30 SEP 1991

M E M O

From: P.A. Feldman

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27th September, 1991.

9MC CTX Application

I have now reviewed the CTX Application as sent to MCA with covering letter LA/AWW/bt. perves, 12th September 1991. Some of the following observations reiterate my implicit concern (memo of 6th September, 1991) regarding the release of details of the 9MC process and product in advance of corroborating data, analysis and comment.

P.3 (A1-11): The quantity of factor II is less than 10 iu/vial and of factor X is less than 40 iu/ml.

P.5 (A1-13), also 000005: The dose is stated as 75 iu/kg body weight. All production calculations for the clinical trial 9MC batches have assumed a dose of 50 iu/kg (PF memos 16.5.91 and 26.7.91). Was this assumption incorrect? If so, the 50% increase in dose may deplete the carefully allocated stock.

P.6 (A1-14): The quantities of TNBP and TWEEN 80 are more than 300 times too large and do not contain any definition of units.

The limits for TNBP and TWEEN are less than 10mg/L (<10 ppm) and less than 100 mg/L (<100 ppm) respectively.

P.7, also 000055: I do not think we can describe any product as "virus free". The accurate terminology in the flow chart (and I admit to missing this in earlier drafts) should be "solvent-detergent treated prothrombin complex concentrate solution".

P.7B, also 000076: This finished product specification is only provisional and without data to support it. The QC data from the batches of 9MC prepared for clinical trial are only now being collated. These will be reported as soon as possible and we will then be able to produce a genuine specification which relates to the product we are now manufacturing.

P.9 (A1-17), Note 1.3, also 000002. This allows for a total of 30 patients. We do not have enough concentrate to support such a programme. If copies of this protocol go to participating clinicians, are they alert to this limitation on actual numbers of patients who can be tested?

000022: Should read "gamma-carboxyglutamic acid".

000054: (a) The "cryoprecipitate" and the "supernatant and discarded wash"

co-fractionate with the main flow chart. They are not derived from the cryosupernatant and DEAE-Sepharose/adsorbed protein. In genealogical terms, they should be siblings, not progeny (ref. my reply 27.8.91).

(b) Eluate from DEAE-Sepharose. In-process control limits at this stage are NAPTT ≯150 secs; FCT 37°C ≯3h.

000056: In the "In Process Control" column, individual eluate fractions can be <55 iu/ml, if the overall pool is ≯60 iu/ml. I suggest that the "(≯55 u/ml)" is simply omitted.

000078, Section 7, Stability of Solution: The limit on this test, quoted on Page 000076, is ≯1 hour. Are we digging a hole for ourselves by specifying that the test continues for three hours, even if that is how we choose to perform the test for whatever reasons of our own?

000080, Note 9.i: We can provide supporting data on why the factor IX assay initial dilution is made in deficient plasma instead of buffer. This relates in part to the destabilising effect of the buffer alone on highly purified factor IX at low protein concentration - an effect which does not occur in PCCs with much higher protein concentrations. It may not be worth adding this to the CTX text, but a full justification (more complete than the above) can be provided by HE/PF if required.

000084: The full name for TNBP should be "tri-n-butyl phosphate", i.e. lower case "n", as this refers to structure, not nitrogenation. The abbreviated form can optionally use upper case "N".

000088: While the description of packaging may reflect the BPL standard, I am not sure whether we have enough clinical trial material to supply all participating clinicians in this format. This will depend on the actual number of participant and trial volunteers in the study.

000090 Paragraph 3: Plasma donations are also now tested for HIV-2. The intermediate supernatant plasma pools for the CTX batches were tested for HIV-1 and HIV-2. You may want to check the status of RTC testing for the individual donations used in these pools.

000093 Paragraph 4, Administration: Reference is made to a filter needle provided with the product, through which the product should be drawn into the syringe. However, the description of packaging on Page 000088 does not include any needles.

000096 onwards: I am particularly concerned about the form of reporting these studies on a number of counts:

000096 (1). (a) The report of the dog thrombogenicity study has been directly transcribed from an internal BPL memo I wrote on 16th May, 1991. The form, level of description and level of discussion are not suitable or appropriate for external evaluation and the report was never intended for such a purpose. The TNT data are a particularly irrelevant distraction and poorly defined. The original programme for the CTX application included a section, assigned to be written by me, covering the current round of dog infusions upon which, until this month , I had understood application would wait.

(b) The 9MC material infused in this study was not prepared in the batch consistency series; it was an early development batch without full QC. the infusions were performed to give us an early warning of any untoward reaction, not to demonstrate safety.

(c) Factor IX results (paragraph 7): Surely statements that "it is merely reassuring that there is an active ... effect" have no place in a serious CTX application?

000097 (d) Paragraph 2, Fibrinogen. A grammatical error: "The final sample(s) show(d)(s) a fall ...".

000097 (e) SNBTS is not defined.

000098 (2) (a) What does all the acute toxicity data mean? Do we have a comparison with 9A equivalents? Were the responses due to the 9MC itself, or due to the fact that, at a four-fold concentrated level, the rats were being infused with 0.9M lysine and more than 1.0M chloride? While this is referred to indirectly in note (2), there is no discussion of it in the detailed results sections. Given that this is the only formal report I have seen of the acute toxicity study, it may be helpful to include some discussion of the results in context with other products and hypertonic effects.

000098 and 000099 (b) On specific points, the quoted unitage of 600 iu per vial is inconsistent with the normal product specification.

(3) The rabbit data reported is a direct copy of Elaine Gray's report without interpretation or discussion. If NIBSC also have to comment on the CTX, perhaps we should write our own report on the basis of data collected by an outside contractor, i.e. as for the Acute Toxicity study, but, in this case, NIBSC.