DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEMORANDUM

To: Review Committee Chair, STN 125612

From: Leslyn Aaron, Biologist, LACBRP, DBSQC, OCBQ

Through: Lokesh Bhattacharyya, PhD, Chief, LACBRP, DBSQC, OCBQ

William McCormick, PhD, Director, DBSQC, OCBQ

Sponsor: Octapharma Pharmazeutika

Product: Fibryna® Human Fibrinogen

Subject: STN 125612: Results of in-support testing to measure the total clottable protein in Human Fibrinogen, Fibryna, drug product.

Background: A request was made by the review committee Chair to measure the total clottable protein in five lots of Human Fibrinogen, Fibryna, drug product.

Method: The fibrinogen content of five lots (A433A3473, A440A3472, A441A3474, A425A3471 and A423A3472) of the drug product were measured at DBSQC/ CBER using LACBRP's Assay for Fibrinogen Potency by Total Clottable Protein method, TM000771 version 02. A WHO international standard (IS) for fibrinogen concentrate (NIBSC Fibrinogen Reference Standard, 09/242) is used in each run of the method as an assay control sample.

One determination of each lot of drug product and assay control was measured.

Conditions allowing clot formation are established by addition of thrombin in calcium chloride and HEPES buffer at pH 7.0 ± 1.10 to 0.5 mL (10.0 mg/mL) of the drug product, reconstituted in 50 mL of water. After incubation for 30 minutes at 37°C to complete clot formation, the clots are separated by centrifugation and washed 3 times with 9 g/L Sodium Chloride solution to remove any residues of thrombin and other components. The clots are completely dissolved by alkali digestion in 6.7 M Urea/0.2M Sodium Hydroxide Solution at room temperature for 90 minutes then overnight at 2-8°C. The absorbance is then determined using an ultraviolet (UV) spectrophotometer at 280nm. Two aliquots of each sample and the assay control are measured.

The total clottable protein in the sample is calculated from the measured OD_{280} using the extinction coefficient of fibrin under alkali conditions ($E^{1\%}_{1cm} = 15.87$).

Results:

The assay validity criteria and the results obtained are as follows:

- The potency of the assay control (WHO IS for Fibrinogen Concentrate; NIBSC 09/242) is 80% of the assigned Total Protein content. The results were within the DBSQC qualified acceptance range of 71% – 94% of the NIBSC assigned Total Protein content.

  The %RSD of the assay control measurements was <0.23%, which met the acceptance criteria, <10%.

- The fibrinogen content of the five lots of Human Fibrinogen, Fibryna, drug product are summarized in Table 1. The proposed BLA specification is (b) (4). Table 1 shows that all results from the five lots were within the proposed specification limits ((b) (4)).

Table 1: FDA/CBER Fibrinogen content measurements using a total clottable protein assay method and Octapharma's reported results.

Sample ID (Lot #)	Octapharma		FDA/CBER	
	Reported Result (mg/mL)	% Target Content (20 mg/mL)	Measured Content (mg/mL)	% Target Content (20 mg/mL)
A433A3473	24	120	19	95
A440A3472	20	100	21	105
A441A3474	20	100	17	85
A425A3471	22	110	21	105
A423A3472	22	110	22	110

Conclusions:

The results presented in Table 1 show that the fibrinogen potency, as measured by CBER's Assay for Fibrinogen Potency by Total Clottable Protein method for the five lots (A433A3473, A440A3472, A441A3474, A425A3471 and A423A3472) submitted for evaluation and measured at CBER are comparable to those obtained by the sponsor and are within the specification limits. Measured values from both, CBER and Octapharma, are within the proposed specification, (b) (4).