasma Mexicano.

SIR BRIAN LANGSTAFF: That's a different supplier --

MS RICHARDS: Yes, it is.

SIR BRIAN LANGSTAFF: -- because the other one was

Banco de Sangre.

MS RICHARDS: Yes, it is a different supply. If we then go to BAYP0003777, this is October 1975 and, again, this is a letter directed to the Bureau of Biologics at the Food and Drug Administration, and this is a request for:

"... authorization to ship 15,434 liters of Fresh Frozen (Human) Plasma, collected from normal donors to, Cutter Laboratories ..."

We can see in the second paragraph that:

"The use of this plasma will be for manufacturing purposes into Human Injectable Materials."

We can see from the third paragraph reference made there to this organisation having been already authorised to make the same shipment to Abbott Laboratories, but it said it didn't then take place because they were over stock.

The organisation making this application, if we look at the letterhead at the top of the page -- sorry, the very top of -- no, actually, we can see it from this. It's okay, I was going to look at the top of the first page but, actually, this is probably easier to read. We can see that permission is granted, and this is to a source of plasma in Nicaragua in Managua, Centro Americana De

Plasmapheresis, Managua, NA.

If we then lastly go to BAYP0003793_002, this is the same facility at the Centro Americana De Plasmapheresis in Managua, but we're now 6 April 1976, and this a further request for authorisation to ship 7,000 liters of fresh frozen plasma to Cutter Laboratories. Again, the use is for manufacturing purposes into human injectable materials.

Those are some documents which show that Cutter Laboratories, in the first half of the 1970s and into 1976, was obtaining some plasma from various sources outside of the US.

I'm going to ask you to look next at a couple of documents, which seem to be speeches or parts of speeches by people from Cutter which you may find interesting in providing an insight into the thinking within the organisation at the time. The first is IPSN0000481_002. This is headed "Blood Transfusion Business -- International", the date you'll see in the top right-hand corner is July 1977.

It's an incomplete document. But it seems to be the text of a report setting out views about the blood transfusion business, and I'll just read some parts of it:

"Although there are present problems and

uncertainties in the area of blood collection systems development for Cutter, we must be careful to avoid being sidetracked from our central mission, which I understand to be the protection of current plasma fraction business and development of a stronger, more secure future position in the wider enterprise which constitutes the 'Blood Transfusion Business'."

If we look at the bottom of the page:

"The plasma fractionation industry, which was largely built upon the Cohn process and has developed since World War II, has enjoyed relatively unrestricted growth and usually good profits to date. Certain companies have established an enviable trading record and only minor problems of raw material supply and usually price-related market phenomena have served to limit progress.

"Now, however, with the voice and interests of the 'Third World' ever more prevalent, and a conscience-stricken 'Developed World' trying to secure its future in the most socially-acceptable fashion through an 'all things to all men' international façade, whilst pursuing various degrees of broad ranging [international] protectionism" --

SIR BRIAN LANGSTAFF: "Internal protectionism".

MS RICHARDS: Sorry:

"... internal protectionism, the ability of the plasma fractionation industry to continue operating as in the past must be closely questioned.

"The philosophical and pure at heart will want to sell the concept of blood as an international resource, and this would generally be approved by industry, but in reality blood can never be considered in this light within any real world situation which may reasonably be predicted today.

"In the first place, it is a strategic resource with the obvious implications for national and area security. In the second place, blood/plasma is an intense social issue simmering never far below the surface, and one which neither politicians, members of the scientific community, nor local leaders can allow to get out of control. These statements do not preclude a degree of international cooperative effort, especially in times of acute need and in areas of technological development, but they do point to certain fundamental issues which are causing the blood transfusion business to evolve in ways which traditional commercial enterprise may view as irksome at best and disastrous at worst."

Then it continues:

"In point of fact, the future could be

commercially most attractive if industry can recognise a need to allow local blood transfusion specialists a large element of primary control of the blood resource through the donor, whilst it goes ahead to provide the total means, under industry control, to collect, process, and deliver blood and plasma fractions. The subjective and objective problems of donors, and thus blood quality, associated with paid donors and the bad light in which commercial involvement is cast in this regard, is likely to remain for some time at least, and it seems to me that in placing the major responsibility for raw material supply squarely on the shoulders of transfusionists, they will either have to do a good job and shut up, in which case we all have plenty to do in supplying the patient needs, by combining our resources to effectively use plasma; or they will do a bad job and equally have to shut up because they would have demonstrated that some financial incentive for donors is the only way to get enough plasma."

Then if we go to the bottom of the next page, I'm just going to pick it up in the last two lines on that page:

"... in other words, there is no room for industry to falter in developing new blood collection,

handling, and processing systems if two unfortunate circumstances are to be avoided ..."

And then these unfortunate circumstances are defined as:

"1. Market entry of major new commercial competitors ...

"2. Self-sufficiency/active participation on the part of local scientific/quasi-industrial/government groups based on lack of technological growth and development within the industry, allowing the non-innovators to catch up."

It's not always easy to unpick what's being said here by someone within Cutter, but it does appear to be said that self-sufficiency is regarded as an unfortunate circumstance to be avoided.

If we just pick things up in the next paragraph -- sorry, paragraph below that, my apologies:

"It goes without saying that if you cannot effectively collect the raw material, no-one is in business -- us, our commercial competitors, the transfusionists, the doctors and nurses, and finally and most importantly, the patients who need blood products."

Then unfortunately at the end of the paragraph it stops mid-sentence and we don't have the rest of it.

But some insight into a perspective from I'm afraid an unknown person within Cutter in 1977.

We then, at BAYP0003885 --

SIR BRIAN LANGSTAFF: Was there any form of response to that, do we know?

MS RICHARDS: I don't know, I'm afraid, sir. I've seen it only as an isolated document like this.

SIR BRIAN LANGSTAFF: What in summary is it actually saying?

MS RICHARDS: Well, it appears to be pouring a degree of scorn on -- these are inferences rather than what's said in terms, but a degree of scorn on what's said to be those stricken with conscience wanting to change the way in which blood is collected and commercialised, is one way of putting it.

Maybe we can find out more, find a complete copy or ascertain what the context was within which it was being articulated. Or it may be, I'm afraid, it stands as it is: an incomplete picture into a commercial perspective within Cutter in the seventies.

SIR BRIAN LANGSTAFF: Well, it's an unknown person's reflections using a lot of words to say something.

MS RICHARDS: Yes. We have got a complete text from 1979 by a named person within Cutter at BAYP0003885. This,

we'll see it's prepared for a managers' meeting on the topic of "Blood Products Industry in the US and internationally", by a J Ashworth, 7 May 1979.

It's a document that is probably worth reading in full. I am only going to alight upon a couple of passages. The first is the bottom half of the third page. There's a long paragraph there talking about the position of fractionators, it says:

"In the United States the four big ones are Cutter, Hyland, Armour and Alpha."

Then it says:

"Each of the fractionators has of necessity become involved itself in the collection of plasma and each own from 10 to 20 pheresis centres. Cutter utilises the output of about 100 centers and I think at latest count we own 20 of them".

Just pausing there, in contrast with what we were looking at at a similar point in time in relation to Armour, in which it said -- whether this is factually correct or not, it certainly said on a number of occasions it derived all its own plasma from its own centres.

In relation to Cutter, what's being said here is ownership of about a fifth them.

"There are about 275 centres in the US that are

licensed to produce Source Plasma (Human) ..."

Then, skipping on to the next sentence:

"We are restricted in our raw material to plasma from plasmapheresis centers or blood banks licensed or otherwise registered by the US FDA."

SIR BRIAN LANGSTAFF: Just pausing there for a moment. If each of the main -- the big four, own between 10 to 20 pheresis centres, but there are 275 centres in the US, that would suggest that the maximum is 40-80, call it 80, or you've got about 200 centres which are taking plasma and selling it somewhere. They're licensed to do it for -- by plasmapheresis, and it says here it's used for the principal starting material for preparation of fractions. So it would be interesting to know who the other 200 centres are supplying.

MS RICHARDS: Yes. We will see some examples of individual organisations with whom Cutter contracted for the supply of plasma in a handful of the documents.

Just looking at this in context, it may be I should have shown you the previous page. Because what this article, speech or report does is identify, if we look at the third paragraph on this page, four groups involved in the collection of whole blood.

We have, in this first long paragraph on the

page, the American National Red Cross operating 58 centres, it said.

The next paragraph deals with blood bankers, and refers to the American Association of Blood Banks, with its multiple members.

Bottom of the page describes then another maverick group of blood banks, dissidents from, it's suggested, the American Association of Blood Banks.

Then, if we go on to the next page, we then have the paragraph I was looking at which talks about the remaining group of plasma or plasma processes.

SIR BRIAN LANGSTAFF: Yes.

MS RICHARDS: But the numbers don't entirely add up in any event, in response to --

SIR BRIAN LANGSTAFF: But they are banking blood for use as, on the face of it, whole blood.

MS RICHARDS: Yes. Yes. So I'm not sure, I'm afraid, sir, what the answer to your question is about who the other centres may be.

SIR BRIAN LANGSTAFF: It may simply be that one or other of them does what Cutter does and utilises the output of about 100 centres.

MS RICHARDS: Yes.

SIR BRIAN LANGSTAFF: But it does suggest that Armour is an outlier so far as owning all its own is concerned.

