



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

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**To:** To File (BLA STN 125430/0)

**From:** Douglas Frazier, Biologist, CBER/DH/LPD/HFM-345

**Through:** Dorothy Scott, MD, Chief, CBER/DH/LPD/HFM-345

**CC:** Nanette Cagungun, RPM, HFM-350

**Applicant:** The Cangene Corporation

**Products:** Varicella Zoster Immune Globulin (Human)  
Trade name: VariZIG<sup>®</sup>

**Subject:** Original BLA: Final review, Drug Substance and Drug Product stability & potency assay validation

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**Recommendation**

This supplement is recommended for the following PMC request:

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**Background Summary**

The Cangene Corporation, located in Winnipeg, Manitoba, Canada, manufactures a varicella-zoster hyperimmune human gamma globulin (VZIG) for intramuscular administration (IND BB 7201). This VariZIG<sup>®</sup> product is made from high-titer anti-varicella-zoster-virus human plasma using anion-exchange chromatography and two viral-clearance steps (solvent/detergent ---b(4)-----), and is formulated to contain 0.1 M glycine, -b(4)----- sodium, and -b(4)--- polysorbate 80 at pH 7; each vial contains b(4)125 IU/vial of anti-VZV antibody.

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This review is concerned primarily with assessment of product stability, both as bulk Drug Substance and as final Drug Product, and validation of the anti-varicella-zoster virus potency assay. The issue of testing for anti-Protein S in Varizig was raised by clinical reviewer Charlie Maplethorpe MD PhD, and after internal discussion, the matter was taken to the CBER Blood committee for consideration; the resulting policy decision is not included in this memo.

**Review**

**Stability, Bulk**

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### Stability, Final Product

***The proposed shelf life for VariZIG is 36 months at 5±3 °C; this dating period and storage conditions are supported by the submitted data, and may be accepted.*** This interval was chosen based on real-time stability studies using the current container-closure system and based on samples taken from lots made via the commercial-scale production process. Testing included: potency, reconstitution time, pH, --b(4)-- ---- appearance, total protein, sterility, and bacterial endotoxins. Cangene lists the supporting stability studies, reviewed below:

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Real-time & accelerated stability – The VZIG lots appear to have been either IND lots or destined for the Canadian market, where VariZIG is already approved. The final-product stability program includes potency, pH, reconstitution time, --b(4)--- -----and sterility. Results at storage at 2-8 °C for between 36 and –b(4)---- demonstrate good stability, with no parameters showing statistically-significant trends. Select data (potency, ----b(4)-----) are displayed in Appendix 1, and show the expected increase in product lability at increasing temperatures, and also the confidence intervals of linear-regression fits for the combined data from –b(4) VZIG stability lots. –b(4)----- (expressed as –b(4)-----) shows similar stability, except for VZIG lot –b(4)-----, with a single value of –b(4)--- of protein/---b(4)-----of protein) at –b(4)----- (below). This result, although significantly out of trend, is anomalous and not supported by any other results, all of which indicate superior stability in the lyophilized presentation stored at 2-8 °C. Cangene also calculates the time points at which the data trendlines intersect the acceptance limits (Appendix 2).

Aggregate data with out-of-trend value

Aggregate data without out-of-trend value

8 pages determined to be not releasable: b(4)