Cutter

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TO Paul Brown

DATE 8/10/83

FROM John Hink

COPIES TO Carol Moore

SUBJECT Wet HT-Koate[R] PLA Options

Over the past several months we have proposed several options to the wet HT-Koate[R] PLA process section. Each of these deserves confirmation, justification and explanation, as follows:

1. option to by pass heat treatment - this is simply a means to piggy-back on the wet HT process ~~to obtain a glycine ppt. process~~ to obtain a glycine ppt. product which (with dextrose) shows good clarity and solubility with few fibrils and little or no color. With the current AIDS situation this non heated product will probably not be made for commercial sale, but then who knows? The two "Glycine Ppt" lots presently included in the PLA draft support this option.

2. option to add albumin to thawed/diluted bulk - as the wet HT process produces a final product with composition of greater than 80% fibrinogen and the British Pharmacopea states that AHF must contain less than 80% fibrinogen it seemed logical to add albumin to product destined for the International market (especially after learning that albumin was not detrimental, and in fact beneficial, to the glycine ppt. product as described below). No wet HT product with albumin has been made to date.

3. option to delete dextrose from the "dissolving buffer" and "diafiltration/ultrafiltration buffers" when it appeared that the wet HT process was in trouble we did some "quick and dirty" work to produce a glycine ppt. product which would withstand a dry heat treatment. As predicted, a product with dextrose was unstable due to dextrose-protein interaction. Without dextrose the product was stable but difficult to dissolve. We tried a number of excipients to improve solubility and found albumin the best. Currently Clayton is manufacturing 100% of their Koate[R] by the glycine ppt. method without dextrose and with added albumin. Preclinical and clinical work has started or scheduled and we expect a PLA submittal for the product in Nov.

On the remote possibility that this dry HT product could be registered/sold in International market prior to U.S. licensing, it seems prudent to piggy-back again on the wet HT process. By showing or describing an option to delete dextrose in addition to the albumin addition and wet HT by-pass we could legally manufacture a non-heated dextrose free Koate[R] containing albumin which could be exported and dry heat treated abroad. (I doubt

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that we would want to do this until we complete our neoantigen and clinical studies, but as I said before, who knows?) As Cutter is seriously limited in the ability to produce wet HT-Koate[R] (only Berkeley has the required equipment) and the yield for wet HT-Koate[R] is one half that of the dry HT product, this option has considerable potential value.

I am suggesting the following wording for the option for albumin addition:

PREPARE BULK

Thaw (if frozen) dilute with buffer (dextrose optional) and/or WFI.

pH 7.0 ± 0.4

(Optional) add Normal Serum Albumin (Human) to reach final product concentration of 5 to 7.5 mg. albumin/ml.

Filter to clarify
Filter to sterilize

etc.

JHH:gml