MS RICHARDS: Then, in any event, picking the matter up from where Mr Ashworth or Ms Ashworth is talking about centres registered by the US FDA, it says this:

"We are restricted in our raw material to plasma from plasmapheresis centers or blood banks licensed or otherwise registered by the US FDA. There are none licensed outside the US."

So this is the position now in May 1979.

"The last one was in Nicaragua. The turmoil down there 2 or 3 years ago resulted in the burning of this center."

Then:

"When I mentioned that we get plasma from blood banks, I was referring to about 10% of our input. This is plasma derived from whole blood which has either gone outdated or has been used for the preparation of components such as packed cells. For completeness I should also mention that some of the output of pheresis centers and blood banks goes to the manufacture of clinical laboratories."

And so on.

In any event, the main purpose of referring to that is what is being said by Cutter as at May 1979 is now its sources of plasma are within the US.

Then the second passage I wanted to refer to is on

the next page, bottom half of the next page, and it talks about the issue of hepatitis, and the issue of volunteer versus paid donors, in these terms:

"Then there is the issue which is perhaps the most ridiculous. The highly emotional volunteer donor versus paid donor controversy has wasted more time than it is worth. Most of this derives from the basic danger of transmission of hepatitis. Studies were done supposedly with proper selection of controls which have purported to show that the incidence of hepatitis from blood or its components from donors who had received payment is significantly higher. I won't spend time relating many of the ridiculous and irrelevant issues that have been raised in the course of this controversy. If it were not such a serious issue I think it might be possible to laugh at some of the things that have been done and said. Nevertheless, we ended up having the BoB pontificate a definition of a paid donor and as you can imagine, some of the interpretations of this are peculiar. Apparently one is not a paid donor if one takes a day off from work for giving blood but you are a paid donor if you get a merchandise certificate for some item donated by a well-meaning store. This last issue of the differentiation between a volunteer and a paid

donor has worldwide ramifications also, but more on morality grounds than on safety grounds."

So, again, you'll see the perspective there, from someone addressing this to a managers meeting within Cutter, is to, it would appear, disparage the view that blood collected from paid donations has any safety implications in terms of viral transmission as compared to blood from voluntary donations.

If we can then look at now a document moving forwards from 1979 to November 1983, BAYP0004952. This is, again, just on the theme of sources of supply. This is a minutes of a meeting of the Biological Coordinating Committee, 14 November 1983. We can just see there are some corrections to an earlier set of minutes. This is in paragraph 1 under the heading "Review of Minutes", "Corrections", and it says this:

"The balancing figure used in conclusion 4 of 1,398,000 liters for Factor VIII is clarified to show that this figure includes 1,273,000 liters of source plasma, 90,000 liters of outdate and prison plasma, and 11,800 liters for RhoD and HBIG."

The latter relates to immunoglobulins.

It's the reference there to prison plasma. We're going to pick up on a number of further references to

prison plasma but this is a reference as at November of 1983.

Just so that we don't have to come back to this document for a further purpose, if we go to the bottom of page 3, there's a heading "AIDS material", and it says:

"With regard to the AIDS work in process material planned for GP production, it was decided that two lots of this material would be heat-treated for possible submission to the OB [that is, presumably, the Office of Biologics]. This would result in an indication from the OB as to what their policy would be with regard to approval of heat-treated product obtained from possibly contaminated sources."

So again just flagging up there, in terms of any consideration of plasma source, what appears to be Cutter's own characterisation of this, or the use of this term, "possibly contaminated sources". But, I'm afraid, we know no more from the context of what that was specifically referring to.

I mentioned that we have various documents which refer to Cutter entering into agreements with organisations for the provision of plasma. A sample agreement is at BAYP0005642. We can see this is an agreement made on 1 October 1984 between

Cutter Biological, described there as a division of Miles Laboratories Inc, and Central Georgia Plasma Labs, that's the organisation that's going to be supplying products. And we can see from the recital that the:

"Supplier [so that's Central Georgia Plasma Labs] operates three (3) plasmapheresis centers... at which Source Plasma ... is produced. Currently ... located at ..."

Then we've got three locations there identified.

And then it goes on to talk about the supply to Cutter of plasma from the centres. If we go to the top of page 2, we can see there, under the heading "B. Quantity of Source Plasma", what's envisaged is 3,000-4,000 litres per month being purchased by Cutter.

If we go to the next page, under the heading "E. Price Adjustment", we can see there examples of two other contract supplies to Cutter, so it says there:

"Other contract suppliers to Cutter are Yale Blood Plasma and Atlantic Plasma Corp."

So just examples, no specific information in relation to the particular plasma providers, but we can see there clear evidence through into the latter

half of 1984 of Cutter obtaining plasma from this range of apparently commercial sources.

If we then go to CGRA0000545, this is a document we looked at in the context of Armour. It's one of a number of industry meetings that take place around this time -- this is April 1985 -- with representatives from the different fractionation companies. And we'll come back no doubt to this or similar documents in November when we look across the board at the pharmaceutical response to risk. We can see there's a discussion here about ALT testing in particular.

I just want to go to the second page and pick up upon the heading "Prison Plasma". We looked, I think yesterday, at what was said by Armour in relation to that, which was that they will never have any.

The position of Cutter is different. So:

"This subject [elicits] even more diverse viewpoints. Cutter and Alpha believe that science has progressed to the point that we can screen this plasma through testing (HTLV-III etc) and we now heat treat the products."

And then the viewpoints of different companies are expressed, and then it says:

"Nevertheless, we agreed to hang together for

a try with the FDA. We will propose to begin using prison plasma cryo and abandon our 'Gentlemen's agreement' unless the FDA takes issue and threatens regulatory action."

Now, it might be thought from reading this and looking at the date, which is April 1985, that Cutter, in saying, "we'll propose to begin using prison plasma" that it hadn't been using prison plasma for a considerable period of time, but whether that's correct or not, we'll see from other documents that would seem to cast some considerable doubt on that.

If we then go to BAYP000024_183, this is an internal Cutter memorandum 22 April 1985. It says:

"... we have the following information on importation of plasma to US during the 1970s for use in the manufacture of Cutter products."

It's said that there were none in 1970 and 1971. 1972, we can see the reference to there being the importation of plasma from Mexico, from Haiti, again from Mexico. None, it's said in 1974 and '75. Then 1976, 1977 and 1978, records there of importation of plasma from Nicaragua.

Then, obviously we've seen some of the underlying documents that probably pertain to this. It then said:

"No other plasma was imported for our use during these years and we have never procured plasma from Africa for any use including the manufacture of Cutter products."

If we then go to CGRA0000307. This just picks up upon what we saw in that meeting from April 1985, the discussion about whether to use prison plasma on the basis it could be tested. What's being said here, in a letter dated 29 August 1985, is:

"Against my personal feelings, based on the evidence that we can and should use screened prison plasma for our heat-treated plasma products, it appears we will have to abandon that idea for now."

Then the second part of the next paragraph:

"The fact that the other US manufacturers of coagulation products have agreed not to use prison plasma pretty well dictates our position for the moment."

So it may be inferred from that that, from Cutter's perspective, they would have been keen to be using prison plasma on the basis of it being screened or heat treated, but felt unable to do so as at August 1985, because other US fractionators were not taking the same position. As I say, there's going to be some more documentation in relation to the use of prison

plasma that I'll come back to.

The next document picks up on the theme of prison plasma at a much earlier stage, CGRA0000884. This is an article from 1968 praising a plasmapheresis programme at Parchman State Penitentiary, and we can see, if we look in the second paragraph, it's said that:

"This program authorized by [a particular Senate Bill] is conducted under contract with Cutter Laboratories ..."

Then the next paragraph goes on to say that:

"Participation in the plasmapheresis program by Parchman inmates is voluntary, and the present rate shows that as many as 20 per cent of the 3,000 prison population are offering plasma weekly."

So we can see there an early indication of the use of prison plasma in 1968.

I'm moving to look more now at issues relating to donor screening. We have a document from 1981 at BAYP0000019_018. I'm not going to take you through the detail of it, sir, because it's a long document. It's entitled "Cutter System of Plasmapheresis".

In fact, if we go to the next page, we have, at the very bottom of the page, what looks like it might be a date of 27 September 1976, but on the pages that

follow, and if we just look by way of example, the date is then 1981. In any event, this appears to set out effectively a standard operating manual or procedure about the kind of steps that need to be taken in the plasmapheresis centres.

If we just go to the previous page, please, Soumik. We can see, if we go to the top half of the page, reference to donor health checks and record-keeping, and then there is a fairly detailed description of the various steps to be taken. If we go to the next page, we pick it up about ten lines or so down. We've got -- this is -- looking at the index is a convenient way of not going through the whole document -- 2.5.1.2, "Report of Donor Reported to Have or Have Had, Clinical Serum or Infectious Hepatitis ..."

So, for example, this sets out number of procedures that are supposed to be taken in the event of a donor appearing to have or being reported to have hepatitis.

Then if we go, just by way of example, to page 9, this is in a section of the document about donor health check, and there's a description of medical history and physical examination. So steps that are supposed to be taken in the plasmapheresis centres.

What the status of this document is and whether it applied only to centres owned by Cutter, as opposed to those from whom it had contractual commercial arrangements for the supply of plasma, I'm afraid is unclear.

