Fletcher
Dr. Dawson 1835

Your reference: 0116/0011
Our reference: RA. 191

JB/TB

26th August, 1977

Product Licence Variation Section,
Department of Health and Social Security,
Medicines Division,
Finsbury Square House,
33-37a Finsbury Square,
London EC2A 1PP

Dear Sirs,

Application for Variation to Product Licence for HEMOFIL Antihaemophilic Factor (Human)

Please find enclosed an application for variation of the above product licence to include the Travenol facility at Lessines, Belgium as a manufacturer of the AHF contentrate and as an additional manufacturer of the Sterile Water for Injection used for product reconstitution.

A completed Undertakings and Declaration, as required under Section 19(3) of the Medicines Act 1968, has previously been submitted to the Licensing Authority in respect of this manufacturing facility (reference PL 0116/0043, RA. 232).

Additional variations included in the application are:

1. A correction to the test method used for screening each plasma donation for hepatitis B surface antigen. The method used is a solid-phase radioimmuno-assay procedure and not counterelectrophoresis as stated in the original application file.

2. The solubility characteristics of the finished product have been improved and the finished product specification has been amended accordingly.

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3. Recent developments have shown that the AHF concentrate may be stored at room temperature, not exceeding 30°C, for time periods up to six (6) months within the dating period. This upgrading will be notified to the customer by means of a "Flier" included with the kit and a self-adhesive label on the carton.

Tb facilitate the approval of this variation, I have also included re-typed copies of the following pages of our original application file RA. 191:

Part 2, pages 5 and 6 - Section 13.b) Place of manufacture or assembly has been updated per the enclosed variation and previously approved variations.

Part 2, page 7 - Section 14. Quality Control now makes reference to the submission of samples and protocols to the Licensing Authority prior to release for sale in the U.K.

- Section 16. Labelling Sample printed packaging materials as currently used, are enclosed for inclusion in the registration file as Appendix 1. These enclosures will replace Appendices 1,2,3, 5 and 6 of the original application file. New specifications will be prepared, upon receipt of variation approval, to reference manufacture in Belgium.

Part 3, pages 2 and 3 - Section 3. Method of manufacture. Subsection 3 has been rewritten to relate to the Active Substance and not the finished product. An updated copy of the FDA regulations on Source Plasma (Human) are enclosed to replace those included in the original application as Appendix 1 and referenced in Subsection 4.

Part 3, page 6 - Section 3.4 Quality Control Checks made at each stage of of the process Point e. has been corrected to reference testing of each plasma donation for hepatitis B surface antigen by radioimmunoassay. Appendix 3 of the original application file thereby becomes obsolete.

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Part 3, page 15 - Section 3.5 Final Purification Stages has been rewritten to relate to the active constituent (plasma) and not the finished product. Sections 4, 6 and 8 in the original file also relate to the finished product and not the active constituent; therefore, pages 15 - 20 (inclusive) of the registration file can be replaced by the re-typed page 15 enclosed.

Part 3, page 24 - Section 11.4 Finished Product Specification Point d) Solubility has been revised per the enclosed variation application.

Part 3, page 33 - Section 17. Containers The data contained in the original application file has been rationalised to reflect the current range of vial sizes and activities. Details of storage have been updated per the enclosed variation submission.

I hope I have provided sufficient information on this variation and the enclosed retyped pages to enable this application to be reviewed as soon as possible. Approval of the variation is urgently requested; an approval date of 30 September, 1977 has been indicated on Form MLA 221.

Please do not hesitate to contact me if any additional information is required.

Yours faithfully,
for TRAVENOL LABORATORIES LTD.,

J. Brazier (Mrs.)
Senior Scientific Officer