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MEETING OF FACTOR VIII WORKING PARTY
FOR SCOTLAND AND NORTHERN IRELAND
HELD AT SNBTS HQ UNIT, EDINBURGH ON 15.11.90

Present: Dr C A Ludlam (Chairman)
Dr B E S Gibson
Dr G D O Lowe
Dr I Walker
Dr E Mayne
Professor J D Cash
Dr R J Perry
Dr R Stewart (Secretary)

In Attendance: Mr D McIntosh
Dr C V Prowse

1. WELCOME AND APOLOGIES

Dr Ludlam welcomed the group to the meeting and in particular welcomed Dr Walker who had recently assumed the role of Co-Director of the Glasgow Haemophilia Centre. He also thanked Mr McIntosh for supplying the venue for the meeting.

2. MINUTES OF PREVIOUS MEETING

These were agreed as a true record of the meeting.

3. COAGULATION FACTOR USAGE AND DISTRIBUTION

Dr Stewart reported that no problems had been encountered with the new distribution system for Factor VIII. He presented an update of the Coagulation Factor Usage which showed that demand for S8 was within that anticipated.

Mr McIntosh pointed out that due to the recent change in distribution system it had been considered appropriate to alter the graphs from having an allocation line to an estimated demand.

Dr Ludlam thanked Dr Stewart. Dr Stewart then presented data on PFC issues of Factor VIII and commercial purchases in the NHS in Scotland from 1980 to current, these are shown in appendix 1. These were discussed fully and it was noted that the 1984 PFC issues figure may be an overestimate as product in that year was issued and returned for heat treatment.

Dr Perry presented data on PFC stocks of both Factor VIII and plasma these are shown in Appendix 2. Professor Cash pointed out that recent increase in demand for platelets was starting to have an impact on plasma collection as the production of each unit of platelets removed 50ml of plasma from fractionation.

4. PUP STUDY

Dr Stewart reported that 3 further patients had been entered from the Royal Hospital of Sick Children, Glasgow which took the number enrolled to 20. No new data had been received on either infusions or liver function testing of any patients in the study.

5. FUTURE ARRANGEMENTS FOR FACTOR VIII MANUFACTURE AND SUPPLY IN SCOTLAND AND NORTHERN IRELAND

Dr Ludlam pointed out that Dr Savidge would no longer be attending the meeting and said that he had had the opportunity to discuss Dr Savidge's opinions fully with him and would be able to present them to the group where appropriate.

Professor Cash was then invited to review the process options for a high potency Factor VIII concentrate. Professor Cash reviewed the range of topics involved and the decision making process, these are shown in Appendix 3.

The Haemophilia Directors were invited to comment whether they had a particular preference between solvent/ detergent treatment or pasteurisation. Dr Mayne said that she would appreciate an expert toxicologist's opinion on the likely effect of life long exposure to traces of solvent/detergent in patients. She said that she felt that terminal dry heat treatment had an enviable safety record and that should not be dismissed easily. It was noted that pasteurisation would be more effective against a wider range of viruses than solvent detergent treatment would.

Dr Ludlam enquired whether there would be any strong preferences between pasteurisation and terminal dry heat treatment. Dr Mayne said that she was still in favour of dry heat treatment and Dr Lowe agreed with this view.

Dr Perry commented that as few fractionators were using dry heat treatment as the virucidal step the Regulatory Authorities were becoming less comfortable with applications which contained this as the only virucidal step. He suggested that a licence application may receive a smoother run through the Medicines Control Agency if a virucidal inactivation process used by other fractionators was included in the process.

Dr Mayne felt that we should not rush to follow the FDA and that there was evidence from the UK to suggest that heat treatment was a valuable and effective virucidal process.

Dr Prowse was invited to comment on scientific aspects of the process options. He stated that there was considerable discussion taking place with NIBSC, who seemed to be concerned that some high purity Factor VIII concentrates were partially activated and that this could affect the label potency. He also reviewed the protein content of a likely ion exchange product versus an immuno purified product which would require to have albumin added back to it, these are shown in Appendix 4.

Professor Cash outlined a proposal to use a modified version of the process used in Lille. Under this option an upstream component of the S8 process would be added onto the column. The target product would have the following specification:

specific activity of >100 IU per milligram
a dispensing volume for 500 IU of < 20 ml
viral inactivation by solvent detergent

He pointed out that current experience with a non-modified Lille process was 130 batches made in France since July 1988, and a total use of 200 million international units. In addition other countries were using this type of technology and these include Norway, Denmark, Australia, Republic of Ireland, Luxembourg, Belgium, Israel and Germany.

The Haemophilia Directors enquired about the likely licence position of this process and it was pointed out that Bio-Transfusion have committed to apply for a product licence which will cover the European community in 1991.

Professor Cash described additional advantages to using a modified Lille process, these were

a. an option for a further terminal virucidal step
b. agreement for a further licence of other products, processes for example von Willebrand factor or a high purity IX.

Dr Mayne enquired exactly what modifications to the Lille process were needed. Dr Perry replied that through collaboration with Lille it was intended to alter the cryoprecipitate stage to that which had been used in S8 and both Centres would thereafter produce the modified Lille process ie PFC and Lille would both be producing the same product.