As I say it's a lengthy document, I'm not going to go through it, but it certainly purports to set out various steps that should be taken including in relation to the undertaking of certain forms of health screening in relation to donors.

As I say, I think that is dated 1981. If we go to another document from 1981, BAUM0000012. This is dated 19 May 1981. We've got the heading "Cutter Laboratories, Inc, Oakland Plasma Center", at the top of the page, and it's addressed to the Plasma Procurement Manager at Cutter Laboratories Inc.

It refers to an inspection by a Department of Health service examiner for the State of California, and says this:

"Mr McClelland [the examiner] found the center to be in compliance in all areas except for the practice of accepting donors into the programme who have a past history of illegal IV drug use. The standard operating procedure at this facility is to accept these prospective donors if they meet all other

requirements and if the drug use was more than six months prior to their plasma donation.

"Mr McClelland felt that this procedure is not in compliance with both the State Regulations ... and [it's said there] the CFR [I think that's the Federal Regulations].

"This procedure is allowed by the Cutter [standard operating procedure] ..."

That, I think, is the document we were just looking at, which certainly has a paragraph 4.0.4(e):

"... so conforming to Mr McClelland's interpretation would result not only in a manual change, but would also adversely affect many plasma donors."

So, again, some insight into the approach being taken apparently in one of Cutter's own plasma centres.

If we then turn to BAYP0004282_002, this is a Cutter letter sent to the National Haemophilia Foundation. It's in response to the National Haemophilia Foundation having written to Cutter, and indeed others, concerning various resolutions about exclusion from donor groups in light of risks of AIDS. This letter is 15 November '82.

It picks up in the second paragraph on the issue

of donations from intravenous drug users. So it asserts here:

"All suppliers of plasma to Cutter conduct screening of their donors in accordance with written procedures to assure freedom of the arms and forearms from skin punctures or scars indicative of intravenous drug abuses. In situations where doubt exists (skin punctures claimed to be the result of previous plasmapheresis) the origin must be verified or a conservative judgement for donor rejection is made."

So that is what Cutter is saying, as at the end of 1982, is supposed to be the approach in the centres from which it obtains its plasma, to the exclusion of drugged users from donation.

Then the next paragraph says this:

"Since the first reported incidence of AIDS was confirmed in haemophiliacs receiving plasma components, Cutter has excluded from coagulation products all plasma collected from plasma centers known to encourage donations from the homosexual population. Because of the sensitivity of the issue, we have not made overt efforts to identify the adventitious active homosexual or Haitian refugee in our normal donor population."

Now, just -- sorry, can we go back into that

paragraph? Again, the inference that you may think can be drawn from this letter, sir, is that, prior to November 1982, there were plasma centres known to encourage donations from the gay population from whom Cutter was procuring plasma, and whether that situation, in fact, came to an end, as at November 1982, or not, is an issue explored in some of the documents. We might look at a handful of them today, but it's more likely to become an issue to come back to thematically in November.

SIR BRIAN LANGSTAFF: The next sentence as well, perhaps, shows what they weren't doing.

MS RICHARDS: Yes. Yes. As at that point in time, that was I think, effectively, the only step being taken. We will -- I think we saw a document this morning but there are a number of other documents which then look at the position as at February, March 1983 when there is the introduction of the questionnaire and attempts made to exclude others from donation.

SIR BRIAN LANGSTAFF: Well, by March the FDA were --

MS RICHARDS: Yes.

SIR BRIAN LANGSTAFF: -- introducing recommendations.

MS RICHARDS: If we then go to CGRA0000425. Again, this is a document that we will probably come back to in November, but it contains important information in

relation to Cutter's approach. So dated 13 December 1982 and we can see it says:

"Dr Donohue asked for an informal meeting with the four Blood Product Manufacturers following the PMA/FDA Liaison Committee Meeting on Friday to explore possible actions to minimise the risk of AIDS. Although the transmission of AIDS via blood products (and specifically AHF) has not been conclusively demonstrated, there is some evidence that a possibility does exist. Donohue wanted to know what we manufacturers could do immediately to minimise the risk of potential exposure.

"Donohue specifically asked if we could simply exclude high risk plasma taken from areas such as New York, San Francisco and Hollywood from AHF production. Mike Rodell (Hyland) responded that he felt a more meaningful response would be to attempt to educate the high risk populations (homosexuals, Haitians and drug users) and have them voluntarily exclude themselves from the plasmapheresis programme."

Then there's further discussion about what steps could be taken in that regard.

Then the next paragraph is this:

"Donohue then asked if we were willing to exclude plasma collected at prisons because of the homosexual

link, and because it constituted only 2% of collected plasma. The other manufacturers had no problem with this suggestion, but it was pointed out that this was the source of our hyperimmunized donors. Donohue then suggested that we exclude this plasma from any AHF production. It is my opinion that they will remain relatively non-negotiable on this point. It was indicated that there had been no cases of AIDS reported from prison, and Donohue responded that that was because of the etiology of the syndrome and insufficient time had transpired."

Then what's written -- sorry, if we can go into what's written in the handwriting, to the left of that paragraph.

"This will be a problem at Cutter."

I think that's then:

"John Hink will want to look at the [percentage and] costs", or something along those lines.

Anyway "This will be a problem at Cutter", I think is fairly clear.

So, as at December 1982, documentation here demonstrating Cutter obtaining plasma from prisons. Then we can see:

"The final item of discussion related to recovered plasma. Donohue pointed out that we would have

distinctly less leverage over any voluntary reduction of high risk donors in recovered plasma. He said he felt we should consider very carefully if we should accept any recovered plasma collected from high risk populations. (He indicated the Irwin Blood Bank specifically.)"

Then, if we go over the page, we can see in the last part of this memo:

"Dr Donohue asked that I get back to him by Friday of this week ... with our company position on the following:

"Voluntary education programme to exclude high-risk donors [someone has written 'support'].

"Plasma collected at prisons [?].

"Recovered plasma [?].

"Financial support for buts on AHF transmission of AIDS [support]."

Again, we'll be coming back to a number of these materials in November, but useful in terms of looking at source of plasma.

SIR BRIAN LANGSTAFF: Yes, recovered plasma, I take it, is the plasma which is part of a blood bank donation which isn't used because it's time expired?

MS RICHARDS: Yes. What's not clear to me, I'm afraid, sir, and this may be my own lack of knowledge, is

precisely what the concern was there about having distinctly less leverage.

SIR BRIAN LANGSTAFF: Well, I would think it may be because it comes from blood banks who are responsible for their own collection, and haven't been scrupulous to eliminate donors whose contributions to a big pool might be particularly dangerous.

MS RICHARDS: Yes. That may be right.

SIR BRIAN LANGSTAFF: That's a possible interpretation. I mean, plainly, there may be others and, in due course, we can look at that.

MS RICHARDS: Then there's a further document from Cutter dealing with these discussions with Dr Donohue, but this is, I think, a more specifically Cutter discussion. It's at BAUM0000009, and this may cast some further light, sir, on the point you've just raised:

"John Hink and I spoke with Dr Donohue on Tuesday [21 December 1982], regarding our proposed actions on eliminating high risk plasma from our coagulation products. We outlined our proposed education programme to attempt to identify and exclude high risk donors. Donohue commented that we should also consider a program for sources of potential recovered plasma. Once again Irwin Blood Bank (which the CDC

have reported obtains 30% of their collection from the homosexual population) and border locations in Texas were specifically mentioned.

"We reviewed the use of source plasma collected in prisons and Donohue stated that the actual risk was less important than the perceived risk. He felt that pressure would be applied to [insure] that this source of plasma did not end up in the manufacturing process for coagulation products. He mentioned that we should very seriously consider excluding the prison derived plasma from AHF [antihaemophilic factor] and Factor IX."

There is then reference to there being a further meeting in early January and a request in the last paragraph to sending some official notification of Cutter's plans.

Over the page:

"Our course of action at this point would appear to be:

"1. Attend CDC meeting ...

"2. Continue work on education program for high risk donor.

"3. Coordinate the same with the other fractionators.

"4. Consider removing prison derived plasma from

coagulation product production."

Again, that would again appear to suggest, at this point in time, end of 1982, prison derived plasma was being used by Cutter in coagulation product production.

And there is, I think then a further account of, on this issue, it may be an account of the same conversation, this time from Mr Hink, I'm not sure. BAYP0004321. The first paragraph -- you can see it's from J Hink, the first paragraph refers to discussion with Dr Donohue, from the Office of Biologics.

Then the second paragraph says this:

"We told him that we had discontinued the manufacture of coagulation products from plasma collected from pre-dominantly homosexual donors ... We described our plan for requiring all donors to read a brochure describing AIDS and identifying what are considered 'high risk' donors (IV drug abusers, homosexuals and individuals recently living in Haiti), and then asking each donor in the confidentiality of the predonation screening booth if he/she considers himself a 'high risk' donor. If so, we would request that he voluntarily remove himself from all bleeding programs.

"I described to Dr Donohue the manner in which

homosexuals are segregated within the prison and explained to him that we do not bleed known homosexuals in our two prison centers."

So, again, the clear inference would appear to be from that that Cutter had, whether directly operated them, or they were regular suppliers, but two centres within prisons from which it obtained plasma.

