

Final Review Memo (12/19/2008) - RiaSTAP

MEMORANDUM

To: File of 125317 & Vasantha Kumar

From: Roman Drews, HFM-392

Through: Tim Lee, HFM-392, Acting Chief, Laboratory of Hemostasis/DH/OBRR

Subject: Final review of CSL Behring BLA for Human Fibrinogen Concentrate , Pasteurized [Riastap®]

CC: Laura Wood, HFM-340, Chair of the BLA review committee

Background

CSL Behring's approach to mitigate the risk of viral contamination of the Human Fibrinogen Concentrate, Pasteurized final product is based on the following three principles:

- Testing the source material for viruses, and selecting units that are negative in viral testing for further manufacture
- Testing the plasma pool for viruses, and selecting pools that meet viral testing criteria for further manufacture
- Selected steps in the manufacturing process were validated for their capability to inactivate and/or remove viruses

The presented data regarding testing of source material, human plasma, and control of plasma pools for the absence of viral contamination demonstrate that the firm follows FDA regulatory requirements, and these measures are generally acceptable. Also, the submitted data showed that CSL Behring performed a series of small-scale validation studies that adequately mimicked the commercial-scale manufacturing steps. The results of viral infectivity assays and calculation of the reduction factors of viral titers were performed according to the recommendations of pertinent guidance documents. Thus, the capability of the tested manufacturing steps to reduce the titer of relevant and model viruses has been assessed adequately by CSL Behring. Moreover, since its licensure in Europe in 1985, there has not been any proven viral transmission to treated patients. The issues identified by this reviewer during the mid-cycle review concerning the contribution of manufacturing steps with the similar removal mechanisms to the overall reduction factor for viral clearance claim and clarification of testing paradigm for HAV RNA in plasma (Riastap starting material) were adequately addressed by the firm. Therefore, I recommend approval for STN 125317.

Scientific Information Reviewed

Viral control of plasma collection

Plasma collection centers are licensed by FDA and have also been audited by CSL Behring/ZLB Plasma. A physical examination before each donation is required for all donors. Each donation is tested for the absence of viral markers: Hepatitis B surface Antigen (HBsAg), antibodies against Hepatitis C Virus (HCV), and Human Immunodeficiency Virus (HIV-1/2). The sample pools of donations are tested for the absence of viral genome of Hepatitis B Virus (HBV), HCV, and Hepatitis A Virus (HAV). These assays are based on a nucleic acid amplification technique (NAT) a polymerase chain reaction technique (PCR). The NAT/PCR tests are performed at the ----- (b)(4)----- to detect genomic sequences of HCV and HIV-1 based on the FDA

licensed assay and to detect genomic sequences of HBV based on an investigational assay as well as for genomic sequences of HAV and high titers of B19V DNA as in-process control assay. -----(b)(4)-----

----- A positive PCR signal will result in testing smaller pool sizes and then discarding the positive donation(s). The HAV reactive donations and all donations with a B19V DNA load of around -----(b)(4)--- are discarded prior the fractionation. Discarding NAT/PCR reactive mini-pools and/or donations result in NAT/PCR non-reactive plasma pool for fractionation. The release criterion for plasma pools for fractionation for B19V DNA is no more than 4 log₁₀ of IU/mL, i.e. the sensitivity of a quantitative B19V NAT assay is defined such that a fractionation pool will not exceed 4 log₁₀ B19V DNA IU/mL. Furthermore, as quality control measures, the plasma pool for fractionation is tested for the absence of HBsAg, antibodies against HIV1/2, and genetic material for HBV, HCV, HIV-1 and HAV.

Validation Studies for Viral Clearance

The virus validation studies were performed by spiking samples collected at various manufacturing steps with a virus and measuring the virus removal or inactivation in the scaled-down step. As demonstrated by CSL Behring, the composition of the spiked samples and yields of the studied steps were comparable to the commercial-scale historical data. Validation studies were performed with the samples derived from the manufacture of Haemocomplettan P, the same fibrinogen product that is licensed in Europe since 1985. The viral spikes did not exceed -(b)(4)- of the total volume. --(b)(4)-- independent runs were performed for every virus tested by the scaled-down step. Viruses chosen to the validation study are acceptable, i.e., they are relevant or resemble closely the potential contamination of the product. In addition, the studied viruses represent a wide range of physicochemical properties to demonstrate the robustness of clearance. The relevant viruses include HIV and HAV. The model viruses include bovine viral diarrhea virus (BVDV) as a model for HCV, herpes simplex virus type 1 (HSV-1) as a model for HBV, and canine parvovirus (CPV) as a model for B19V. Review of cell cultures used for detecting levels of infectious viruses revealed that the infectivity assays are acceptable. The appropriate cytotoxicity studies were performed demonstrating that pre-dilution of samples -(b)(4)- before -----(b)(4)----- was required to avoid interference. In addition, appropriate controls were set to demonstrate the effect of the duration of the experiments on viral titer. The viral infectivity titers and standard error were calculated according to the Spearman-Kärber method. The standard error for each virus titration was below -(b)(4)- logs and the -(b)(4)- confidence limits for the reduction factors were in order of -(b)(4)- logs or lower.

Validation of Cryoprecipitation (Stage 1) and Al(OH)₃ adsorption, glycine precipitation, and the 2nd Al(OH)₃ adsorption (Stage 2).

