

Final review of Adventitious Agent Safety Evaluation - Wilate, November 27, 2009

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Subject: Final review of Adventitious Agent Safety Evaluation for the manufacture
of Octapharma's von Willebrand Factor/Coagulation Factor VIII Complex
(Human) [Wilate]

Adventitious Agent Safety Evaluation

Viral Testing of the Starting Material

The starting material for the manufacture of Wilate is human plasma. All donations used by Octapharma comply with the requirements of 21 CFR 640.30 and 21 CFR 640.60. The limit for the titer of human parvovirus B19 DNA in the manufacturing pool follows the FDA recommendation of 104 IU/mL. As stated by Octapharma, US Source Plasma used for the manufacture of Wilate is 100% tested for human hepatitis A virus at the level of --(b)(4)--. Only non-reactive plasma is shipped to the firm.

Viral Clearance Steps

----- (b)(4) -----

Scaled-Down Validation Studies

The scaled-down studies were performed by the Octapharma pilot facility in Vienna, -----(b)(4)----- group at their -----(b)(4)----- facilities or in collaboration with contract facility -----(b)(4)----- . The scaled-down factors for the S/D treatment studies were -(b)(4)- and -(b)(4)-; for the chromatography step - (b)(4)-; and for the terminal heat treatment step -(b)(4)- as studies were performed at the final container stage. As indicated by the Scaled- Down Study Report, all the studies were performed at least in duplicate and included the worst-case scenario (robustness) conditions with regards to the critical parameters like temperature, duration of time, and composition of the test article (e.g., concentrations of protein or S/D reagents). The material used for the S/D treatment validation studies was prepared at pilot scale from the commercial-scale cryoprecipitate paste and included Al(OH)₃ treatment and -----(b)(4)----- steps performed at -(b)(4)- scale before ----- (b)(4)----- to the test articles and further scaled-down laboratory studies of the S/D treatment step. The controls of -----(b)(4)----- and -----(b)(4)----- indicate that intermediates from the commercial and pilot scale are comparable.

For the chromatography column and TDH treatment, appropriate samples were taken from the commercial-scale process before the viral spike and scaled-down studies. The performance of the scaled-down column mimicked the commercial process that was also confirmed by the composition of the eluates evaluated by the -----(b)(4)----- . In addition, Octapharma presented results of the scaled-down manufacturing steps performed in Vienna and --- (b)(4) -- demonstrating their comparability. The TDH validation studies for the inactivation of HIV and PRV viruses were performed by -----(b)(4)----- . -----(b)(4)----- during the TDH studies was assessed by -----(b)(4)----- ----- that was comparable to the results obtained by the ----(b)(4)--- method. The description of the scaled-down manufacturing steps indicates that the studies mimic the commercial scale adequately and are acceptable.

Viral assays

Studies were performed with the following enveloped viruses: human immunodeficiency virus (HIV-1), Sindbis virus (SBV) - model for Hepatitis C Virus (HCV), bovine viral diarrhea virus (BVDV) model for HCV, pseudorabies virus (PRV) model for Hepatitis B Virus (HBV), and the following non-enveloped viruses: reovirus-3, hepatitis A virus (HAV), and porcine parvovirus (PPV) model for human parvovirus B19. The studies of relevant and model viruses provide an adequate combination of physico-chemical properties of viruses to assure the validity of the performed viral clearance studies. Infectivity assays were performed according to the requirements of current guidance documents with regards to the preparation of viral stock, adequate controls

including time of study, cellular toxicity, calculation limit of detection, and kinetics of inactivation. The calculation of TCID₅₀/mL, i.e., 50% of the infected cultures was performed according to the method of -----(b)(4)----- . Also, the virus reduction factors, and statistical analysis were performed according to the current guideline recommendations.

Results: Overall Reduction Factors

Virus reduction factor claimed for the Wilate manufacturing process:

Step	HIV-1	SBV	BVDV	PRV	PPV	REO	HAV
S/D treatment	>7.52	>8.63	>4.18	>8.54	n.d.	n.d.	n.d.
Log10							
Ion-exchange chromatography	n.d.	n.d.	n.d.	n.d.	3.29	1.86-2.33	3.29
Log10							
TDH treatment	4.91-5.79	>5.51	n.d.	3.99-4.87	2.57-4.12	>6.40	2.57-4.12
Log10							
Global Reduction Factor	>12.43-13.31	>14.14	>4.18	>12.53-13.41	5.86-7.41	>8.26-8.73	5.86-7.41
Log10							

The results presented in the table correspond to the data obtained in the validation studies and are acceptable.

Prion Clearance Validation Studies

Octapharma submitted results of prion removal studies using -----(b)(4)-----
----- by the combined steps of the cryoprecipitation/treatment with Aluminum Hydroxide and combined steps of S/D treatment/ion exchange chromatography. The studies resulted in a Global Reduction Factor of ---(b)(4)----. However, to assess the removal rates, the firm used -----(b)(4)----- that is not considered as sensitive and reliable as -----(b)(4)----- assay. Therefore, the results of the prion reduction studies, although provide estimated values, will not be used to claim capacity of the Wilate manufacturing process to reduce the Transmissible Spongiform Encephalopathy (TSE) agent.

Recommendation

The measures proposed by Octapharma to control adventitious agents in the manufacture of Wilate are acceptable. Therefore, from the perspective of the control and mitigation of risk associated with adventitious agents, there are no outstanding issues that prevent the approval of this BLA.