Dr Ludlam commented that Dr Savidge had said that his early experience with Lille product had been excellent but that recent batches had experienced solubility problems. He further commented that he was aware of similar problem occurring with the Octapharma product.

Professor Cash replied that this was not a universal problem with Bio-Transfusion and while the Company had been aware of some problems they said that it had not occurred in a significant number of batches.

Dr Mayne said that solubility was a very important feature and in her opinion once she had experience with a monoclonally purified Factor VIII product which went into solution quickly it was extremely difficult to go back to using products which were more difficult to solubilise. However, she commented that she was unaware of any problem with the Octapharma product having been experience in Dublin.

Professor Cash said in discussion with Bio-Transfusion it was suggested that it may be important that the dissolution water is at room temperature and not a 4°C and that Bio-Transfusion were looking at altering their packaging to allow the water to be stored separately from the Factor VIII. They also are developed an alternative needle which assists in solubilisation.

Dr Lowe asked if this product and process are so good why did BPL take it up? Professor Cash and Mr McIntosh agreed that they were not in a position to respond for BPL. However, when they had done a full option appraisal on the likely benefits of the various processes including additional costs, the modified Lille process appears to be the best choice.

It was agreed that the Haemophilia Directors should be left for a period of time to discuss the various options before making any recommendation to the SNBTS on which fractionation procedure they should adopt in future.

At this point Dr Gibson left the meeting and Dr T G Taylor joined.

When the meeting reconvened Dr Ludlam reported that all the Haemophilia Directors were happy to accept the modified Lille process and that they would support the SNBTS in doing so. However, they would appreciate clarification as to why if the Lille process is so good, they are developing a monoclonal purification process.

Professor Cash replied that this was not been developed by Lille but by CNTS Paris and it is believed that this monoclonally purified Factor VIII product is in clinical trial. He added that to the best of his knowledge

Bio-Transfusion believe that they should have a immuno-purified product available in case there is a major marketing pressure exerted from American companies for such products in Europe. The ion exchange process, as used in Lille, is Paris's first option but the immuno-purification process is in place as a back up to that.

Dr Ludlam enquired the likely time scale for a modified Lille process to be in place in PFC. Professor Cash replied that according to the plan the actual first production runs of a high purity Factor VIII concentrate in PFC would take place in May/June in 1991. A CTX would be applied for in December 1991, clinical studies would commence in February 1992 with increasing clinical use thereafter. A product licence application would be submitted in October 1992 and allowing sufficient time for MCA processing of this application it is anticipated that the product would be licenced in August 1993. It was agreed that this would be an acceptable time schedule.

The Haemophilia Directors then enquired what were the plans for coverage of Factor VIII supplies through to this time schedule and the SNBTS representatives replied that one alternative was to continue with the development of S8 but to do so would result in a product whose clinical use would be of a short term nature. In addition getting the S8 process running routinely would take up R&D time which would be considered to be more appropriately used in concentrating on the high purity product.

Mr McIntosh said that while nothing could be guaranteed at this stage, it was planned to get product made in Lille from French volunteer donors as quickly as possible for use in Scotland with those groups of patients which the Haemophilia Directors decide would require such a high purity product. This may include HIV positive patients or anyone else who, in the Haemophilia Directors opinion, would benefit from such a product. He could not put an exact figure at the time but hoped that 2.00 million international units may be available for clinical trial purposes.

Thereafter it is planned to make cryoprecipitate in PFC from Scottish volunteer donors which would be shipped to Lille for processing. This would give Lille experience of working with an S8 front-end-derived product and they would benefit from this also. It was hoped that the 2.00 million units would be so processed.

Mr McIntosh stated that this was all achievable but at this stage he could not guarantee the 4 million units, although this was the planned figure. Dr Ludlam

presented some in vitro data on the effect of Z8 on lymphocytes. He said that these data were sufficient to raise the level of concern so that he could not longer feel comfortable treating HIV positive haemophiliacs with Z8.

The Haemophilia Directors were then asked would they agree to the discontinuation of S8 as a clinical product. The Haemophilia Directors agreed that in the circumstances it would not be appropriate to continue development of S8 as a clinical product. Dr Lowe commented that he could keep some patients on Z8 but he felt that he should couple that to a need to increase the use of high purity product from month to month so that his use of Z8 would be tapered off. It was agreed that this would be an appropriate strategy.

Dr Lowe enquired what would be the fall back position if the Lille process fails. Professor Cash replied that the ultimate fall back would be Z8 but this would only be a temporary measure as the SNBTS is fully committed to the production of a high purity Factor VIII concentrate in principle.

Dr Lowe pointed out that there was still a need to get access to more extensive clinical data on patients who had been treated with the Lille product. Professor Cash agreed it would be valuable and he said that he would take the issue up with Bio-Transfusion.

Mr McIntosh asked the members of the group to maintain a high level of confidentiality on this matter at present. It was pointed out that neither the SNBTS nor the Haemophilia Directors could actually make decision, however, their recommendations would be passed on to the Scottish Office where the decision would be made.

6. ANY OTHER BUSINESS

There was no other business.

7. DATE OF NEXT MEETING

To be arranged by Dr Stewart and Dr Ludlam.

Dr Ludlam thanked the group for their valued contribution to the meeting.