On 2/16/88 at 9:30 two inspectors from the DHSS Medicines Inspectorate, D.Warburton and M.Kavanagh, arrived at the plant for a routine inspection of Plasma products licensed in the United Kingdom. They were joined by T.Monroe (Plasma Production Manager), L.Franke (QA Operations Manager), and P.Wiggins (GMP Manager).

During the opening conversations the inspectors requested that to start the inspection they would like an overview of the process for each product (Koate, Konyne, IGIV and Albumin) and then tour through the manufacturing areas. Copies of plant organizational charts and a current floor plant of building 300, plasma processing facility, were requested and provided.

T.Monroe provided the process description overview, inspector comments were noted at the following areas:

1. Plasma receiving, sorting and pooling. Current sources of plasma include: Cutter owned and contract centers; Canadian Red Cross (we process their plasma for products going back to the CRC); and BSI (Blood Systems Incorporated, we process their plasma to Albumin for them and have the option of buying other fractions from them for our own use). Products for the UK would be from Cutter/contract plasma and possibly BSI plamsa. The inspectors commented that BSI would have to listed on our UK license as an acceptable source before we sould include this material in UK products.
2. Plasma donor testing performed at the Special Testing Lab in San Diego was outlined as well as the testing of all plasma pools for HBsAg (performed in house). The inspectors commented that the safegaurds etc. we have in place should be included in the Product License.
3. Heat treat cycle for Koate - viral inactivation data? It was indicated that cycle was developed in Berkeley and this data would be available there.
4. Pasteurization cycle for Albumin - viral inactivation data? That information would not be at the plant. Albumin pasteurization cycle is specified in the CFR, any viral inactivation data would be available in Berkeley.
5. Albumin final container incubation temperature of 20 - 35°C, incubation performed at 20 - 27°C. This was pointed out as being different from the UK requirements.
6. IGIV was noted not to undergo a heat treament cycle during processing, when asked by the inspectors it was indicated that we had never had complaints for Hepatitis for any IG product and that there may be some data in Berkeley which showed that the Cohn fractionation process had some viral inactivation properties... (to be followed up in Berkeley).
7. The question was asked as to the advantage of Koate HS over Koate HT and T.Monroe indicated that data appeared to show that the Koate HS gave a better reduction of the risk of transmitting non-A/non-B hepatitis.

After the initial process overviews it was indicated to the inspectors that Clayton had licenses pending with the OoB for production of Hyperimmunes to final containers and that we would be making our initial qualification lots of Koate HS in the near future. The process flow for Koate HS and in which rooms each of the operations would take place were then reviewed with the inspectors (a separate site visit by the UK may be eliminated based on the inspectors comments...).

Copies of process flow charts were requested and copies were provided (copies of PLA flow diagram).

The inspectors then left for lunch and when they returned the remainder of the afternoon was spent on the initial walk through of the plasma production areas.

The initial walk through included the entire plasma processing facility (Bldg.300). Each of the plasma departmental managers provided a description of the operations taking place. There were no specific questions or observations reported by the inspectors during this walk through.

Mr.Warburton and Kavanagh arrived the morning of 2/17 at 9:05 and were joined by P.Wiggins. The agenda for the day was established: Tour the warehouse, Incoming QA and go back to the Plasma Receiving and Pooling areas for a detailed review of the operations taking place.

P.Wiggins escorted the inspectors to the warehouse (Bldg.100) were they were joined by L.Franke and S.Cullen (Materials Manager). The material flow through the warehouse was reviewed. The only comment noted was that the red pen trace on the +5°C cold box was very light, S.Cullen indicated that a new pen would be installed in the recorder.

Incoming QA Inspection area was reviewed with S.Flores (Inspection Manager) and E.Norris providing a description of the QA On Test/Off Test process and demonstrated on the RMICS inventory computer system the system security for changing raw material status from On Test to Off Test. No problems were noted by the investigators.

The inspectors then asked for and was provided with a description of the QA release of plasma for pooling by E.Norris (QA Release Supervisor/acting Inspection Supervisor). Plasma status was indicated to be controlled by the RMICS system and that QA Release personnel were the only people with access to changing the status to a released status.

The inspectors were then escorted to the plasma facility by L.Franke and P.Wiggins where they joined T.Monroe and J.Johnson (Plasma Pooling and Coagulation Manager). They went to the plasma receiving aera where they requested and were provided with a detailed description of plasma receiving, sorting and verification of acceptable test results. The group then proceeded to the pooling area and since the pools for the day were completed, the inspectors said they would like to come back to this area when a pool was in process.

The inspectors requested that they would like to review the following items later in the inspection: 1) Microbial load data for pools, 2) Pooling kettle rinse test data, 3) Environmental Monitoring data for the pooling room.

Testing of pools was questioned and it was indicated that all pools are tested for HBsAg, protein, factor VIII, and anti-D. The inspectors asked if we test pools for HIV and it was indicated that we did not. When asked what is done if a pool tests positive for HBsAg it was indicated that: 1) Cryo paste and fraction II + III would be discarded, 2) Material in this pool would be processed to Albumin only (packaged with different labeling and allowed for domestic sale only), 3) All equipment contacting this pool would be cleaned by more stringent cleaning procedures. Cleaning procedures were reviewed and no problems noted. The inspectors only comments were that any Albumin from a pool positive for HBsAg should <u>not</u> be sent to the UK.