"Although I indicated that our AIDS educational program would be used at the prison, Donohue was quite clear that the explanation would not be expected to be accepted by the news media, haemophiliacs or even the scientific community. He strongly advised that all prison plasma be excluded from use in the manufacture of coagulation products.

"We asked his thoughts on Recovered plasma and again he brought up Irwin Memorial and the infant who contracted AIDS following a platelet transfusion from a donor who 8 months later came down with the disease. He indicated that 30% of Irwin's donors are homosexuals (a high degree of altruism!) Donohue later made assertions about centers located on the Mexican border and in Florida."

So I think that's Mr Hink's perspective on the meeting described in the earlier document.

Then there's what's described as a trip report

account of an AIDS meeting in January 1983 at BAYP0004345. If we look at the top, again, we can see it's a Cutter document. It's from JJ Peterson, subject "Trip Report, AIDS Meeting - Orthopaedic Hospital, [Los Angeles]", and I think the date there is 3 January 1983.

I'm not going to go through most of the document, but if we go to the fifth page -- I'm sorry, can we start from the third page, just so we can see the context.

Just below the first paragraph we can see it refers to written questions from the audience and responses. Then there are various questions and various answers. Note, the first:

"Question: Does taking concentrate transmit AIDS?

"Answer: Presumably yes."

In any event, if we go then to a question that was answered by Cutter on the fifth page, so it's the last question and answer:

"Question: Dr Kasper to Cutter -- These centers seem to be in rundown centers of town. Is there a move to move them to rural towns?"

Then the answer isn't necessarily an answer, direct answer to the question. The answer from Cutter appears to be:

"Many of the centers are in smaller communities, and in towns such as Ypsilanti, Seattle, Clayton ... and San Diego. We do not have centres in LA or San Francisco."

Again, there are other aspects of that meeting to which we'll return in November.

Then if we look at BAYP0004386, this is still January 1983. You'll recall, sir, that yesterday I showed you a couple of documents which appear to be from public relations firms, pushing forward proposals for a PR strategy or initiative for the concentrate manufacturers to embark upon, and I pointed out that it was by no means clear whether that was a document that was commissioned by or reached Armour. We can see that Cutter had direct knowledge of it. It says this:

"Bud, Carolyn and I interviewed three public relations firms this week to see if it made sense to select one of them to provide counsel and other assistance with regard to the AIDS situation. We felt that even Burson-Marsteller or Hill and Knowlton [and those were the two names on the documents we looked at] both could do a good job for us. Today we selected Hill and Knowlton, one of the larger national public relations firms."

Then the next paragraph:

"We anticipate our relations with them to be in two phases. Phase I will start immediately and they will help us prepare a company position on AIDS, advise us as to training in our plasmapheresis centers, and also the training of a company spokesman. We expect to have this completed by February 7 or 8. With this in place, then we will begin the screening of our plasmapheresis donors to exclude the high risk groups during the week of February 7. After this is accomplished, Hill and Knowlton will supply us with a longer term program of costs for our evaluation."

Then if we go to BAYP0004434, this a Biological Management Committee meeting dated 15 February 1983. If we can go to the second page, we can see paragraph 10 is headed "Plasma from Prison":

"It was decided that we will no longer release Koate from prison plasma as commercial product, thus forestalling regulatory action. Instead this plasma will be processed separately and the AHF produced will be used internally in R&D [so research and development] and technology programs."

This would appear to suggest that it's mid-February 1983 when Cutter decide that they will no longer be using -- selling Koate which has been made

from prison plasma. But the words "thus forestalling regulatory action" might be quite telling in themselves as to what has driven Cutter or what might be thought to have driven Cutter to taking that decision.

If we can then -- and we're still in 1983 at this point -- go to BAYP0004531, we've a letter here from Mr Hink at Cutter, and we can see his job title there: director of plasma procurement, dated 8 April 1983, to the president of the Valley Medical Blood Research Institute, and we can pick it up I think -- well, the first paragraph refers to what I think, there, are the FDA recommendations that we know were issued in late March of 1983. The second paragraph then says this:

"It is my understanding that the plasma you supply to Cutter is collected from a predominantly homosexual donor population. Cutter has for some time [doesn't tell us how long] excluded such plasma from use in the manufacture of coagulation products. It is the request of [the Office of Biologics] that all plasma collected from donors suspected of being at increased risk of transmitting AIDS ... be labeled in the following manner to prevent its possible misuse ..."

Then we can see that the label is:

"CAUTION: For Use in Manufacturing Albumin PPF, or Globulin Only."

So the position that we appear to derive from this as of April 1983 is that plasma acquired from centres known to collect from a predominantly gay donor population is no longer to be -- well, was no longer being used, it is said -- not quite clear for how long that had been the case -- in the manufacture of factor concentrates; and now there was going to be a labelling requirement in relation to such plasma, presumably to assist in securing that objective.

If we go then to BAYP0004647, we can see in what's described as a "Marketing Bulletin", July 6, 1983, a description of what is, by this point, the initiatives or measures that Cutter say they've put in place in order to reduce the risk of donations from high risk groups. So we can see the first paragraph says:

"Earlier this year Cutter Laboratories intensified its plasma donor screening program in response to the increasing medical concern over AIDS. This intensification keeps the emphasis on providing quality products squarely where it belongs. By eliminating potentially unhealthy and hepatitis B positive donors, Cutter has traditionally reduced the risk of transmission of serious disease agents to the

blood products.

"With the initiation on March 1, 1983 of additional screening procedures to reduce the possibility that AIDS may potentially be transmitted through certain blood products ... Cutter has reinforced its existing program of donor screening to assure that the raw material for its quality plasma products continues to be of high quality."

Then we can see towards the bottom of that page reference is made to intensive work to develop and refine a process to exclude both hepatitis and other viruses. And it continues over the page with the discussion of the attempts made to develop a heat-treated product.

Then if we go to two documents now which show interactions within the United Kingdom between the Department of Health and Cutter in the UK.

BAYP0000002_183.

This is a letter dated 3 June 1983 from Cutter to Dr Fowler in the Department of Health. We can see this is in response to Dr Fowler's request for information about measures being taken in relation to AIDS.

What's said in the third paragraph:

"One of the major difficulties in dealing with the

many issues concerning AIDS is the absence of persuasive data ..."

Not quite sure what that means.

"... and this is complicated by the oft-times sensationalist and erroneous reporting in the press. We have seen recent examples in The Mail. As a result, false conclusions are arrived at and patient treatment as well as product supply are endangered.

"The facts about AIDS are very limited:

"1. The syndrome is quite ill-defined and cases may not be fully reported outside the US. The WHO has recognized it as a world-wide health problem.

"2. The etiological agent is unknown. It is not known whether it is a virus.

"3. Hence, it can only be an assumption that AIDS can be transmitted by certain blood products. This has not been shown.

"4. Also, it is unclear whether the syndrome contracted by hemophiliacs really is the same as the AIDS syndrome contracted by other high risk groups."

Now, whether what's being said here by Cutter in the UK to the DHSS is an accurate and fair reflection of what was being said and had been said for some months by now within the US is a matter that you may wish to consider in due course.

The letter continues:

"As medicine and the plasma suppliers (commercial and NHS) struggle to find the correct actions to take to exclude the elusive AIDS donor, it is imperative that the supply of products (in particular Factor VIII) not be reduced to levels where patients can not be treated. The statement by Professor Bloom in the attached communication from The Haemophilia Society is particularly pertinent."

So we have Cutter there relying upon what Professor Bloom had said.

"All participants in the procurement and supply of Factor VIII (either cryoprecipitate or concentrate) face the same dilemma. There is no test for AIDS. What we (and presumably other countries, including the UK) are doing is to attempt an unproven and probably inadequate screening of donors by certain gross definitions of high risk groups and general physical examinations. Only time will tell if these checks on donors are accurate.

"More specifically, addressing your questions" --

Sir, sorry, I should have said, I said I thought this was from Cutter in the UK. It's not. It's from Cutter Inc, so the US organisation. Mrs Tatt, from the UK company, had sent the letter from Dr Fowler to

them for response, so I should correct that.

Then this:

"More specifically, addressing your questions:

"By common agreement and with the regulatory pressure of the US DHSS, all plasma donors are screened to an extent consistent with present medical-scientific knowledge. This program is spelled out in the attached Cutter documents and FDA directives which may be the same as already supplied to you by Mrs Tatt. Cutter and the other manufacturers are supplying in every detail.

"2. The cases of AIDS in haemophiliacs are of course complicated to follow up but our investigations indicate that none received Koate.

"3. So far, we have not had to make a decision concerning disposition of a lot of Koate from a donor who has become an AIDS victim. It is our plan that if this circumstance should occur, the decision concerning the lot would depend on many factors including, most importantly, receipt of advice from government health authorities based on the latest knowledge concerning AIDS.

"Cutter intends to keep aware of progress in the world and the identification of the mechanism of the syndrome itself, of possible tests which may be

applicable and of methods of treatment of product designed to prevent transmission of AIDS."

So that's the -- it's from J Ashworth, possibly the same J Ashworth we saw in that May 1979 speech earlier this afternoon, to Dr Fowler, June 1983.

Then if we look at BAYP0000028_143, there's a telex which refers to that letter. So the date, I think, is 15 July 1983. And it's from the same JN Ashworth. It says:

"Obviously the pipeline from donor to recipient is long."

Then there's a description of various lot numbers and earliest plasma collection dates.

