STRICTLY CONFIDENTIAL

MINUTES OF MEETING BETWEEN REPRESENTATIVES OF RORER HEALTH CARE AND THE DHSS AT MARKET TOWERS, LONDON - 3.10.86

Present: **Dr Jeffreys**)
Dr Rotblat) **DHSS**
Dr Purvis)

Mr K Fitch
Dr P Harris
Mr R Christie

Dr Rotblat introduced the meeting by a brief summary of the current position as seen by the DHSS. There were two cases of clear-cut sero conversion in response to Armour's heat treated Factorate, these being the case of Dr Whitmore at Lewisham Hospital and one patient of the two reported by Dr Hill of the Birmingham Children's Hospital and, in addition to these, three other cases where there was not quite such a definite product relationship. These were that reported by Dr Ten Cate in Holland, the Chapel Hill case in the United States, and the second case reported by Dr Hill. It is recognised that the heat treated Factorate involved in all these cases were non-donor tested and that all material now being sold in the UK is from donor-tested plasma pools.

Dr Harris agreed with this summary of the present position but reminded the Department of Health that Dr Whitmore's (Lewisham) case and the Holland case were associated with a defective batch of heat treated Factorate which contained a donation from a donor who subsequently developed AIDS. The Department of Health accepted that, at the moment, these are only immune responses and nobody could interpret the significance of them and also, it did amount to only two cases, but that this situation should be put in context of the size of the data base. Because of the fact that the majority of haemophiliac patients had already sero-converted to HIV antibody positive, there was only a very limited population who are negative patients, so that, in spite of the low numbers, these two cases would assume a higher significance, and it was felt that it was necessary to make a decision on the information which was available. This information should include an input regarding the technical and virological safety of the product.

The DHSS accept that Dr Rodell's original data on viral inactivation, presented at the last meeting, did look good and in favour of our heat treatment process, with an adequate margin of safety. However, it must be recognised that our heat treatment process in terms of time and temperature is the lowest of any product on the market. They would wish to know from our US technical staff if we have any plans to improve this situation with regard to either a new product or increasing the time and/or temperature of heat treating of the existing product. Dr Harris replied that the ultimate long-term answer to the problem is monoclonal antibody purified product which had been heat treated to the state of the art. This would not be available in the immediate future and so the interim solution, upon which our American parent company has already conducted a considerable amount of work, was to increase both the temperature and the time of exposure of dry heating to the product. Our United States colleagues will give full details and data concerning this process at the meeting on Monday.

Contd/...

Mr Purvis then interjected a question regarding the water content of our current Factorate. He asked if there was any possibility that the water content of the lyophilised cake was variable from batch to batch since, in a dry heat situation, the water content could be critical to viral inactivation. He would also need to check whether the water content of our production material resembled that of the special material made for the viral inactivation studies. This would ensure that the viral inactivation studies were truly valid in the context of our standard production, and it was agreed that this question would be put to our United States technical team.

Mr Jeffreys then changed the tenor of the meeting and asked how Rorer were proposing to handle the current situation. It was inevitable that news of this additional sero-conversion and its circumstances would be in the public domain fairly shortly, possibly by the end of the next week, as there was a meeting of all Haemophilia Centre directors in Edinburgh. Mr Christie mentioned that Dr Hill did not intend to disclose the details of his case to the Haemophilia Centre directors' meeting unless it was absolutely essential to do so. He had only discussed it with Dr Rizza and the area supplies clinician apart from ourselves and the DHSS. If this was the case then it might be possible to hold the information from breaking into the public domain for a little longer, although Dr Hill would have to inform the parents of the children who had sero-converted and, inevitably, there will be discussion amongst parents and haemophilia patients at meetings of the Haemophilia Society.

Dr Harris indicated that the course of action would depend very considerably on the outcome of the Monday meeting. It was necessary to consider very carefully the scientific evidence on whether or not there was a defined risk to the patient. It was also necessary to ensure that we could retain credibility in the face of the evidence of the sero-conversions. If the answer to both of these questions was negative, ie. the product did not appear to be safe, and we could not maintain credibility, then we would have little alternative but to agree to a voluntary withdrawal. The DHSS indicated that if we did not agree to a voluntary withdrawal in these circumstances then they would need to consider the case further as to what their course of action should be. Mr Fitch re-confirmed that we needed the input of research workers from the United States so that we had all available data upon which to base a decision. The small data base upon which the decision would have to be made was again raised at this point. In response to a comment from Dr Harris, Dr Rotblat agreed that this was a very small number of patients but asked, "Do we make a move on these two cases or do we wait for the third or fourth sero-conversion?" This is particularly pertinent in the context of the fact that no other manufacturer or other source in the UK had reported a sero-conversion in response to the heat treated product. We would wish to see a written report of the facts on the Hill case and the DHSS confirmed that they had received nothing yet in writing.
We were then asked what percentage of the market was held by Armour and we revealed that we currently held 37% of the UK commercial market. This information was partly requested to assess the relative risk of us picking up a sero-conversion, and Mr Christie pointed out that, at the time the patients in question were treated, we in fact held 60% of the UK commercial market and therefore our risk at that time was nearly double that of the current market share.