Processsing of Koate up until the concentrate stage was then reviewed. The only area questioned by the inspectors was that the cryo paste was being cut up into pieces for solubilization outside the LAF hood and then placed in the kettle which was inside the LAF. The inspectors requested that environmental monitoring data for this area be reviewed later.

The Koate/Konyne heat treat ovens were reviewed. The inspectors requested that our validation data for the equipment and cycle be made available. P.Wiggins indicated that we would only have validation data at the plant relating to the equipment. The heat treat cycle was developed by the technology group in Berkeley and the data relating to cycle development would be available at Berkeley.

The chemical weigh room was reviewed with one item noted by the inspectors. A container of glycine without QA release indication was present in the room. The inspectors asked what the status of this material was and L.Franke indicated that QA had a question on the test results and that it had not been completely Off Tested (used on a "provisional release"). The inspectors took exception to this and said this contradicted what they had been told in Incoming QA on how raw materials are controlled. Any attempts to clarify this situation at this point in time without all supporting documentation would have been difficult so no further clarification was offered.

The inspectors then left the plasma facility and left for the day.

The inspectors arrived 2/18 at 9:10 and were escorted by P.Wiggins to the QA conference room where they joined L.Franke and E.Greene (International Regulatory Affairs). The point of the glycine was reviewed in detail with the inspectors. Test results conflicting between Clayton and Berkeley were reviewed with the inspectors. Due to the preparation of the glassware for the test the Clayton results were invalidated and additional samples had been sent to Berkeley. Due to the need by manufacturing for this material and the high assurance that the material would pass all test criteria the material was allowed to be issued to manufacturing in an On Test status, with a Nonconforming Material (NCM) report issued against all steps in process which had used the material (as allowed by QAP 535). The NCM system which would have prevented release of the product using this material was reviewed with the inspectors. The controls in place satisfied the inspectors concerns and showed that this was in control. The inspectors then asked if a copy of the NCM had been attached to the manufacturing BPR and it was indicated that it had not, the NCM was held by the QA Release Office. The inspectors then commented that they still felt that in this type of situation a copy of the NCM should have been attached to the BPR so that the manufacturing personnel were more clearly aware of the status of the material.

Also in clarification of a question the previous day on the disposition of materials from a pool testing positive for HBsAg, QAI 601 (PI 1.C) was reviewed. This supported the answer provided earlier, a copy was requested by the inspectors and a copy was provided.

The inspectors commented that BSI plasma or Source Plasma Salvage (due to temperature excursion during storage or shipping as per the CFR) should not go into products for the UK unless they were indicated in the UK Product License. E.Greene indicated that he would clarify this item when they were in Berkeley.

The agenda for the day was established with plans to spend the rest of the day looking at fractionation. The inspectors then commented that if we had any other products which would be "new" for the plant in the foreseeable future, that we should review the process flow and facilities used on each step. The inspectors also requested that validation data for the pasteurizers as well as the heat treat ovens be reveiwed later.

The inspectors were then escorted to the plasma facility by L.Franke, E.Greene and P.Wiggins where they joined T.Monroe and R.Bokeny (Fractionation Manager).

R.Bokeny provided the description of the Albumin process and all areas and equipment were reviewed. In the Buffer Prep Room the inspectors noted that one kettle of stock buffer solution used in fractionation did not contain an Off Test label. When the procedures were reviewed the plant agreed that these procedures needed to be revised for clarity as to who, when and under what criteria the Off Test labeling should be applied.

Also in this room clean equipment was stored. The inspectors noted that some portable kettles and one hose contained residual wash water. It was not clearly indicated as to if the equipment would be rinsed immediately prior to use.

In the fractionation area the inspectors questioned the Sharples centrifuge drip pan material and the current procedure of recentrifuging this material was reviewed with them. They were uncomfortable with this due to the containers noted to contain some particulates (drippage from centrifuge housing and/or pieces of burnt drag bushings). They suggested that the containers should be "protected from the environment. In addition they requested to see microbial load data for this material (the only data available for this was some LAL testing).

The inspectors then looked at the bulk freeze dryers used for PTC, Albumin powder and IG powder (for export). They expressed concern that there appeared to be a potential for cross contamination of any viral contamination between the different products since the freeze dryer chambers were not sterilized between runs (as done on the final container freeze dryers), and especially for the IG powder since this product does not undergo a heat treat cycle as part of further processing.

The inspectors asked for and were provided with a description of how chemicals are weighed and dispensed for IGIV. D.Waddell (Dissolving and Filtration Manager) provided this description and showed how the weighing and dispensing are

performed. While the inspectors were in the chemical weigh room the inspectors noted that the glycine noted earlier had been released for use by QA and confirmed the receipt of the test data from Berkeley.