Then the text says this:

"At the risk of being repetitious on points you are already aware of, we suggest stressing the following:

"1. Cutter instituted supplemental screening and the donor form immediately after the February 23 press release. Nevertheless, a case can be made that the standard procedures before February 23 were such as to be effective in detecting what are now called AIDS symptoms. Marie [Mrs Tatt] has the before and after procedures for plasmapheresis screening on which were highlighted the additions.

"2. It is also significant, as we pointed out in our news release, that Cutter does not obtain plasma from the high risk areas where most of the AIDS cases have occurred -- San Francisco New York, Los Angeles and Miami."

Of course, what is not pointed out is that Cutter had been obtaining, it appears, plasma for years from prisons.

"3. Our letter of June 3 [that's the one we just looked at] ... to Dr Fowler and particularly the attached statement by Professor Bloom [so further reliance on Professor Bloom's statement] seem very pertinent.

"It would appear our present stock does not qualify for DHSS arbitrary decision that something magic happened on February 23. We share whatever frustration you may feel."

You may find that, sir, telling in relation to demonstrating the attitude of the author as to the enquiries that were being made from a regulatory and public health perspective from the Department of Health.

SIR BRIAN LANGSTAFF: Yes.

MS RICHARDS: Then, if we turn now to a letter dated 23 November 1983. BAYP0004975.

This is a letter written by Cutter to an American doctor. It follows, and I won't go into all the other background documents, the identification of a donor who had AIDS. The relevance of this letter for present purposes is what's said about the size of the donor pool in the third paragraph.

"We have been assured by Federal Authorities and several AIDS experts, that due to the enormous dilution of his plasma in the AHF pool, it is highly unlikely that transmission of AIDS to a recipient would occur. Each AHF pool contains plasma from as many as 7,000 to 15,000 individuals. While we are not required to recall the lots involved, we felt a moral obligation to do so."

You'll recall the terminology used in the licensing material and, indeed, as we'll see later, in various product sheets, uses that phrase, "at least 1,000 donors", and I drew attention this morning, sir, to the phrase "at least". It's not untrue to say "at least 1,000", but this suggests it may be regarded as something of an understatement to say "at least 1,000 donors".

SIR BRIAN LANGSTAFF: Yes, and if it contains plasma from as many as 7,000 to 15,000 individuals, that will be at least 7,000 donations, assuming that each

individual only gives one donation to the pool.

MS RICHARDS: Yes.

If we then just look at BAYP0005729, this is another set of minutes from the Biological Coordinating Committee. We're now in April of 1985. You'll see the heading "Update on Plasma Procurement", and we can pick it up in the fifth line:

"We expect 4,000 liters per month more of prison plasma by 3rd quarter. S Ojala and other manufacturers will be meeting with the FDA regarding prison plasma for AHF."

So apparently prison plasma is still being collected, albeit that it may be that it's not being used or hadn't been used at this point in time for factor concentrates. But what seems to be contemplated is a discussion with the FDA about now using it for the manufacture of factor concentrates.

Then I think the last document perhaps, before we break, then follows up on that at CGRA0000311. 1 May 1985.

We can see from this document that Cutter remain, I think it's fair to say, keen to be able to use prison plasma in the pool but the Bureau of Biologics don't necessarily seem to agree, so it says:

"... I informed Charles Carman and Peter Levine of

our planned efforts by the Bureau of Biologics ... to cancel the 'gentlemen's agreement' not to prepare coagulation products from prison plasma. Peter Levine spoke personally rather than as a spokesman for the NHF [National Haemophilia Foundation] but it's pretty clear to me that he believes he is correctly representing the NHF's point of view when he indicated that he did not want to see us return to prison plasma as a source for AHF. Although he accepts the HTLV-III inactivation data with heat treatment, he still feels that by returning prison plasma to the pool, we are taking risks that are not justified. Specifically, increased risks for hepatitis Non-A and Non-B, as well as hepatitis B.

"I told him that we would be continuing our dialogue with the BOB in an effort to use the cryo from prison plasma because we felt it was safe, and we felt our request was justified. I also said we would continue our dialogue with him. Needless to say, this matter is not resolved and Dr Levine still has to be convinced. He felt that treaters would pay up to 1c more to avoid prison plasma. Obviously, a very general comment that means nothing to us."

So that I think then brings the position in relation to prison plasma up to the middle of 1985.

Sir, I've a handful more documents relating to donors and prisons but I can pick that up after the break.

SIR BRIAN LANGSTAFF: Yes, just before you do, was it the marketing bulletin in July 1983 that you showed me earlier which talked about the important thing being to make sure that you got the donor selection, the quality product, rather than concentrated upon treating product which you've got?

MS RICHARDS: I can't remember, I'm afraid, sir, off the top of my head. I'll check over the break.

SIR BRIAN LANGSTAFF: We might have another look at that because, on the face of it, if that's right, what was said for public consumption was not actually what Cutter were then doing in looking to use prison plasma. They were relying upon the treatment rather than the source.

MS RICHARDS: Yes. I'm just seeing if I've got the reference to hand for the document.

SIR BRIAN LANGSTAFF: It may be BAYP4647 -- 0004647. But it may not be that document.

MS RICHARDS: Yes, there's the marketing bulletin from July '83.

SIR BRIAN LANGSTAFF: Yes. That's it. It's the second paragraph:

"... Cutter has reinforced its existing program of donor screening to assure that the raw material for its quality plasma products continues to be of high quality. This approach is in keeping with philosophy of Good Manufacturing Practices which holds that quality safeguards to control the quality of starting material are preferred to procedures to remove and reduce risk at a later point in manufacturing."

MS RICHARDS: Yes.

SIR BRIAN LANGSTAFF: That's an interesting contrast to the approach which it appears to be taking to prison plasma now that they can heat treat.

MS RICHARDS: Yes. And indeed, again, it may be a theme we'll be able to tease out in November, but it's not uncommon, if I can put it this way, to see a contrast between what is being said -- this is a general comment, not specific to Cutter, I should say -- for public consumption in, for example, marketing materials, and then what is said when one looks at often confidential internal memorandums recording conversations and discussions.

SIR BRIAN LANGSTAFF: Yes.

Yes, thank you.

MS RICHARDS: Sir, what time are we resuming?

SIR BRIAN LANGSTAFF: Sorry. Yes, we'll start again at

quarter to.
MS RICHARDS: Thank you.
(3.19 pm)
(A short break)
(3.45 pm)
MS RICHARDS: Sir, just two or three documents in relation to the dates by which Cutter introduced screening of donors. First, in relation to screening for HTLV-III, if we go to BAYP0000007_129, this is a Cutter/Miles document dated 25 October 1985, and if we go to the right-hand side you'll see one of the boxes is headed "Please state methods for screening donors", and the answer that's given is:

"Screening according to FDA requirements. Cutter have tested for HTLVIII antibody from March 1985."

So that's the given date in relation to testing, obviously that's taking place in the States and you'll no doubt, in due course, want to compare that with the date of introduction of screening in the UK.

Then there's a second date given in BAYP0000007_165. This is a letter of 5 December 1985, it's to the contract administrator in the South West Thames Regional Health Authority, from Mrs Frith. It refers to a change in price of Koate-HT:

"The change in price has been necessary because

two lots, where it's said that they were 100 per cent HTLV-III screened:

"The last two lots were 100% donor screened for HTLVIII antibody. The previous four lots were partially screened and I am waiting for information as to the split of screened and non-screened plasma in these lots."

Sir, again, that's a partial picture of the position in relation to HTLV-III screening and the implications in terms of the products being used in the UK.

Then one document --

SIR BRIAN LANGSTAFF: Just reconciling those, to what does the date relate? The date of supply or the date of manufacture?
MS RICHARDS: That I'm not sure of, sir.
SIR BRIAN LANGSTAFF: Because if it were the date of manufacture it wouldn't be consistent with either of the other two comments.
MS RICHARDS: No. I'm afraid I don't know. The heading says, "Product used by Oxford since the introduction of Koate HT", but the date doesn't seem to correlate to -- wouldn't correlate necessarily to usage. So it would most obviously potentially be the date of collection or manufacture but, I'm afraid, I simply

the HTLV III antibody test is being performed on each donor unit. Cutter were testing all donations by July 1985 and this cost is now being passed on to the UK from January 1986."

Now, there may not be any tension between the two, it may have been an introduction in March 1985 and then everything, all donations tested by July 1985. But I just identify it so that we can -- as an issue that we will hopefully be able to give a definitive answer to when we come back to the response to risk in early November.

Then still on the question of HTLV-III screening, if we just go to BAYP0000008_330, this is a letter to Dr Rizza, dated 1 August 1986. Again, it's from Linda Frith, and it appears to be in response to a request for information. We can see there that, of course, whilst screening was introduced at a point in 1985, there will still have been lots of produced and in circulation prior to that, and this throws that into so much sharp relief.

We can see a number of lots issued, the dates are identified in terms of -- I'm not sure what the date precisely pertains to there. We've got an expiry date. Then 100 per cent HTLV-III screened, and the vast majority of them is no, until we get to the last

don't know. We may well be able to find the answer to that question but I can't give it to you today.
SIR BRIAN LANGSTAFF: There may be an inference in the absence of further information that, because of the span of the dates, it was when the product was used or supplied, as opposed to when it was made, when it was released, that is, from manufacture --
MS RICHARDS: Yes.
SIR BRIAN LANGSTAFF: -- but still ...
MS RICHARDS: Yes, we will try and work out the answer to that, sir.

