Cutter

TO: Dr. W.F. Schaeffler, Dr. K.H. Fischer, Jan Hjorth.

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FROM: M.M. Sternberg

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SUBJECT: Pasteurization of Plasma Products

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The suspicion that AIDS may be caused by an infectious agent present in human blood refocused attention to the fact that plasma products are potential carriers of agents of serious disease. Indeed, with the exception of albumin which undergoes a grandfathered pasteurization process, all other plasma products have a potential risk of being contaminated with viruses. Scientists and regulatory agencies have always been aware of this problem but because of the lack of acceptable pasteurization means the products have been sold on the basis of benefit to risk balance for the patient.

Approximately three years ago Cutter R&D made a strategic commitment that all new plasma products will be pasteurized and programs will be instituted for the development of pasteurization methods for AHF and Factor IX. As far as immune globulins, because of the natural concentration of antibodies in the gamma globulin fraction, they were never considered potential sources of infection for the user. Pasteurization was meant to be a process that would destroy viruses that may be carried in plasma and in particular hepatitis B, a virus known for its resistance.

Nothing short of this scope, that is a claim that the plasma product is as free from contamination as any routine pharmaceutical product given intravenously will be acceptable in the long term. The long term means also a day when products made from plasma may have to compete with products made by new technologies which will intrinsically be free from human viruses.

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DEFENDANT'S EXHIBIT 695

On a short term we are facing a crisis. Our competitors have succeeded to come out first with a limited claim product. Forced by circumstances, the FDA granted approval without asking for solid evidence, as they asked Cutter two years ago. It is clear, that we have to fight the fire with a short term solution that will preserve our market position but not relent work and resources to be able to claim freedom from contamination by disease causing agents.

On May 23, we reviewed, product by product, our activity in this field:

1. AHF

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1.1 Short term approaches

Wet pasteurization, a process developed at Cutter is currently experiencing difficulties in scale up. Admitting that these will be overcome we can go ahead, file and expect approval within a relatively short time. We will still face the need to improve yields which are not satisfactory.

Dry heat pasteurization

Experiments are in progress in PMT and viral challenges are studied by Drug R&D who has allocated two Ph.D. virologists, Drs. Louie and Dobkin for this work. If successful, the process might face patent infringement difficulties. Technically speaking, it is a process that will not be easy to control because of the individual heating received by each vial, and on the long range I would personally expect product quality problems. Yet, in case the wet pasteurization does not succeed we may not have a short term choice but to go ahead with the dry pasteurization.

1.2 Short term backup

Treatment of plasma products with a chemical reagent (O.phenantroline-Cu) was discovered at Cutter by Dr. Ken Lembach and the patent application filed. To date six different viruses were tested, five of them were inactivated completely and one was reduced by five logs. We are accelerating toxicology and if all looks well we will file for approval of this process. The procedure is simple,

the yields are high and it will lend itself to quick scale up.

1.3 Long term approaches

Combinations of chemical treatment and either of the above heat treatments (wet or dry) to yield a truly pasteurized product.

2. Konyne^{R}

Dry heat pasteurization of Konyne was tested at Cutter in 1971. One should expect in this case that we would have a good chance to avoid patent restrictions. We have already shown with model viruses that dry heat at 60° for 48 hours is equivalent for Konyne with wet heat at 60° for 10 hours. We expect that a total of six-nine months will be necessary to take us to approval by the OB.

We expect to learn about the possibility of licensing the Biotest betapropyolactone process and have asked Regulatory Affairs to discuss this with the OB.

3. Alpha1-PI

Wet pasteurization for alpha1-PI has already been developed and PR lots prepared and ready for clinical testing. This process does, however, contain less excipient than the AHF wet pasteurization, which gives us a good chance for complete kill of the hepatitis B virus. Moreover, because of its nature we believe that the process will be easier to handle than AHF with much smaller yield losses. We will, therefore, continue through clinical trials with product pasteurized by the wet pasteurization and also test it in chimpanzees.

4. AT-III

A wet pasteurization process was tested by American Red Cross and OOB scientists and shown to inactivate hepatitis B virus. We intend to use the same process as the ARC, thus avoiding chimpanzee trials and being able to claim virus inactivation.

5. Gamimune^{R}

As we mentioned before, historically Immune Serum Globulin made by the Cohn process did not give identified cases of hepatitis. This perception of not being a virus carrier may now change due to AIDS. Experiments are in progress to determine, with model viruses, if the reduction and alkylation which is being used for preparing Gamimune has virucidal activity.

6. Fibronectin

Though a wet pasteurization has been developed it is still too early to decide whether it will be the choice procedure.

The problem of investments for a hepatitis-safe dedicated unit has been raised, and it was pointed out that dry pasteurization avoids this costly investment. In our opinion, a validated hepatitis-free unit for a hepatitis-free product cannot be avoided. As long as we do not claim a hepatitis-free product and neither the dry or wet pasteurization as we know them now do claim it, we do not have to invest in such a manufacturing facility.

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