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APPENDIX 6

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2nd February, 1979

Hyland Production Visit

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The full report of my visit to Lessines and the Swiss Red Cross is attached.

The following are key points arising from the report:

The Lessines Hyland facility does not meet U.K. requirements for aseptic processing.

If Lessines is inspected imports of Hyland products to the U.K. will probably not be allowed to continue, i.e. Buminate 5% and 20% from Lessines are at risk.

There is no possibility of importing Lessines manufactured Hemofil made under the present conditions.

Our U.K. Licence suggests that plasma originates in the U.S. In fact plasma originates from other sources outside the U.S., e.g. Lesotho and Berlize - this information should be submitted to the D.H.S.S. or plasma from these sources should not be used for U.K. products.

The Swiss Red Cross facility is of a high G.M.P. standard; there would be minor problems in obtaining U.K. approval (See report) which can be overcome.

C. Chard
CC/SMN

HYLAND PRODUCTION REPORT FOR U.K.

A. Lessines Hyland Facility

The Lessines Hyland facility was visited on 29th January, 1979. The production of Hyland products is very well controlled and carried out by competent personnel, however the facility does not meet present U.K. G.M.P. requirements in several important areas.

1. Aseptic Filling Room Area

The change room for aseptic filling room does not have a sink and washing of hands is carried out in a cloakroom approximately 50 metres away. After washing hands the operator dons sterile gloves, walks through a black area and proceeds to the changing room. He then changes into aseptic garments and changes the sterile gloves for a fresh pair of sterile gloves.

The aseptic filling room is really only a clean room with laminar flow inside:

Lights are not recessed - they hang from the ceiling.

U.V. lights (not used during the day) are not recessed and do not look to be in good condition.

There is an excess of electric fixtures and fittings.

The finish could be improved.

Laminar flow over the Hemofil operation is not included in a proper hood and bench arrangement.

There is a considerable amount of mechanical equipment in the area e.g. pumps etc. Ideally this could be outside the area or properly constructed for aseptic production.

Non sterile equipment, e.g. labels are routinely handled by these operators in the aseptic room.

The changing room was full of material being processed, e.g. labels.

The area was not being treated by operatives as a aseptic area, e.g. one operator took a pair of gloves off exposing his hands in the area and then whilst still inside put another pair of gloves on.

A U.K. inspector would require the filling room to be regarded as an aseptic area, this is because there is no automation of production with a consequent "over" handling of open product post sterilisation. Hemofil product remains open to the atmosphere until after lyophilisation, it is thus carried from one part of the room to another in an open state.

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2. Thawing and Pooling Room

Frozen plasma is thawed and pooled in this room, it is exposed to a non-filtered environment and floor and wall surface are very poor.

3. Albumin Filtration Room and Hemofil Laboratory

Material is sterile filtered in bulk in these rooms. Precautions are taken to ensure that there is no contamination of product post sterilisation, this is achieved through a closed system concept. There is no air filtration in this area and a U.K. inspector would expect clean room conditions i.e. HEPA filtered air plus correct finish etc. or even aseptic conditions to minimise the chance of contamination post sterilisation.

4. Preparation Room

Bottles and stoppers are washed in this room prior to sterilisation. There is no air filtration apart from a laminar flow cabinet. A U.K. inspector would probably require HEPA filtration also in this room.

5. Plasma Sourcing

The U.K. licence files refer to U.S. produced plasma. In fact plasma is received also from Lesotho and Berlize, plasma from Lesotho was readily visible in the plasma freezer. As this plasma is routinely used for U.K. product it is important that either we inform the U.K. D.H.S.S. or discontinue using this plasma.

6. Albumin Powder

An update of the U.K. file may also have to include more details on manufacture of Albumin powder which is used at Lessines. This is manufactured by Kabi in Sweden from cryo-poor plasma ex. Lessines.

7. Conclusion

If Lessines is inspected (this is a possibility if a variation to source, Buminate 5% from the Swiss Red Cross, is submitted) it is highly likely that import of all Lessines manufactured Hyland product will be stopped until the areas are upgraded. This is a high risk area for the company and was avoided by the inspectors during their visit only because they were not aware we imported Hyland product from Lessines. There is little possibility of a U.K. inspector allowing Lessines to manufacture Hemofil for the U.K. market.

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HYLAND PRODUCTION REPORT FOR U.K.

B. Swiss Red Cross Facility

The Swiss Red Cross facility for the production of Albumin 5% is newly upgraded and of a high G.M.P. standard. The area consists of three rooms: Bottle preparation, Filling, Labelling and Pasteurization. Nearly all the process is automatic, it is well designed and purpose built and consists of a continuous production line consisting of:

> Bottle washing,
> Bottle sterilisation moving into a white area for bottle filling and capping, then moving into a grey area for over-capping and racking

The contrast between Lessines and the Swiss Red Cross is dramatic - for instance in the filling area at Lessines there are five people manipulating product thus there is a high risk of people contamination of the product, at the Swiss Red Cross there is one person who is merely there to ensure the smooth running of the production line and does not routinely handle the product. The filling area production line is surrounded by a laminar flow hood and although in theory the filling room is not an aseptic room but a clean room, in practice the whole area I believe to be of an aseptic area standard. The only criticisms of this area were:

1. There was probably not enough routine environmental control carried out e.g. settle plates were only put out weekly and since commissioning the new equipment there had not been any media fills and were no plans for any.

2. The changing room although divided into two parts did not have a "step over".

3. The finish of the filling room was of high quality but could have been better e.g. corners were not coved.

4. One conveyor belt moved from the white area to a grey area and then back into a white area again.

The plasma processing areas were not inspected, however we understand that asbestos filters are used in this processing, the current D.H.S.S. position is that asbestos filters should not be used unless completely necessary and that a membrane filter is placed post asbestos filter to pick up any fibres. Such a membrane filter is used for sterilisation and there is probably a justification for using asbestos filters so this problem can be overcome.

The Swiss would not allow an inspector from our inspectorate as this is illegal in Switzerland however they would be happy for a U.K. inspector to accompany a Swiss inspector, preferably on the annual Bureau of Biologicals Inspection.

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HYLAND PRODUCTION REPORT FOR U.K.

Conclusion

A variation to include the Swiss Red Cross as manufacturers of Humanate 5% can be submitted to D.H.S.S. this variation will be a major one with the following changes:

1. Raw Materials - plasma sources outside U.S.

2. Use of Albumin paste rather than Albumin powder

3. Manufacturing Changes - there is no sterile bulk and consequently no heating for 72 hours, also asbestos filters are used.

This variation will attract the attention of the Medicines Inspectorate who may want to inspect the Swiss Red Cross and Lessines. A Lessines inspection would expose the Company to a number of risks as outlined in the report.

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2/2/79/SMN