Then, just finally on the question of screening, ALT screening, BAYP0000008_373, this is dated 29 September 1986. If we just pick it up, the heading is "ALT testing of donors -- Koate HT", and then the second paragraph:

"August of this year marked the date for 100% ALT screened incoming plasma from Cutter owned and contracted plasma centers. However, because of existing inventories of non-screened plasma, there will be a phase-in period before all final product is routinely prepared from 100% ALT screened plasma."

Then there is reference to two specific lots, and what is proposed in relation to those.

Again, we don't, I think, know the date by which

all material being used in the UK would have been 100 per cent ALT screened, but it would be some point after this date, presumably.

Can I then return to the question of prison plasma as a source, by reference to three documents. One I'm going to take you to -- two I'm going to take you to, one I'm just going to refer to. The first document is JEVA0000104. If we go to the second page, what we've got here is the deposition during the course of litigation in the States of a Dr Shohachi Wada, who worked for Cutter. If we go to, I think it's page 8, Soumik -- sorry, can we go back a page. That's it.

Can we just pick it up in the top left quarter of the page, where Dr Wada describes joining Cutter Laboratories in 1964, remaining an employee of Cutter until 1984. The testimony goes on to explain that, largely from 1970 onwards, that was doing work in relation to, I think, platelets.

But the first few years involved work on, amongst other matters, Factor IX. If we'd go to -- can we try three pages further on, please, Soumik. Yes, that's it. I'm just going to pick up a handful of parts of Dr Wada's testimony. So again, top left-hand corner, picking it up at line 21. The question is:

"Question: Dr Wada, I want to ask you to focus with

me on the years 1970 to 1972.

"...

"Question: And for some time now I'm going to ask questions, [so we're now on the bottom left-hand quarter] with reference to the years 1970 to 1972."

Then we can see lines 6 to 8 reference to the Factor IX products sold by Cutter called Konyne, licensed in 1969, that's obviously in the States, not in the UK.

Then the question at line 14:

"Doctor, in the period 1970 to '72, were you aware of the fact that the plasma that was being used to manufacture Factor IX --

"...

"Question: -- at Cutter carried a risk of transmitting hepatitis virus?"

At line 20:

"Answer: Yes, I was aware."

Also the next question:

"Question: ... Also, in those years, Doctor, were you aware that the plasma used to manufacture Konyne --"

Then we go to the top of the right-hand column:

"Question: -- was pooled from many different donors?

"Answer: Yes."

Then there's a question about whether Dr Wada was aware of the risk of other viruses, and he says he wasn't aware. Then if we pick it up at line 15:

"Question: Were you aware ... in the 1970 to '72 time frame that the plasma used by Cutter to manufacture Factor IX --

"...

"Question: -- was in part collected from prisoners in prisons? Were you aware of that?

"Answer: Yes, I knew that.

"Question: In other words, from penitentiaries where individuals were incarcerated plasma was drawn and, in part, plasma from those sources was used to manufacture Konyne.

"Answer: Yes.

"Question: You knew that?

"Answer: Yes.

"Question: Did you have or, rather, did you take any precautions to protect yourself against being infected with hepatitis virus?

"Answer: Yes. Periodically, I received a gammaglobulin injection at Cutter.

"Question: ... About how often did they give you that, if you remember?

"Answer: I think it was once in every two to three

months or something. I don't remember the exact interval."

If we go to the next page please Soumik, bottom left-hand quarter, picking it up at line 3:

"Question: Doctor, in the period 1970 to '72, were you aware of the fact that on certain occasions there were reports of patients receiving Konyne --

"Answer: Yes.

"Question: -- developing hepatitis and dying? Were you aware of that?

"Answer: Yes.

"Question: So my understanding, then, would be, Dr Wada, that as an employee of Cutter at that time working with plasma, you understand that there were risks associated with the plasma and that there were reports in particular of patients developing hepatitis --

"Answer: Yes.

"Question: -- in association with Konyne --

"Answer: Yes.

"Question: -- and on occasion deaths occurring?

"Answer: Yes. However, I was understanding that was a very rare occasion."

So that, I think -- the full transcript probably merits being read but that is part of the evidence

given in US litigation by Dr Wada.

The second document I wanted to refer to but not ask you to look at is just to remind you of the testimony of Dr Francis, again in US litigation, which -- so Dr Donald Francis, which Mr Hill referred to earlier in the week. The reference, for your note, is CGRA0000404, I think, and Mr Hill took you to various passages in which Dr Francis was giving his opinion and his understanding of the practices of Baxter in collecting plasma specifically from urban gay men.

I'm not going to go back to that, but just to point out that Francis's evidence also covers his views in relation to -- or his understanding of the position as regards Cutter, and Cutter similarly obtaining plasma from those sources as well as from prison sources.

Dr Francis's report, in fact, also refers to a number of the documents that we've already looked at in that regard but, again, it's probably worth reading Dr Francis's report in full.

The final document, before I turn to questions of product labelling, which is the last topic for today, is at CGRA0000204_026. You'll recall, sir, as I indicated I think it was yesterday, or possibly the

day before, that the primary focus of the presentations had been on contemporaneous documentation but I observed that there were a number of other sources of information including investigations, books written and, indeed, documentaries produced by -- and other investigations undertaken by journalists.

This is a letter dated November 2003 from Kelly Duda, who had undertaken investigations as a journalist and documentary filmmaker. I think it's, perhaps -- it's his summary, you'll see the subject "Peter Longstaff & US prison blood", and you'll recall that Mr Longstaff was the husband of Carol Grayson from whom this and a number of other documents have been obtained by the Inquiry, and it is perhaps worth just reading a little of this because it paints what might be said to be a fairly powerful picture in relation to prison sources, and ties that in with Cutter.

So he says this:

"For more than three decades, the Arkansas prison system profited from selling blood plasma from inmates infected with viral hepatitis and AIDS. Thousands of unwitting victims around the world who transfused products from this blood died as a result."

Then he refers to Mr Longstaff. Then he says this:

"As a journalist and documentary filmmaker, I have conduct a six-year investigation into this subject. That investigation uncovered a great deal of information relevant to the Longstaff case, demonstrating that", and then he sets out his conclusions.

Obviously, it will be a matter for you, sir, to reach your own views on these matters, but he says, amongst other things:

"US federal regulations were violated, allowing drug users, prostitutes, and sick inmates to routinely donate in the prison plasma programs.

"Blood companies claimed prison plasma was safe even though they knew it was harmful.

"Despite 20 years of blood industry studies showing that prisoners were a high-risk population for diseases, drug companies continued taking blood from inmates because it was cheap.

"Factor concentrate products made from prison plasma were exported throughout Europe and the [UK], and British officials were warned of its risks."

Then he refers to having conducted:

"... in-depth interviews with former officials

from the [CDC] and the [FDA], state prison officials, former employees, high-ranking politicians and inmate donors, all of which paint a horrifying portrait of an industry with few safeguards."

He uses the phrase:

"Haemophiliacs were considered 'canaries in the coalmine' for blood-borne diseases."

If we go over the page, we can then pick up references, specifically to Cutter. He says:

"In the early 1960s, Cutter Labs opened its first collection facilities in Oklahoma, Alabama and Arkansas prisons and the 'biologics' industry was born. So, too, were the problems.

"The prisons were plagued with viral hepatitis outbreaks because of sloppy practices and the use of unsterile equipment. Hundreds of infections and an undetermined number of inmate deaths occurred as a result. More prison operations sprang up in the late 1960s and 1970s as medical journals began reporting cases of viral hepatitis in users of blood coalition products."

Then he refers to the blood letting continuing, even though prisoners were labelled a 'high-risk group of plasma donors' for spreading hepatitis and other diseases.

If we then go down a further paragraph, he says:

"Despite this, Cutter Biologics continued to purchase plasma from this and other prison systems."

Then he refers specifically to Mr Longstaff being treated with Koate. Then the next paragraph refers to a John Andervont:

"... former inspector and retired director of Blood Center Licensing for the FDA, remembered catching inmates performing phlebotomies at the Arkansas prison. [A reference then to] a former ... inmate infected with hepatitis C, who sold plasma regularly [stating]: 'They didn't care. If you could crawl to get there you were able to give blood'."

Then the bottom of the page, refers to Cutter, Baxter Healthcare, a division of Hyland Laboratories, and Alpha Therapeutics, purchasing and using prison plasma in their manufacturing of factor concentrates.

Now, those are obviously Mr Duda's own observations, and you will yourself reach your own conclusions.

I just then ask you to go to the next paragraph -- sorry, the next page, last paragraph.

He says this:

"Should the [UK] choose to hold a full and open public inquiry into contaminated blood products

including imported plasma, I would welcome the opportunity to present more information/evidence about the prison plasma trade. People around the world need to know what happened."

And I can indicate, sir, that we do have a witness statement that Mr Duda has provided to the Inquiry, and we will disclose that ahead of the November hearings when we come back to the question of knowledge of and response to risk.

SIR BRIAN LANGSTAFF: Yes, I have already read it. But this is a letter to Stephen Grimes QC.

MS RICHARDS: Yes, in the context of specific litigation that was taking place.