Mr Jeffreys then asked if we could possibly look carefully at the options open to us, although it was evident that we could not make a firm decision at the present time. If it were necessary to make a voluntary withdrawal of product the DHSS asked how we proposed to do this, who should be informed, and how were we to disseminate information. Dr Harris indicated that we had not yet reached a definite position, although this had, of course, been discussed over the past two or three days. We had paid far greater attention to addressing the various medical and scientific issues

Contd/...

which have been raised by the current situation, including contacting other clinicians who had reported sero-conversions to try and assess their significance. We were aware, from our experience with a letter which was circulated to all Haemophilia Centre directors two or three months ago requesting withdrawal and exchange of non-screened donor material, that information does not go all the way down the line from the Haemophilia Centre directors to hospital stores, pharmacies, patients, etc. It would be necessary to take adequate steps to ensure that the information reached all patients and those holding stocks and supplies. We had, of course, looked at the various elements - blood transfusion centres, the haemophilia centre directors, patients' associations, etc. - but we had not pulled the information together into a firm plan. One critical point was that we would not wish the press or the media to obtain information on a proposed recall or the problems experienced with sero-conversion before we could get information to the doctors. We had a very effective telephone contact system and we could bring this into effect to try and make sure that there was no leakage to the press before information could be properly disseminated to doctors, patients, etc., and minimise the anxiety associated with the current situation or a recall.

We will discuss this over the weekend and try and have a definitive position in time for the Monday meeting, when we will decide if it is necessary to withdraw the product or to disseminate information if we do not. This is important because in approximately a month or so Dr Hill is intending to publish his experience in a medical journal. Dr Jeffreys confirmed that the DHSS would wish to see a recall or dissemination of information done properly and Dr Harris confirmed that this would need a proper timeframe and that we could not rush a recall through in a day or two.

Dr Rotblat then asked Mr Christie concerning the current situation regarding Monoclate and he gave a brief resume of the three virgin patients who are currently on treatment, who have shown no adverse effects either with regard to adverse reactions or elevations in ALT. Naturally, as these patients have only been treated for a month, their HIV status has not been checked. Dr Rotblat asked whether the heat treatment of the Monoclate was the same as our standard Factorate. Mr Christie confirmed that at the moment it was, although, obviously, the intention would be to heat treat to the state of the art in the medium term.

Dr Harris then disclosed that the patient of Dr Ten Cate in Holland has now become ill and the doctor has diagnosed AIDS-related complex and the patient has been referred to the department of the hospital that deals with patients suffering from AIDS. Dr Rotblat also mentioned that Dr Hill was screening a further three patients who were sero-negative and who had received at least one of the batches involved in the other two patients with sero-conversions. The results of these tests are expected today.

Mr Fitch confirmed that it was our intention to discuss any action plan, either of product withdrawal or dissemination of information, with the DHSS. This was intended to provide the DHSS with information and also to give them an opportunity to make comments and recommendations.

The composition of the Armour team for the Monday meeting was then discussed. Dr Harris indicated that we were proposing to bring over a virologist who had been involved in the virology studies and another scientist who was an expert in the field of Factorate. The DHSS indicated that they would appreciate a representative from the Quality Control/Manufacturing side who could answer questions regarding the uniformity of the process, moisture residues and so on. On the DHSS side, it was expected that Dr Rotblat, Dr Jeffreys, Dr Purvis and a representative from their

Contd/...

administrative side would be present. Armour would be represented by Dr Harris, Mr Christie and possibly Mr Fitch.

There was then a general discussion regarding timeframes for possible introduction of a product with a more intensive treatment. The Department of Health view appeared to be that if we presented full data at the Monday meeting then we could move quite quickly to the introduction of an alternative heat treated product. However, Dr Purvis was starting two weeks' holiday on Monday and Dr Rotblat was leaving for three weeks' holiday at the end of October. We understood that it was probable they would not wish to discuss detailed moves to introduce an alternative heat treated product at the Monday meeting but, if we had the data available, they would like to arrange a specific meeting in about three weeks' time to discuss the data. If we had not got adequate data almost immediately to hand, then the process of introducing the alternative heat treated product could take longer.

Mr Fitch mentioned the fact that if this problem had affected another commercial company and we were asked whether we could provide an extra 1-2 million units of Factorate heat treated to fill any deficit in supply, we would find it extremely difficult to find that additional amount of material. Dr Rotblat confirmed that she had not contacted the other manufacturers with regard to increased supplies of Factorate regarding the current situation. Dr Harris mentioned the significant worldwide impact of Armour withdrawing the product. The DHSS stated they are interested only in the UK supply situation.

At this point it was agreed to meet again at **9am** on **Monday 6th October.**

RBC/LEW
3.10.86