



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

To: STN: 125596/0

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Applicant: Baxalta US Inc.

Product: Immune Globulin Subcutaneous (Human), 20% Solution
Proposed Brand Name: CUVITRU®

Subject: Executive Summary and Final Review – Baxalta BLA: Viral Clearance

Recommendation

Approval

Executive Summary

Baxalta US Inc. submitted this BLA for approval on Cuvitru® (as IGSC, 20%), which is a 20% human IgG solution subcutaneously administered for PID patients.

The starting material of plasma collection pools are tested with FDA approved licensed HIV-1/2 and HBsAg kits, as well as NAT tests for viral nucleic acid of HIV-1/(b) (4), (b) (4) and HCV, (b) (4) and (b) (4). Only plasma pools which are NAT-non-reactive for HIV, (b) (4), HCV, (b) (4), and contain (b) (4) are released for further manufacture.

The manufacturing process of IGSC, 20% (b) (4). There are four viral clearance steps from its manufacturing process that are claimed to have effect and the overall Log Reduction Factors (LFR) as listed below.

Overall Log Reduction Factors (Mean) by manufacturing steps

	HIV-1	HAV	(b) (4)	PRV	BVD V	WNV	EMC V	MMV
Virus Property								
Genome	RNA	RNA	(b) (4)	DNA	RNA	RNA	RNA	DNA
Envelope	Yes	No	(b) (4)	Yes	Yes	Yes	No	No

Size (nm)	80-100	27-32	(b) (4)	120-200	50-70	50-70	25-30	18-24
Process Step	Mean LRF							
S/D treatment	>4.5	NA	(b) (4)	>4.8	>6.2	4.1	NA	NA
Nanofiltration	>4.5	5.7	(b) (4)	>5.6	>5.1	>6.2	1.4	2.0
Low pH treatment	>5.8	2.4	(b) (4)	>6.5	>5.5	>6.0	>6.3	3.1
EtOH Fractionation	>5.1	3.9	(b) (4)	>4.9	1.3	>6.1	4.2	4.9
Overall Reduction (Log₁₀ Units)	>19.9	12.0	(b) (4)	>21.8	>18.1	>22.4	>11.9	10.3

HIV-1, human immunodeficiency virus type 1, a model for HIV-1 and HIV-2; HAV, hepatitis A virus; (b) (4); PRV, pseudorabies virus, a nonspecific model for large enveloped DNA viruses (e.g., herpes virus); BVDV, bovine viral diarrhea virus, a model for hepatitis C virus; WNV, West Nile virus; EMCV, encephalomyocarditis virus, a model for hepatitis A virus; MMV, minute virus of mice, a model for a small highly resistant non-enveloped DNA virus (e.g., parvovirus); LRF, log₁₀ reduction factor; NA, not applicable; ND none detected.

Dr. Jennifer Reed (LPD/DHRR/OBRR) is the chair of this BLA submission. My review will focus on the Viral Validation section of this BLA.

Viral Clearance Studies Validation Review

The screening and manufacturing process of IGSC, 20% (b) (4). All claimed viral control and clearance steps are the same except the low pH with elevated temperature for (b) (4). Baxalta Inc. provided a bridging study to support that the viral clearance capacity for the last step is similar to that of IGI, 10%.

1.Starting material screening:

Test Level	Test Method	Test Name	Acceptance Criteria
Individual Plasma Unit	Serology	HBsAg	Non-reactive
		Anti-HCV	Negative
		Anti-HIV-1/2	Negative
Plasma Mini-Pool	NAT	(b) (4)	(b) (4)
		HCV	Negative
		HIV-1	Negative
		(b) (4)	(b) (4)
		(b) (4)	(b) (4)
Plasma Manufacturing Pool	(b) (4)		

Criteria for release of plasma pools:

(b) (4)

2. Manufacturing process viral clearance studies:

2.1 Dedicated steps in manufacturing process of IGIC, 20%

Three dedicated virus clearance steps are integrated into the IGSC, 20% manufacturing process:

- a. Solvent/Detergent (S/D) treatment of (b) (4) (an effective inactivation step for lipid-enveloped viruses)
- b. 35 nm Nanofiltration (an effective virus removal step of lipid-enveloped and non-lipid-enveloped viruses)
- c. Incubation at low pH and elevated temperature (b) (4) (an effective inactivation step of lipid-enveloped viruses and some non-lipid-enveloped viruses; contributes to viral safety with respect to Parvoviruses)
- d. Ethanol fractionation steps was not claimed for IGI, 10%, but investigated for IGSC, 20%.