Virus reduction of the non-enveloped viruses HAV and CPV were studied using the combination of Stage 1 and Stage 2 steps. Virus reduction for the enveloped viruses HIV, BVDV, and HSV-1 was studied by Stage 2 but since virus removal was achieved by ----(b)(4)----- (same principle as -----(b)(4)-----) it was not used to calculate the overall reduction value. Furthermore, overall reduction of HSV-1 titer was insignificant. The robustness of the tested manufacturing steps to remove viruses was

tested by changes in fibrinogen content, -----(b)(4)-----, and -(b)(4)- time. The studies were scaled-down to up to -(b)(4)- times.

Pasteurization (Stage 3)

Pasteurization by 60 oC heat treatment in stabilized solution (in the presence of -(b)(4)-) for 20 hours is considered as an effective and robust step for inactivation of all enveloped viruses and HAV. The validation studies were performed on the commercial scale. The enveloped viruses were inactivated below the detection limit of the infectivity assays within -(b)(4)- of incubation. HAV was completely inactivated within --(b)(4)-. The kinetics of inactivation illustrated by the graphs was acceptable. The clearance of CPV was low, i.e., in a range of 1.6 logs. Critical process parameters such as ----(b)(4)---- and --(b)(4)--- concentration, which may influence the inactivation capacity of pasteurization, were tested beyond the process control limits demonstrating no significant impact. The decrease in ----(b)(4)---, especially -(b)(4)-, which is beyond the manufacturing specification, results in a slight delay in the kinetics of inactivation for HSV-1 and a considerably slower inactivation for HAV. In addition, using the experimental infectivity assay, CSL Behring assessed the level of reduction of B19V titer as ≥ 4.5 . Since the result is obtained by the experimental assay, the following disclaimer should be included to the PI:

The virus evaluation studies for parvovirus B19 employed a novel experimental infectivity assay utilizing clone of cell line UT7 that contains erythropoietic progeny cells; (Residual) virus titer was determined using an immunofluorescence-based detection method.

1 st and 2 nd glycine precipitation (Stage 4)

Viral removal occurred through -----(b)(4)----- resulting from ---(b)(4)--- precipitations of proteins. The step is mostly effective for HIV removal (3.9 logs). It was much less effective for non-enveloped viruses and is repetitive with regards to the mode of action when compared to the Stage 1 and Stage 2 precipitation studies. Thus, the titer reductions obtained for the non-enveloped viruses by Stage 4 are not used to calculate the overall reduction factor. The removal rates were not affected by the -----(b)(4)----- after adding glycine (----- (b)(4)-----), ----- (b)(4)-----, and up to -----(b)(4)----- . The studies were scaled down ----(b)(4)-----.

Viral clearance claims

Production Step	Viral Reduction Factor (log 10)						
	Enveloped viruses			Non-enveloped viruses			
	HIV	BVDV	WNV	HSV-1	HAV	CPV	B19
Cryoprecipitation	n.d.	n.d.	n.d.	(1.6)			n.d.
AL(OH) 3 adsorption/ Glycine precipitation/ Al(OH) 3 adsorption	(2.8)	(1.5)	n.d.	(0.9)	2.4	2.8	n.d.
Pasteurization	≥ 5.7	≥ 9.1	≥ 8.3	≥ 8.1	≥ 4.3	1.6	≥ 4.5
Glycine precipitation (two subsequent steps)	3.9	2.1	n.d.	1.0	(1.0)	(1.6)	n.d.
Cumulative virus reduction	≥ 9.6	≥ 11.2	N/A	≥ 9.1	≥ 6.1	4.4	N/A

Viral safety of other biological materials used during manufacture

----- (b)(4) ----- and human (b)(4)- albumin (-(b)(4)-) are biological materials of human origin added during the manufacture of fibrinogen concentrate drug substance. The biological material of animal origin added during the manufacture is (b)(4)- derived from ----- (b)(4) ----- . ----- (b)(4) ----- and (b)(4)- are used in process during the ----- (b)(4) ----- .

The ----- (b)(4) ----- product, ---- (b)(4) ---, is licensed in Europe for therapeutic use and is manufactured by ---- (b)(4) ----- . The submitted virus validation clearance rates are acceptable.

--- (b)(4) --- is (b)(4)- human albumin solution manufactured by --- (b)(4) -- in --- (b)(4) -- ----- , and is licensed for therapeutic use in USA and several European countries.

The product is used in the final formulation of Riastap.

The production process of ----- (b)(4) ----- consists of several harsh condition manufacturing steps including ----- (b)(4) ----- , and --- (b)(4) ---- treatment. It is expected that this production process will be effective in removal and inactivation of potential viruses. Furthermore, the fibrinogen process should contribute to the viral safety of (b)(4)- product and due to the purification procedure of Riastap, (b)(4)- is removed and should not be present in the final product. The detailed assessment of the qualification of ----- (b)(4) ----- as raw material and its removal by the Riastap product is reviewed by Ms. Laura Wood, the principal CMC for the BLA.

CONCLUSION and RECOMMENDATION

The provided validation of viral clearance studies is acceptable. The firm introduced changes requested by the FDA to the label claims regarding capacity of the Riastap purification process to clear relevant and model viruses. Therefore, I recommend approval for STN 125317.