SIR BRIAN LANGSTAFF: So it doesn't say why it's been written, precisely?

MS RICHARDS: No, I'm afraid I don't know the answer to that. I've no doubt we can find the answer, but I don't know specifically what prompted this particular letter. There is more information from Mr Duda in the statement that he has given to the Inquiry, which will assist in understanding more about what he says he uncovered about the collection of plasma from prisons and its use by pharmaceutical companies.

SIR BRIAN LANGSTAFF: Yes. And that's plainly probably

a more direct source than a letter which is written summarising it.

MS RICHARDS: Yes, and I don't have the statement available to display today, which is really the reason for referring to the letter by way of shorthand. We will have the statement available by the time we come back to the issue in early November.

SIR BRIAN LANGSTAFF: Thank you.

MS RICHARDS: Sir, those are the documents in relation to sources of plasma supply, prison plasma usage, and donors -- approach to donor selection and screening, that I want to refer to.

That leaves one final topic for the afternoon, which is looking at product labels and data sheets. I'm going to focus for these purposes on Koate and Koate-HT. The Konyne, as well as the fact that we have less information about Konyne, such information as we have suggests that the -- where we do have copies of product labels and leaflets and so on, it's essentially in the same terms, similar terms, to that in relation to Koate, which was the primary product and the licensed product in the UK.

So if we start -- we've looked at some of these already so I'll hopefully be able to take it fairly quickly.

If we start with BAYP0000032_045. You can see there are documents saying:

"We shall use the labels shown overleaf in the UK ..."

I think we can go just to page 3.

So this is a draft effectively, I think, probably for the purposes of the licensing application -- sorry, that's the wrong page. Go to the next page. That's it, yes.

Right-hand side we've got the text of a warning -- sorry, I should have said the date of this I think is 1973 -- but the warning there, on the right-hand side:

"Since the presence or absence of the virus of hepatitis in Koate cannot be proven with absolute certainty, the presence of such virus should be assumed and the hazard of administering Koate should be weighed against the medical consequences of withholding the use of Koate."

We can see there a reference to US Federal law, so I think these were essentially taken from the labelling used in the US and the proposal was to overprint that with the name Bayer (UK) Limited.

As we know, Bayer (UK), as things happened, withdrew their licence application and Speywood took over.

If we go to BAYP0000022_083, we've got a document headed "October 1975" which has various forms of suggested wording for the package insert and labelling. Picking it up in the second paragraph in capitals:

"This product is prepared from units of human plasma which have been tested and found non-reactive for hepatitis associated (Australia) antigen. Unfortunately this test does not with certainty preclude the presence of hepatitis virus. See warning."

Then the wording of "Caution", and we saw effectively this wording or very similar wording in the licence application we looked at this morning, albeit we don't have then have a copy of Speywood's licence application. But.

"Caution: Because of the possibility that any lots of Koate might contain the causative agents of viral hepatitis, its use must be considered in light of this hazard, particularly in persons with few previous transfusions of blood and plasma products."

Then we've got the reference to the Kasper and Kipnis application, and then the boxed warning with the italicised -- I'll read the whole bit:

"Koate concentrate is a purified dried fraction of

pooled plasma obtained from many donors. Since the presence or absence of hepatitis [virus] in Koate concentrate cannot be proven with absolute certainty, the presence of such a virus should be assumed and the hazard of administering Koate concentrate should be weighed against the medical consequences of withdrawing it."

SIR BRIAN LANGSTAFF: Interestingly, did they correct the spelling of "virus" in that?

MS RICHARDS: I imagine they did. I don't think we have necessarily got a final original copy, so what we often have are copies that appear in files, photocopies that appear in files that appear to be from the actual package or the actual insert. Or they're the drafts that accompany the licence applications. So we don't have the original documents as they appeared with the lots or the vials.

SIR BRIAN LANGSTAFF: The reason I ask is whether we know that it did actually appear in italics and capitals on the label, but it follows from what you've just said you don't know.

MS RICHARDS: Certainly not at every point in time we don't know. There's a leaflet from I think it's 1981, BAYP0000019_025. This may be a US leaflet. If we look left-hand column, towards the bottom of the

leaflet:

"This product is prepared from human venous plasma. Each individual unit of plasma and each lot of final product has been found non-reactive for hepatitis B surface antigen using a licensed third-generation assay. However, this test does not preclude the presence of hepatitis virus. See warning."

If we go over to the right-hand side there's a box headed "Warning", and we've got the American spelling of haemophilia.

"Antihemophilic Factor ... Koate concentrate is a purified dried fraction of pooled plasma obtained from many paid donors. The presence of hepatitis viruses ..."

Just pausing there, there's a point in time at which the language changes from "virus" to "viruses":

"... should be assumed and the hazard of administering Koate concentrate should be weighed against the medical consequences of withholding it, particularly in persons with few previous transfusions of blood and blood products.

"Kasper and Kipnis have concluded that those who have had little exposure to blood products have a high risk of developing hepatitis after introduction of

clotting factor concentrates, such as this product. For those patients, especially those with mild haemophilia, they recommend single donor products. However, for patients with moderate or severe haemophilia who have received numerous infusions of blood and plasma products, they feel the risk of hepatitis is small. They believe that the clotting factor concentrates have so greatly improved the management of severe haemophilia that these products should not be denied to appropriate patients."

If we go over the page, I think it's not just the spelling of haemophilia that indicates this is a US label, but the bottom right-hand corner, if you zoom in --

SIR BRIAN LANGSTAFF: Yes.

MS RICHARDS: -- we've got the reference there:

"US [Government] [Licence] No. 8, Cutter Biological."

But if we then just zoom out again, if we look, the third column along, top of the third column, that first paragraph ends with:

"It is important that this product be stored properly and that the directions be followed carefully during use, and that the risk of transmitting hepatitis be carefully weighed before the product is

prescribed."

And we certainly saw that language in one of the licence applications we looked at earlier.

If we go to BAYP0000019_012, this is a UK data sheet, and we can see that not just from the spelling of haemophilia but, if we go to the last page, we've got the licencee as Cutter Laboratories Ltd, Guildford Surrey, and the date, if we just look, is January 1981.

If we go to the second page, bottom of the page under the heading "Contra Indications", we've got essentially the very similar language shown. In the second paragraph we've got the reference then to "many paid donors". You've got there "virus" in the singular so:

"The presence of hepatitis virus should be assumed and the hazard of administering Koate concentrate should be weighed against the medical consequence of withholding it, particularly in persons with few previous transfusions of blood and plasma products."

Then there's the reference to Kasper and Kipnis again which continues to over the top of the next page.

If we look at "Adverse Reactions", partway down that page, you'll see that the first paragraph refers

to allergic reactions, and then the second to a reaction that may occur in patients with blood groups A, B, or AB. Then the third paragraph there says:

"The risk of hepatitis is present with the administration of AHF concentrate preparations (see discussion under WARNING)."

So that's a UK data sheet for Koate, January 1981. If we go to BAYP0000019_087, if we look at the date in the top left-hand corner we've got "[Revised December] 1981". This is another US Government licence document. Apologies.

The language is the same. I think I'd been fooled by the spelling of "haemophilia" into thinking it was a UK document.

Then if we go to -- yes, BAYP0004216_002, this is again a US document. BAYP0004216_002.

The date there, the date issued, August 24, 1982. I draw attention to it only, if we look just a little further down, it says:

"Reason for change.

"Change imprint to 'AHF/IU'. Update Hepatitis statement. Change to 'viruses' in Warning statement."

So there's the change from hepatitis "virus" to hepatitis "viruses". Whether that was intended to

reflect an understanding of not just hepatitis B but also non-A, non-B hepatitis, I don't know, because we don't have anything further by way of explanation for that change.

Then if we go to BAYP0000026_065, this is obviously a draft document. It's not a final form of labelling but we can see from the heading:

"Koate labelling.

"Proposed new text complying with UK regulations."

I'm afraid I don't think we know the date of this. Bottom of the page refers to Cutter Division of Miles Laboratories Limited, Slough. So it may be that will assist us in providing a date. If we go to the fourth page, we can see, just over halfway down the page, a "WARNING", in capitals:

"Koate concentrate is a purified dried fraction of pooled plasma obtained from many donors. The presence of hepatitis virus should be assumed and the hazard of administering Koate concentrate should be weighed against the medical consequence of withholding it, particularly in persons with few previous transfusions of blood and blood products."

Then, if we go to BAYP0000028_056, you'll see that this is the licence application, September of 1983, for a licence in the UK.

If we go over the page, we probably looked at this morning, but we can see the name and address of proposed licence holder there: Miles Laboratories Limited. And then the text, if we go to page 12. We've got the text of the warning. I won't read it out again, because it's in essentially the same or very similar terms to what we've previously read.

You'll see "viruses" in the plural in the first paragraph under "Warning". We've still got the reference to Kasper and Kipnis.

Then if we go to the next page, under the heading "Adverse Reactions", we've got the allergic reactions paragraph, the paragraph about the possibility of complications in patients with blood groups A, B, or AB, and then we've got the third paragraph about hepatitis.

There's nothing there, as you'll see, in relation to risk of AIDS. This is being submitted, as I understand it, in September 1983.

And then ... so this is -- the next document is a US label, or product insert, BAYP000027_087. I'm drawing attention to it even though it's an American one because it does refer to AIDS. Sorry, BAYP0000027_080.

