MEETING AT CENTRAL BLOOD LABORATORIES AUTHORITY SITE IN ELSTREE ON TUESDAY, 24TH APRIL 1990 AT 9.30 A.M.

In Attendance:

David Donald (DD) - Quality Department Manager
Susan Roberts (SMR) - Clifford Chance
Angela Robertson (ACR) - Clifford Chance

David Donald who has been employed with BPL since 1985 explained the processing treatment for FVIII (FIX follows more or less the same process, apart from an adsorption stage midway through the process).

1. Blood has been received from the Transfusion Service since the 1950's. It was first received in the form of whole blood and from the 1970's as plasma. Initially BPL did not have an agreed plasma specification but used the guidelines as applied by the Transfusion Service. The Transfusion Service produces plasma from donated blood for clinical use and then passed it to BPL for fractionation. Only in the past 12 months has the BPL had its own plasma specification which is based on the Transfusion Service guidelines and BPL requirements. BPL insists on HIV antibody and Hepatitis B surface antigen mandatory screening. The Transfusion Service has the care and selection of donor screening and will only send plasma which meets that criteria. Although donors in high groups should exclude themselves, clearly this is not mandatory and donations have to be screened in any case. BPL will only use tested plasma that meets specification.

2. If the Transfusion Service finds a positive donor it will contact BPL and advise it of previous donations which have been sent for fractionation. BPL has the ability to identify the Transfusion Centre/Haemophilia Centre receiving BPL product. Plasma supplied by the Transfusion Service remains on the site for a very lengthy period; it is placed in quarantine storage for the first 3 months. Where a donor has been found to be positive by a Regional Transfusion Centre ("RTC"), previous donations will be checked from Dispatch Records and where possible retained samples of

the previous donations will be tested and also plasma or product produced from that donation which is still on the site. If the results are negative, obviously no further action will be taken. If the results are positive, then the plasma will be destroyed or the issued product recalled. DD added that the BPL has never actually recalled any batches sent out as a result of finding HIV contamination. Although product has been recalled in cases where patients have seroconverted, where the seroconversion was batch specific DD cannot comment.

3. The HIV antibody test indicates if a donor has been infected by identifying the antibodies to the HIV virus rather than the virus itself. Where antibody is not detected additional assurance that the product will not be infective is provided by the lethality of the heat treatment process to kill the virus. The Transfusion Service also carries out tests for markers of venereal disease even though this is not mandatory.

PROCESSING

4. Plasma Dispatch Form (4 Copies)

The plasma dispatch accompanies the plasma to BPL from the Transfusion Centre and is received in the Plasma Receipt Department. The blood is received in cartons, each of which contains approximately 20 single packs from individual donors. BPL does not have the numbers of the individual donations, although the Transfusion Centre keeps a record of the individual donors in each particular carton and BPL can be notified to exclude donations for very quickly. BPL has a number for each individual carton. The cartons are placed in cold storage (there are approximately 300 tons of plasma on site at any one time; that represents approximately 1,200,000 donations. Donations found to be infected are either destroyed or sometimes returned to the Transfusion Centre. DD explained that there was a comprehensive system of quality and stock control.

The plasma receipt documentation consists of 4 copies. The first copy remains with the Transfusion Centre, the second copy is retained by the Plasma Receipt Department, the third copy goes to the Control Unit which operates the 3 month quarantine period and subsequently into the Batch Manufacture Record ("BMR"). The fourth copy is returned to the supplying RTC as a record of fractionation.

Every single incident of which the BPL is informed is recorded and the relevant action documented.

After quarantine the Control Unit carries out all the necessary actions and stamps the form "passed for use". If the delivery meets specifications or if the incidents are cleared.

On 14th October 1985, all Transfusion Centres agreed only to send plasma that had been screened and found negative for HIV antibodies.

All plasma in storage is frozen and accordingly no tests are carried out at the quarantine stage. Quarantine lasts for 13 weeks which is based on the assumption that donors will return in another 13 weeks to donate once again. Although clearly this is not always the case, DD did point out that BPL is one of the very few fractionation centres in the world that has such a long quarantine period. He pointed out that most such centres use the plasma immediately. DD said that the quarantine period does make them less competitive and they have questioned the value of the quarantine period, but it is evidence of yet another precaution or safe guard on the quality of the plasma.

Once the plasma has been cleared for use, the Plasma Receipt Department receives back the control unit copy in the form of a release sheet. The Plasma Receipt Department will then issue the blood in 3.3 ton POOLS i.e., about 15,000 donations, a copy of the release sheet then accompanies the plasma across to the fractionation plant. DD pointed out that all donations from all regions are now mixed. At one time, plasma was fractionated regionally, as it was possible to recover more FVIII from plasma supplied by certain regions, but that distinction disappeared a long time ago and now the plasma is blended.

The 3.3 tonne pool goes into the factory, all defective donations having been removed before that stage i.e., plasma not meeting specification. The frozen plasma packs are transferred from the transit cartons to trays where obviously damaged packs are removed on transfer to the processing floor. The plasma is kept at a pre-conditioning temperature of between-40°C to -15°C. The plasma is held there for 24 hours to condition it, i.e., it helps the plasma to part from the pack more easily the following day. The next day the donations are cut open by machine ("tear down machine") and the contents removed. If the package is damaged in any way, as can happen at a temperature of -40°C, it will be excluded and also any donations which fall out of the machinery will also be excluded. All donations which are excluded will subsequently be noted on the batch record as rejected donations. The BMR includes an additional check on the carton numbers found and used in the batch.