A flow chart for Alpha 1 PI was then reviewed with the inspectors and the rooms each operation would take place was covered with the inspectors. It was pointed out that a time frame for introduction of this product to Clayton had not yet been established.

The inspectors then related that they would not be looking at any filling or packaging operations. An agenda for the following day was established where lot records would be reviewed and a final wrap up meeting was scheduled for 2:30 the following day.

The inspectors then left for the day and returned the morning of 2/19 at 9:00. Upon their arrival they were escorted to the QA conference room by P.Wiggins and joined L.Franke and E.Greene.

The validation data for the Koate Heat Treat ovens and the pasteurizer were reviewed and no problems were noted.

The lot records for Koate 50S021, pool PF2562, and IGIV 40S18 were then reviewed with the inspectors. They looked through the packing lists for pool PF2562 and verified that plant personnel had confirmed that all reactive units had been removed and had not been pooled. QA release verification of the packing lists was also covered with the inspectors. The only comment the inspectors had were that plasma from sources not included on the UK Product License should not be included in product destined for the UK. E.Greene again stated that these issues would be reviewed with them when they were at Berkeley.

The other lot records without comment from the inspectors.

Mr.Warburton then stated that they would like to see:

1. Pooling kettle microbial load data
2. Environmental Monitoring data for upper pooling room, fractionation room, centrifuge area, centrifuge drip pans (microbial load), funda filter, vacuum tumble dryer, pasteurizer water (microbial load).
3. Assay results for recovered alcohol and acetone

-(1) Pooling kettle rinse - limits NMT 10 cfu/100 ml (same as WFI) data showed that this system is "under control". Microbial load of pooled plasma were reviewed and even though approx. 40% of all pools had counts of 100 cfu/ml or less, 12% had counts of 1000cfu or greater/ml. Plant investigations have not been able to show any correlation of any difference in handling of the plasma which results in the difference in microbial load of the pools. Also there does not appear to be a direct correlation between microbial load at the pool stage compared to the microbial load of bulks and/or any pyrogen problems.

-(2) The environmental data for the pooling room, fractionation rooms, AHF processing area,etc. were reviewed. For some of the areas the only data available was surface swab testing (fractionation -5°C rooms) and for other areas such as the funda the data was based on equipment rinse testing. Even though for most of these areas the data which was available was not nearly as complete as the environmental monitoring data for the areas involved in the aseptic areas, enough data was available to satisfy the inspectors concerns, except for the drip pan salvage material whcih only had LAL testing for pyrogens.

-(3) The assay results for recovered Alcohol and Acetone were reviewed and no problems were noted.

At 1:00 the inspectors completed the inspection and started preparation for the wrap up meeting.

UK Inspection Wrap Up Meeting

The wrap up meeting with Mr.Warburton and Mr.Kavanagh was held the afternoon of 2/19/88 with T.Monroe, L.Franke, E.Greene and P.Wiggins in attendance. The inspectors related that they would be classifying their observations into categories of: Critical, Major, Minor and "Licensing Issues". The licensing issues would be followed up with E.Greene in Berkeley and M.Tatt of Miles U.K.

Critical: None

Major:

1. Sharples centrifuge drip pan material
   - containers not protected from environment
   - no microbial load data to support the recentrifugation of this material
2. Bulk freeze dryers allow potential "viral" cross contamination of products, especially IG products not subjected to a final heat treat cycle.

Minor:

1. In the upper pooling "shucking" room - frozen plasma falling on floor is washed in alcohol and returned to pool. Concern over microbial load when this is done (pooling room floor is not monitored for microbial load).
2. Copies are kept of truck drivers temperature recorder charts for deliveries of frozen plasma, but temperature trace on retention copy was not legible.
3. Nonconforming Material (NCM) reports "especially" for raw materials used by manufacturing pending completion of testing should accompany the batch production record so manufacturing personnel are aware of status.
4. Buffer prep room - clean equipment storage noted where residual wash water was remaining in hoses and portable kettles.
5. Buffer prep room - one kettle of buffer solution noted without an Off Test label. Operating procedures were not clear as to who and when Off Test labeling is to be applied to the stock buffer solutions.
6. Plasma "Donor Center Study Material" - procedures not clear as to when this material is to added to plasma pool. Different procedures stated: 1) anytime prior to completion of centrifugation, 2) prior to start of centrifugation. This material should be added to pool prior to pool sample being obtained for pool hepatitis testing.

Licensing Issues: (these issues are to be followed up by the UK inspectors with E.Greene in Berkeley)

1. UK Product License needs to include:

   - BSI as a source of plasma for Koate
   - Use of Alpha II + III (when approved for use by the OoB)
   - use of "Source Plasma Salvage" (source plasma exposed to a temperature of NMT 10°C)

2. Agreements between the UK and Cutter Biological/Miles that we do not have to perform HIV testing on our plasma pools and final product.

The inspectors related that we should wait for a written listing of observations and then provide our responses at that time. In answer to questions over who the written observations should be sent. E.Greene indicated that the written observations should be sent to M.Tatt, who in turn would forward the information to E.Greene and the plant.