

# Mid-cycle review of Adventitious Agent Safety Evaluation-Wilate, May 10, 2007

**Date:** May 10, 2007  
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**Subject:** Mid-cycle review of Adventitious Agent Safety Evaluation for the manufacture of Octapharma's Coagulation Factor VIII/von Willebrand Factor (Human) [Wilate]  
**CC:** Nancy Kirschbaum, Scientific Lead, HFM - 392

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## 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. Octapharma should provide information what measures are implemented to the manufacturing process to control the risk of contamination with Hepatitis A Virus (HAV) and Human Parvovirus B19 virus.

### Manufacturing Process: Viral Clearance Steps

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### Scaled Down Validation Studies

The scaled down studies were performed by Octapharma pilot facility in Vienna, Virus & ----- (b)(4) ----- facilities or in collaboration with contract facility ----- (b)(4) ----- . The scaled down factors for the S/D studies were - (b)(4)- and - (b)(4)-, for the chromatography step; - (b)(4)-, and for the terminal heat treatment; - (b)(4)- as studies were performed at the final container stage. As indicated by the Down Scale 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 validation studies was prepared at pilot scale from the commercial scale cryoprecipitate paste and included Al(OH)<sub>3</sub> 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

---(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)----- 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 diarrhoea 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 parovirus B19. The studies of relevant and model viruses provide an adequate combination of the physico-chemical properties to assure 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 TCID<sub>50</sub>/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	BVDV	PRV	PPV	REO	HAV	
S/D treatment $\text{Log}_{10}$	>7.52	>8.63	>4.18	>8.54	n.d.	n.d.	n.d.
Ion-exchange chromatography $\text{Log}_{10}$	n.d.	n.d.	n.d.	n.d.	3.29	1.86- 2.33	3.29
TDH treatment $\text{Log}_{10}$	4.91- >5.79	>5.51	n.d.	3.99- 4.87	2.57- 4.12	>6.40	2.57- 4.12
Global Reduction Factor $\text{Log}_{10}$	>12.43- >13.31	>14.14	>4.18	>12.53- >13.41	5.86- 7.41	>8.26- >8.73	5.86- 7.41

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 the Global Reduction Factor of -(b)(4)-. However, to assess the removal rates, the firm used ----(b)(4)----- technique that is not considered as sensitive and reliable as -----(b)(4)----- assay. Therefore, the results of the prion reduction studies, although provide estimated values, cannot be used to claim capacity of the Wilate's manufacturing process to reduce Transmissible Spongiform Encephalopathy (TSE) agent.

### **Conclusions and Recommendation**

The mid-cycle review of adventitious agent safety submitted in STN 125251 did not identify issues that will prevent the approval of this biologics license application. However, I recommend communicating to the sponsor the following items:

1. Please describe your current procedures for testing of human parvovirus B19V and Hepatitis A viruses in plasma. Please note that the current FDA recommended limit of B19V DNA in the manufacturing pool is £ 104 IU/mL.
2. Please note that ---(b)(4)--- analysis is not acceptable as a substitute for ---(b)(4)--- assays used to validate the removal of prion proteins -(b)(4)-. Therefore, reduction factors for prion proteins derived from ----(b)(4)----- analysis cannot be claimed in the product circular.