Top left-hand corner tells us it's revised

December 1983. Then if we go to the middle column we have the box of warnings. So:

"... Koate concentrate ... purified dried fraction of pooled plasma obtained from many paid donors. Although each unit of plasma has been found non-reactive for hepatitis B surface antigen ... using a US federally approved test with third-generation sensitivity, the presence of hepatitis viruses in such pools must be assumed."

Then there's the reference again to Kasper and Kipnis certainly in similar terms, it may be identical terms, to what we've seen earlier.

Then the third paragraph deals expressly with AIDS:

"Isolated cases of Acquired Immune Deficiency Syndrome (AIDS) have been reported in haemophiliacs who have received blood and/or coagulation factor concentrates, including Factor VIII concentrates. It is not known if the disease is due to a transmitted specific agent, secondary to multiple antigenic exposures, or to some other mechanisms. The physician and patient should consider that Factor VIII concentrates may be associated with the transmission of AIDS and weigh the benefits of therapy accordingly."

So an express reference there to AIDS on this American sheet.

Sorry, I'm just going to check whether we've got a UK one from around that time. But I think ... no, that's American. Yes. I'm not sure in relation to Koate -- and I'll come on to Koate-HT in a moment -- whether we've got any other labels or data sheets or product inserts which contain anything similar to what we see in this US document with reference to AIDS.

Before I just show you what we have in relation to Koate-HT leaflets -- which isn't, I think, a huge amount -- can I ask you to look at CGRA0000434.

This is a memo, 29 December 1982, in relation to AIDS, and it's a Cutter memo which says this:

"It appears to me to be advisable to include an AIDS warning in our literature for Factor IX and Factor VIII. I realize that very little is known about AIDS and the relationship the products we manufacture have in causing the syndrome. However, litigation is inevitable and we must demonstrate diligence in passing along whatever we do know to the physicians who prescribe the product. In my opinion, three steps are called for, once we agree on the wording of our message.

"1. Include it in the package insert.

"2. Educate the sales force.

"3. Since MDs won't be reading the package insert in most cases, send a letter to haematology specialists informing them of the warning we are putting in the insert."

SIR BRIAN LANGSTAFF: And who writes that?

MS RICHARDS: I can't tell, sir --

SIR BRIAN LANGSTAFF: I think if you scroll down to the bottom, it's Ed Cutter.

MS RICHARDS: Yes. Yes. It looks like it's -- if we go then to the top of the page we've obviously got the left-hand side cut off, but it's being sent, it looks like, to a number of recipients within Cutter.

SIR BRIAN LANGSTAFF: Do we know what his position was?

MS RICHARDS: No. The name would suggest a fairly powerful one, but I don't know --

SIR BRIAN LANGSTAFF: Well, he's part of the family, but the Cutter brand has been around for quite some time.

MS RICHARDS: It has. And of course it could be coincidence. I don't know, I'm afraid, but I'm sure we can do some checks and find out.

Whether that's what leads to what we saw in the insert revised a year later, December 1983, or whether there were some intermediate revisions to inserts, I don't know. And the extent to which this was then

replicated in relation to the UK is unclear. We certainly haven't found anything that obviously looks like a UK package insert or label from this period, so after December 1982, which contains an equivalent form of wording.

That doesn't mean it doesn't exist. And if it does, I think we're yet to identify it.

There is ... we have got documents which are clearly drafts in which someone has scribbled with handwriting all over various suggested amendments, but I don't think it's particularly useful to go to that. It's both American and plainly a draft.

If we look in relation to Koate-HT, BAYP0004702_002, this is a label, but it's a US label, again, I think. If we zoom in left-hand side, there's a warning. It's the language of hepatitis viruses again, in relation to that.

I note that the date of this is November 1983, but at the moment I'm -- it's not clear to me where the date comes from. Just look at the bottom box, please, Soumik.

SIR BRIAN LANGSTAFF: But there's the date.

MS RICHARDS: Yes, we've got the date there. There's the date. 18 November 1983.

So at that point in time, in the States, it

doesn't look like the label in any event had a warning on it, whatever the package insert may or may not have contained, that related to AIDS.

There's an information manual, BAYP0000026_054. Again, however, it's a US document. So it's headed and revised January 1984, "Antihaemophilic Factor (Human) Heat Treated Koate-HT".

Bottom of the page -- sorry, second page -- contains a warning in the box that we see there, if we just go down the further paragraph.

Sir, we can see there the wording that appears to have made its way into the American inserts or leaflets with reference there to AIDS.

Then, if we turn to just a document we've already looked at, but because it's a UK one, I think we should perhaps go back to it. BAYP0000003_309.

We looked at this earlier. It's the licence granted to Miles Laboratories trading as Cutter Laboratories in February 1985, so long after the date of that Cutter memo which talked about the need to update the product inserts.

If we go to the second page, we've got the warnings at the bottom of the page, which don't address AIDS.

Then, if we go to the top of the fourth page,

we've got the familiar language about the presence of hepatitis viruses, but no reference there to AIDS or to HTLV-III.

I'll just check one further reference, if I may. I'll go to it, but again it's a US reference, BAYP0000008_127. Revised March 1986. If we look at the right-hand side, top of the page, the product:

"This product has been heated ..."

Then there's a couple of lines that are slightly unclear but, we can see there, there is then a discussion of non-A, non-B hepatitis, and reference to chimpanzee studies in that regard, and then the next paragraph talks about:

"Additional *in vitro* studies on the effect of the heat treatment process and virus inactivations were carried out with a number of viruses including [HTLV-III] and AIDS related virus ..."

Then there's reference to a table.

Then, if we go over the page, we've got a warning in a different language than previously. So there's reference, then, to Koate-HT being prepared from pooled units of plasma, individually tested, and found non-reactive for hepatitis B surface antigen and HTLV-III.

It then refers to "Other screening procedures ...

used to eliminate high risk donors", and then the heat treatment step.

"However, testing methods presently available are not sensitive enough to detect all units of potentially infectious plasma, and treatment methods have not been shown to be totally effective in eliminating viral infectivity from this product. Individuals who have not received multiple infusions of blood or plasma products are very likely to develop signs and/or symptoms of some viral infections, especially non-A, non-B hepatitis as shown by recent data."

Then there's a reference to the Fletcher paper, and then we see reference again to the Kasper and Kipnis paper, although it looks as this might be a draft, and as I say, again it's a US product.

I don't think we have anything which shows clearly what the labelling position was for Koate-HT in the UK. No, we've got another one from April of 1987, but again, I'll show you it briefly, but it's a US label. BAYP0000010_070.

So this is revised April 1987, the date is in the very top left-hand corner. The warnings are in the third column. It looks similar to the document we just looked at. So we've got reference there to the

testing for hepatitis B surface antigen, the testing for HTLV-III, the other screening procedures, but the testing methods not being sensitive enough to detect all units of potentially infected plasma.

We've got reference there to the risks of non-A, non-B hepatitis and the reference to Fletcher and Kasper and Kipnis.

SIR BRIAN LANGSTAFF: There's also -- the way one might read the warning, it does refer to HTLV-III. And in part of that first paragraph, it does talk about "treatment measures not been shown to be totally effective in eliminating viral infectivity from this product".

So it's open to the interpretation that it's alert to a possible risk of HTLV-III transmission.

MS RICHARDS: Yes.

SIR BRIAN LANGSTAFF: It's not absolutely clear, but it's --

MS RICHARDS: It's not.

SIR BRIAN LANGSTAFF: It's there if one wants to read it that way.

MS RICHARDS: Yes. I should say there's also correspondence, I won't take time up going to it, suggesting -- and this is from Mrs Tatt in the UK -- suggesting that, when asking whether the warning

statement could be amended for the UK, but actually, we will look at this.

One last document for today, BAYP0000015_060. This is actually not about Koate-HT, but about Koate-HS. But, in any event, it's 15 September '86:

"Could the 'WARNINGS' statement be amended for the UK? We would like to delete the reference to the Fletcher paper and potential transmission of non-A, non-B hepatitis."

I think the answer to that might have been no. Because there's a response which says, "Any labelling being applied in the US must" -- oh, no, actually it says you can prepare your own warning in the UK. I'll just read the text of it.

"Any labelling being applied in the US must contain the warning. If we send you unlabelled final containers you may prepare your own labelling", was the response in the States.

So we don't therefore have, I'm afraid, a comprehensive picture of how the risks were presented, at least as we get to the 1980s go and through the 1980s, but there isn't anything at the moment in relation to any UK labelling that seems, in the first half of the 1980s, to reflect any warnings about the risk of AIDS, or non-A, non-B hepatitis.

The rather generic reference is to hepatitis virus or hepatitis viruses and, at the repeated reference to the Kasper and Kipnis paper.

Sir, that's what I am proposing to say in relation to Bayer/Cutter/Miles. Obviously, we'll come back to some of these issues in November. Tomorrow, we move to look at Speywood, and we will hear evidence from Sarah Middleton, in relation to Speywood and its works.

SIR BRIAN LANGSTAFF: Yes. Well, tomorrow, ten o'clock.

(4.39 pm)

(The hearing adjourned until 10.00 am the following day)

INDEX

F:

F:

F:

F:

F:

F:

F:

F:

F:

F:

F:

F:

F:

F:

F:

F:

F:

F:

F:

F: