ANTI-HAEMOPHILIC FACTOR (HUMAN) KOATE - PL/0010/0061

Answers to questions 1 - 3 of your letter of 2Feb. 1976

1a The Number of donations in each pool

Each pool consists of 2500 litres of plasma. Each unit of Source Plasma (Human) is approximately 600 ml. Therefore, the pool would be comprised of approximately 4000 units or more. Generally, the plasma pool is such that it is comprised of approximately equal donations from at least 1000 individual donors. A given lot of Koate™ is usually made up from material fractionated from 3 to 5 pools, i.e. the AHF suspension obtained from 3 to 5 separate plasma pools is combined in solution to form the final product.

1b Method of Assay, the Standard used and its Calibration

The Factor VIII assay method was revised by Cutter in January 1976 and a copy of the new method ASD 72 is attached.

The Plasma Standard currently being used is Lot 1588 - 77 as stated on page 024 of our submission and also on pages 064 and 065. A copy of the official results of the calibration of this standard against the U.S. AHF Standard Plasma by BOB, FDA, is attached. AHF Concentrate Standard Lot 1627-86, which is currently being used, has been assigned the value of 34.4 u/ml. This value was also determined by calibration at the BOB and a copy of their results is attached. BOB routinely uses the two-stage Thrombin Generation Time Method for Factor VIII determination.

1c Batch to Batch Reproducibility

Attached are the testing and release summaries for three recently produced lots.

2. Product Labelling

We did not think that our labelling would have to comply with the BP in every detail, as we are not claiming that the product is of BP standard. In most cases, however, the information required in the BP, if not found on the container label, may be found either on the carton or on the package insert. There now follows comments on each of the 12 labelling points specified in the BP.

I The AHF Units are stamped on both the container and carton labels. One unit of Factor VIII activity is defined in the submission as the equivalent of the anti-haemophilic activity present in 1.0 ml of average normal plasma, which is the same definition as in the BP and so the units are international units of potency.

II This is not stated on the container label but it is stated on the package insert.

III The product is not assayed for fibrinogen content and so there is no statement of fibrinogen content on the labels. However, the package insert states: ' Containing minimal quantities of fibrinogen'. This is because Koate contains Factor VIII in a concentrated and highly pruified form. As shown in the 'Protocols for Investigational Lots' on pages 91 to 94 of the submission, the content of fibrinogen was found to be well below the BP limit in every case.

A limit for the %w/v of total protein has not been set for Koate. Total protein is determined on each lot of product and the protein content in grammes per vial is reported on the label of each vial and on the carton. It is felt that the Specific Activity, for which a limit is set, is more important than the absolute protein concentration.

IV Neither of these two facts are stated on Koate's labelling. A limit of 145 - 185 mEq/L is set for total sodium ions as stated in the specifications submitted but this is not included on the labels as it was not thought necessary.

The product is not assayed for citrate ions and so no limit is set for this parameter, nor is it included in the labelling. Koate contains a minimal amount of citrate ions, being well below the BP limit. The maximum citrate ions that can be present can easily be calculated as shown below. Since sodium, for which a limit is set, comes only from the addition of sodium chloride (limit set for chloride ions) and sodium citrate, the citrate concentration would be determined as follows:

a Total sodium mEq/L - chloride mEq/L
= sodium mEq/L from citrate
185 ($Na^+$) - 160 ($Cl^-$) = 25 mEq/L from sodium citrate

b Sodium citrate mEq/L $= \frac{\text{sodium mEq/L}}{3} = \frac{25}{3}$

Maximum citrate ions = 8.3 MEq/L

The added substance dextrose is mentioned

V The package insert states: 'Warm to room temperature but not higher that 37°C'. This temperature range has been found to be satisfactory for the reconstitution of Koate.

VI The volume of Water for Injections required for reconstitution is stated on the labels. Koate contains dextrose, which facilitates the dissolving process, and usually takes less than 5 minutes. This is stated on the package insert.

VII Stated on carton and package insert.

VIII Not stated; a filter needle is supplied for the withdrawal of the reconstituted Koate solution into a syringe and if a gel had formed, withdrawal would be impossible.

IX Not stated, except package insert mentions 'obtained from many donors'. See also answer 1a to your letter above.

X Stated

XI The upper limit of the storage temperature is stated as 8°C and not 6°C as specified in the BP. The 8°C limit was reached as a result of Cutter's Stability Studies. We note that Hyland's package insert for Haemofil also gives 8°C as the upper storage temperature and we see no reason for altering our statement.

XII Stated on carton and package insert.

3. Expiry Date

The present expiration date in the U.S. is 18 months from the date of the last valid potency test when stored at 2° - 8°C. This expiration date was approved on the basis of the stability data contained in our submission. The nominal storage temperature during these studies was 5°C. The actual range of storage temperature was 2° - 8°C.