2.2 Validation studies

Steps a and b above are the same as IGI, 10%. For step c (incubation at low pH and elevated temperature), IGSC, 20% has double the protein concentration of IGI, 10% but is otherwise identical to the corresponding step in the IGI, 10% process. The parameters such as (b) (4) etc, remained the same for this step. A bridging study (report reg679e) with two selected viruses showed that there is no significant difference in virus inactivation capacities between IGI, 10% and IGSC, 20%.

Relevant and model viruses chosen for IGSC, 20% validations are:

- HIV-1 (Human Immunodeficiency Virus, Type 1) as a relevant target virus and a model for other lipid-enveloped RNA (ribonucleic acid) viruses like HIV-2; particle size: 80-120 nm
- HAV (Hepatitis A Virus) as a relevant target virus and a model for other non- lipid-enveloped RNA viruses; particle size: 25-30 nm
- BVDV (Bovine Viral Diarrhea Virus) as a model for Hepatitis C virus or other lipid-enveloped RNA viruses; particle size: 40-60 nm
- WNV (West Nile Virus) as a transfusion-transmissible virus, consequently of potential concern for plasma derived products; particle size: 45-50 nm
- PRV (Pseudorabies Virus) as a model for other lipid-enveloped DNA (deoxyribonucleic acid) viruses; particle size: 150-180 nm
- (b) (4)
- MMV (Mice Minute Virus) as a model for other small non-lipid-enveloped DNA viruses; this is used as a model for B19V in the 'Low pH Treatment' study and a control in the Nanofiltration study; particle size: 18-26 nm
- EMCV (Encephalomyocarditis Virus) as a model for non-lipid-enveloped RNA viruses; this is used as a model for HAV in the 'Low pH Treatment' study and a control in the Nanofiltration study; particle size: 25-30 nm.

(b) (4)

Scaled-down process models were used to represent large scale process for validation studies based on measurements biochemical parameters and comparison to those of large scale processes. Robustness of the viral clearance was confirmed by adjusting certain critical parameters to the least favorite viral clearance conditions, e.g. (b) (4).

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

7 pages have been determined to be not releasable: (b)(4)

Table 12. Mean (for each manufacturing step and virus) and Overall Log Reduction Factors

Pathogen	SD Treatment ^A	35 N Nanofiltration	Low pH Treatment	Cold Ethanol Fractionation	Overall Log Reduction
HIV-1	>4.5	>4.5	>5.8	>5.1	>19.9
BVDV	>6.2	>5.1	>5.5	1.3	>18.1
WNV	4.1	>6.2	>6.0	>6.1	>22.4
PRV	>4.8	>5.6	>6.5	>4.9	>21.8
HAV	NA	5.7	2.4 ^B	3.9	12.0
EMCV	NA	1.4	>6.3 ^C	4.2	>11.9
(b) (4)					
MMV	NA	2.0	3.1	4.9	10.3
(b) (4)					

Abbreviations: ND, not done; NA, not applicable as no inactivation by S/D treatment expected

^A Data from experiments using S/D at 50% relative to the standard concentration in the commercial process, except for WNV, which was tested only with S/D at 5% standard concentration

^B Data represent incubation in buffer alone as in the presence of product intermediate, HAV was neutralized immediately after spiking (data not shown)

^C Parallel run using buffer alone showed a log reduction factor of >6.7.

(b) (4)

(b) (4)

5 pages have been determined to be not releasable: (b)(4)

Appendix

Study reg643e and Addendume to study report reg643e (IGSC, 20%) – Ethanol Fractionation

Study reg673e (IGSC, 20%) – Ethanol Fractionation

Study reg681e (IGSC, 20%) – Ethanol Fractionation

Study reg630e (IGI, 10%) – S/D treatment

Study reg631e (IGI, 10%) - Nanofiltration

Study reg628e (IGI, 10%) - Low pH at elevated temperature

Study reg649e (IGI, 10% for HAV) - Low pH at elevated temperature

Study reg679e – Low pH at elevated temperature bridging study

Study reg652e - (b) (4)

Study reg668e - (b) (4)