



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

To: STN 125587/0

From: Pei Zhang, LPD/DHRR/OBRR

Through: Michael Kennedy, Team Leader, LPD/DHRR/OBRR

CC: Christopher Hooban, RPM, DBA/OBRR

Applicant: Octapharma Pharmazeutika Produktionsges, m.b.H

Products: Immune Globulin Intravenous (Human), 10%
Trade name: Panzyga (formerly NewGam)

Subject: Final review: Viral safety

Recommendation

Approval

Background

Octapharma submitted a BLA for Immune Globulin Intravenous (Human), 10%. The starting material for the bulk process is (b) (4) plasma which is further manufactured to (b) (4) according to a cold-ethanol plasma fractionation process. The purification process includes (b) (4) steps. Virus inactivation and reduction steps include a solvent/detergent (S/D) treatment, a 20 nm nanofiltration and an ion exchange (b) (4) chromatography. The final product is formulated using glycine as the excipient. This review addresses viral safety of the product.

CMC Review

1. Flow Chart of NewGam Manufacturing Process

The production process of NewGam contains three steps which are part of the viral safety. The scheme below indicates the steps which are relevant for the virus removal/inactivation capacity of the process.

2. Viral Validation

2.1. Scaled down process:

The downscaling protocols were developed by the research and development department of Octapharma, Vienna. The conditions for the scaled-down process are kept to closely mimic that of the manufacturing process. The validity of the down-scaling was confirmed by comparison of in-process parameters between laboratory and production scale.

The manufacturing of NewGam comprises two dedicated steps serving for virus safety, i.e. S/D treatment and 20N Nanofiltration. In addition, an (b) (4)-exchange chromatography with (b) (4) contributes significantly to the virus safety. A detailed comparison of the process parameters between the Octapharma production facility in Lingolsheim and the Octapharma Virus & Prion Validation Group in Frankfurt (Germany) and (b) (4) is provided in the appended down-scale reports.

1. Downscale Validation of S/D Treatment in NewGam Process as Used for Virus Validation Studies - VPV Frankfurt (020STD721.157/00)
2. Downscale Validation of Nanofiltration in NewGam Process (020STD721.155/00)
3. Downscale Validation of (b) (4) Chromatography in NewGam Process (020STD721.156/00)

2.2. Manufacturing steps designed for viral safety

The viral safety of NewGam is mainly based on S/D treatment and (b) (4) nanofiltration, but also the (b) (4) exchange chromatography ((b) (4)) contributes significantly to the viral safety of NewGam, in particular for non-enveloped viruses. The validation studies were performed by Octapharma's Virus & Prion Validation Department in Frankfurt, Germany and (b) (4). All studies were performed in GLP certified laboratories. The studies were performed with relevant intermediate process material from Octapharma SAS in Lingolsheim, collected prior to the process step intended to be validated.

Step 1: Solvent/Detergent (S/D) treatment

The solvent/detergent treatment is based on the lipid-membrane destroying properties of TNBP (solvent) and Octoxynol (detergent) towards enveloped viruses. Due to its mode of action, the validation of the solvent/detergent treatment was performed exclusively with the enveloped viruses HIV-1, PRV, and BVDV.

Step 2: Ion-Exchange Chromatography ((b) (4))

This step has been investigated with non-enveloped viruses (MEV, and PPV). During the chromatography process the main content of the virus is removed from the (b) (4).

Step 3: Nanofiltration (20 nm)

While the S/D treatment selectively inactivates enveloped viruses, the nanofiltration nonselectively removes viruses according to their size. Validation studies were carried out with both enveloped (HIV-1, PRV, BVDV) and non-enveloped viruses (MEV and PPV). All steps have been validated by spiking experiments with viruses belonging to different families and classes. The steps are indicated in the scheme of production and numbered according to their occurrence in the manufacturing flow.

The virus reduction factors by manufacturing steps.

| Manufacturing Step | Virus reduction factor [log10] | | | | |
|--|--------------------------------|---------|--------|-----------------------|-------|
| | Enveloped viruses | | | Non-enveloped viruses | |
| | HIV | PRV | BVDV | MEV | PPV |
| S/D Treatment | ≥ 4.67 | ≥ 6.59 | ≥ 4.47 | Not applicable | |
| Ion exchange chromatography (b) (4) | Not done | | | 5.88 | 5.83 |
| Nanofiltration (20 nm) | ≥ 4.70 | ≥ 6.57 | ≥ 3.69 | ≥ 5.78 | 5.78 |
| Global reduction factor | ≥ 9.37 | ≥ 13.16 | ≥ 8.16 | ≥ 11.66 | 11.61 |

2.3. Viral Validation Study Reports Reviewed

(b) (4)

Reviewer's Comments

The validation studies were performed by (b) (4) and Octapharma's Virus & Prion Validation Department in Frankfurt, Germany in Vienna, Austria. The studies were performed with relevant intermediate process material from Octapharma SAS in Lingolsheim, collected prior to the process step intended to be validated. Viral validation including rustiness studies demonstrated a sufficient viral clearance of the manufacturing process that should contribute to virus safety of the final product.