RN/BSH

23rd April 1991.

Dr. F. Rotblat,
Room 1511,
Medicines Control Agency,
Market Towers,
1 Nine Elms Lane,
London SW8 5NQ.

Dear Dr. Rotblat,

Further to our recent telephone conversation I am enclosing further copies of volumes 6 and 7 for Kryobulin (0215/0027) which contain the Pharmacological/Toxicological and Clinical Expert Reports.

In addition copies of the following Variations are enclosed:

Feiba (0215/0020-21) dated 4th July 1990
Prothromplex (0215/0006-7) dated 25th September 1990

Both these Variations deal with leaflet changes intended to standardise the U.K. texts with those in use elsewhere. They are not primarily linked to the changes in the method of manufacture but were submitted at the same time.

The Variations which deal with the introduction of vapour heating are dated 3rd July 1990 (Feiba) and 26th September (Prothromplex).

To answer the other point raised, clinical data on Prothromplex is contained within the International Factor Safety Study discussed in more detail in the Kryobulin application and the latest evaluation dated May 1990 was forwarded with our letter of 15th November 1990.

As far as Feiba is concerned, the enclosed article by Hiltgartner et al "Efficacy and Safety of Vapour heated Anti Inhibitor Coagulant Complex in Hemophilia Patients" has been published since our application was compiled. This provides comparative data between the vapour heated product and the dry heated product confirming equivalent efficacy.

We believe a comment may be helpful in relation to the extra hour vapour heating for the Factor IX concentrates, Feiba and Prothromplex.

As can be seen from the International Factor Safety Study there is no laboratory or clinical evidence of viral transmission of the parameters tested in this study conducted in accordance with ISTH guidelines. This we would argue confirms the effectiveness of the viral inactivation process applied to Kryobulin, i.e. 10 hours vapour heating at 60°C.

Our own preclinical experience showed that Factor IX concentrates are capable of withstanding an additional period of 1 hour vapour heating at 80°C which is not tolerated in a Factor VIII concentrate without stabilisers. Accordingly, therefore, in line with Immuno's policy of optimising viral inactivation processes to individual products, the additional 1 hour vapour heating has routinely been applied.

We are, of course, aware of the work carried out by Mannucci in the mid 1980s implicating the vapour heated product in Hepatitis transmission. Since our application was submitted, however, further work has been published and this is summarised in the attached document entitled "Recent Aspects of Hepatitis Safety with Respect to Kryobulin Vapour Heated".

This does, therefore, tend to add weight to our argument that the vapour heating process as applied to our Factor VIII concentrate is an effective viral inactivation process.

I must apologise for the length of this letter and for introducing new data at this stage, however as I believe you have not yet started your assessment and as these are fairly important topics, I trust you will understand our reasoning.

Yours sincerely,
for IMMUNO LIMITED

R. Nicholson M.Sc.,
Director.