Expanded Assessment of the Aggregation Profile of Commercially Available Intravenous Immunoglobulin Products

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ABSTRACT

Background:

- Immunoglobulin therapy is the standard of care for patients with primary immunodeficiencies and is increasingly used in other immune-mediated conditions[1,2]
- Global demand for intravenous immunoglobulin (IVIG) has increased along with a parallel need for manufacturing processes that optimize immunoglobulin yield while ensuring product purity, stability, and safety[1,2]
- Reducing residual plasma-derived impurities and immunoglobulin aggregates is imperative because they can enhance immunogenicity, reduce stability, and contribute to adverse reactions[1,3,4]
- To address risks caused by plasma-derived impurities, an enhanced purification process was developed for IVIG-stwk 10% manufacturing[1]

Purpose: The purpose of this study was to evaluate the aggregation profile of IVIG-stwk 10% liquid along with 4 other commercially available 10% IVIG products.

Methods:

- ALYGLO® immune globulin intravenous, human-stwk, 10% (IVIG-stwk 10%) was developed using a multistep manufacturing process that includes cold ethanol fractionation, ultrafiltration and diafiltration, anion exchange chromatography, solvent/detergent virus inactivation, cation exchange chromatography + UF/DF 2, nanofiltration, an additional ultrafiltration step, and formulation (Figure 1)

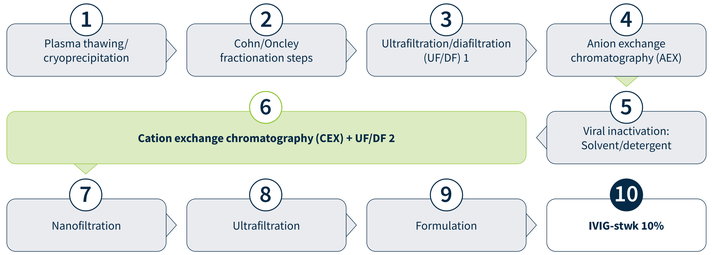

Figure 1. IVIG-stwk 10% Manufacturing Process

- Aggregation profiles were evaluated for 6 lots of IVIG-stwk 10% and 3 lots each of 4 other commercially available 10% IVIG products (Products A-D)
- Molecular size distribution and particle size were characterized using size-exclusion high-performance liquid chromatography (SE-HPLC) and dynamic light scattering (DLS), respectively
- Key measures included monomers + dimers, polymers, and fragments (SE-HPLC), as well as particle size (Z-average) and polydispersity index
- SE-HPLC was performed using a size-exclusion column (TSKgel G3000SW) with a phosphate-buffered saline (PBS) mobile phase and a 50 µL sample injection
- Particle size was measured by DLS, particle size (Z-average) was determined (Zetasizer ZSU5800), and a polydispersity index was calculated to evaluate particle size dispersion
- One-way analyses of variance (ANOVAs) were performed across the 5 products to detect statistically significant differences among the groups.

ABBREVIATIONS

IVIG: intravenous immunoglobulin

SE-HPLC: size-exclusion high-performance liquid chromatography

DLS: dynamic light scattering

PBS: phosphate-buffered saline

ANOVA: analysis of variance

RESULTS

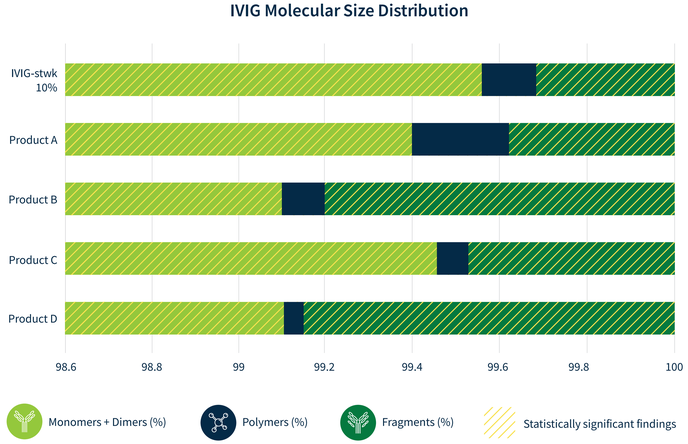

Figure 2. The monomer and dimer, polymer, and fragment averages (%) for 6 lots of IVIG-stwk 10% compared to 3 lots each of 4 other commercially available 10% IVIG products.

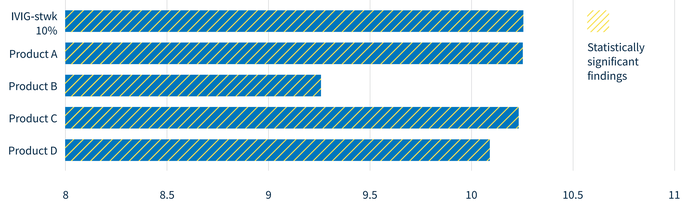

Figure 3. The particle sizes (Z-average) as measured by DLS for the 6 lots of IVIG-stwk 10% compared to 1 lot each of 4 other commercially available 10% IVIG products.

The polydispersity index indicating particle size dispersion did not show statistical significance between products

RESULTS, CONT.

Product	Monomers + Dimers (%)	Polymers (%)	Fragments (%)	Particle Size, Z-average (nm)
IVIG-stwk 10% (n=6)	**99.58** ± 0.09	**0.09** ± 0.07	**0.34** ± 0.05	**10.25** ± 0.16
Product A (n=3)	**99.40** ± 0.02	**0.21** ± 0.08	**0.39** ± 0.08	**10.24** ± 0.16
Product B (n=3)	**99.12** ± 0.19	**0.08** ± 0.04	**0.80** ± 0.16	**9.24** ± 0.09
Product C (n=3)	**99.45** ± 0.09	**0.07** ± 0.03	**0.49** ± 0.06	**10.21** ± 0.06
Product D (n=3)	**99.14** ± 0.18	**0.04** ± 0.01	**0.80** ± 0.19	**10.11** ± 0.05
***P*-value**	**<0.05**	>0.05	**<0.05**	**<0.05**

Table 1. Product composition and particle characterization for 6 lots of IVIG-stwk 10% compared to 3 lots each of 4 other commercially available 10% IVIG products.

DISCUSSION

- Protein aggregation remains a key driver of IVIG stability and safety, with potential implications for immunogenicity and adverse reactions
- The manufacturing process for IVIG-stwk 10% demonstrates a high percentage of monomers and dimers compared to low amounts of polymers and fragments
- Statistically significant differences were detected among the products in monomers and dimers, fragments, and particle sizes
- Further work correlating these statistical differences with clinical immunogenicity or tolerability is recommended to determine clinical relevance
- Understanding these distinctions may inform product selection strategies aimed at reducing immunogenicity due to protein aggregates with the goal of further improving tolerability in patients receiving IVIG therapy

CONCLUSION

- All products demonstrated high purity and low aggregate levels
- Statistically significant differences in aggregate attributes were observed among products, reflecting differences in manufacturing processes and formulation characteristics

REFERENCES

1. Kang GB, et al. *Front Cardiovasc Med.* 2023;10:1253177. **2.** Cook DLM. The expanding role of immune globulin treatment in diseases: utilization and growth. *BioSupply Trends Quarterly.* 2024. **3.** Ratanji KD, et al. *J Immunotoxicol.* 2014;11(2):99-109. **4.** Ovanesov MV. *Am J Hematol.* 2017;92(4):E44-E45.

DISCLOSURES AND ACKNOWLEDGMENTS

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