The plasma has by now lost its individual identity completely and is pre-conditioned for a further 24 hours and the next day placed in a crushing and thawing machine. This machine has a 500 litre capacity which will crush the plasma into a jacketed vessel where it can warm up to a temperature of 0°C at which stage the cryoprecipitate will fall out of solution. This is a continuous process with the plasma from the 3.3 tonne pool being constantly fed into the crushing and thawing machinery. Once the liquid has emerged, it is pumped through centrifuges, which will separate out the cryoprecipitate; the fluid is collected in a 5,000 litre vessel which obviously can collect the entire pool.

This is really the only sensible time at which to take a sample for it is only at this stage that the product is well and truly mixed. Sampling for HIV antibody and Hepatitis B surface antigen is now carried out. The test is carried out on a sample of a donor pool of 15,000 donations and therefore the most important test is that carried out at the Transfusion Centre for the screening of the individual donations for HIV antibody and Hepatitis antigen. For if one donation is infected, the diluting effect of the rest of the pool can be such as to place the sample below the sensitivity of the HIV antibody test and the antibody presence will not be found.

Since 14th October 1986, the BPL has sent samples of every start pool to NIBSC (DD pointed out that a recent directive from the MCA to send start pool samples now, indicates how little is known of BPL procedure, as BPL has been doing this on a voluntary basis on its own initiative since 1986).

The start pool sample will be tested for HIV and Hepatitis B surface antigen - on 2 recent occasions HBsAg been found in the start pool. DD explained that this came about because the Transfusion Centres had made a mistake and sent positive tested plasma although the record indicated the plasma was suitable for fractionation. On one particular occasion 10 transfusion centres contributed plasma to the pool found to be HBsAg contaminated and on another occasion 4 centres. On investigation it was found that one transfusion centre had sent in a contaminated donation which they were able to indentify from their own test records. None of the centres were able to explain the reason for the second HBsAg positive pool from reviewing the plasma dispatch records and test results.
DD said that Hepatitis B surface antigen could be found in the start pool, but he was not confident that it would be possible to find HIV in the same way. He said that testing for contamination was not really sensitive enough but if it was possible to find the contamination, they would obviously reject the plasma rather than try to destroy the viral antigens through heat treatment.

Once the cryoprecipitate has been removed and dissolved into solution, further unnecessary substances are removed through various purification stages. The solution is then adjusted for electrolyte contact before being sterilised by filtration.

A sterilizing filter is used to remove the bacteria and the product enters a "sterile suite" where the filling operation takes place. Everything connected with the filling of 10ml dose volumes is completely sterile, it being impossible to terminally heat sterilize the product due to the proteins being heat labile. Once the vial has been filled, it is freeze dried, the water in the product being removed by lyophilisation. Rubber bungs plug the vials which are now over-sealed and dry heat treated to 80°C (the defined criteria specifies temperatures between 79°C to 83.5°C which must be maintained for not less than 72 hours). The batch records

give a note of the heat treatment and also more recently the actual heat treatment records are attached to the batch records.

As the potency of the product is reduced by heat treatment the actual potency is in fact referred to on the label on the vial. A number of vials from each batch are sent for various tests. Two are sent for general chemical tests. A further two for potency tests. Three are sent to NIBSC for their own tests, the results of which are not disclosed to BPL, but as a result of which NIBSC sends a certificate of release, without which BPL would not be able to release the product. DD said that he did not know whether NIBSC actually carried out an HIV antibody test. DD pointed out the NIBSC' certificate is basically a government instituted requirement and has no bearing on DD's release of a product in that although he could not release product without the certificate, the fact that he does have a certificate does not give him particular confidence in the quality of the product, it clearly being the case that BPL carries out its own testing procedure. The NIBSC' certificate requirement is currently based upon a D.O.H. requirement for NIBSC to test all products for freedom from HIV antibody NIBSC release certification will be applied to all other aspects of product specification with the acquisition of product licences. DD said that a decision was made to submit samples of the product after their own results were known because that basically put BPL in the same position as their competitors who are only able to release the finished product for testing. DD said that he could have a release certificate from NIBSC and still reject a batch once he got their own test results back and in fact that has happened in the past when a sample had been submitted before the BPL had carried out its own tests. NB: this was not HIV antibody related.

After testing, the vials are taken out of a secure area and sent for inspection and packaging. At the inspection stage it is possible for further vials to be rejected purely on a visual assessment of any irregularities in the product or container.

DD pointed out that the BPL is regularly audited by the Medicines Inspectorate and they have obtained good reports of their process.

DD further explained that incident reports are created for all sorts of reasons, the simple transposition of a number on part of a batch would be a reason for recording that fact and opening an incident report which would be filed separately, although the existence of such a report would be indicated on the front of the batch record. Security tabs over the vial container bear a unique number which would be destroyed if there was any tampering with the vials.

Once the batch record has obtained the requisite checks and signatures and the final release signature, it is sent to the warehouse for storage at a temperature between 2°C to 8°C. Batches are then issued to Centres on a weekly basis against their order requirements. Product dispatch records then record the destination of each and every vial.