Assessment of the Aggregation Profile of Commercially Available Intravenous Immunoglobulin Products

Stacey Ness, PharmD, IgCP, CSP, MSCS, AAHIVP[1]; Gil Bu Kang, PhD[2]; Alan Huber, BSc Pharm, PharmD, MBA[1]; Suzanne Strasters, MSN, FNP-C, IgCN[1]; Laura Remy-Martin, PhD, MPH, RN[1]; Jihye Lee, MS[2]
[1]GC Biopharma USA, Teaneck, NJ, USA; [2]GC Biopharma Corp, Yongin-si, Republic of Korea

GC Biopharma

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 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 four 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**)

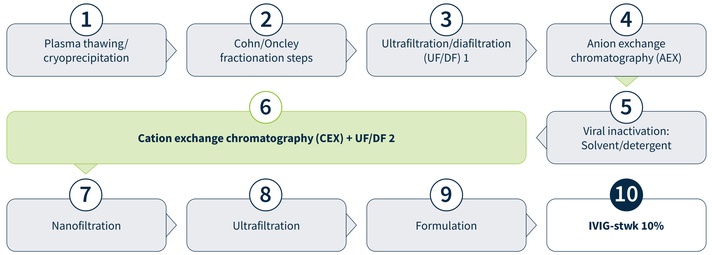

Figure 1. IVIG-stwk 10% Manufacturing Process

- Aggregation profiles were evaluated for six lots of IVIG-stwk 10% and one lot each of four commercially available 10% IVIG products (Products A, B, C, and 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

ABBREVIATIONS

IVIG: intravenous immunoglobulin

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

DLS: dynamic light scattering

PBS: phosphate-buffered saline

RESULTS

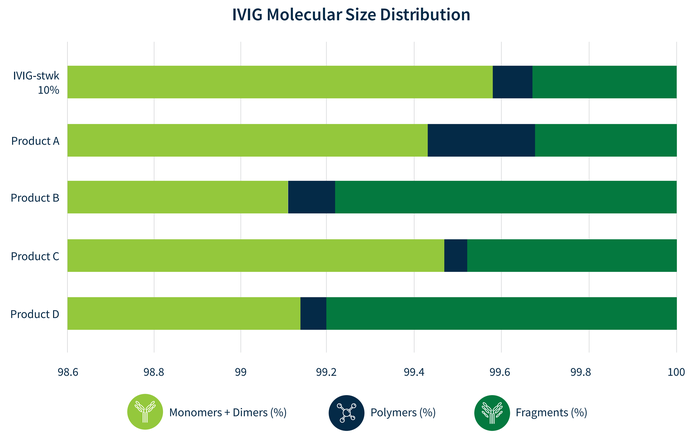

Figure 2. The monomer and dimer, polymer, and fragment averages (%) for six lots of IVIG- stwk 10% compared to one lot each of four other commercially available 10% IVIG products.

Particle Size

Measured by DLS (Z-average in nm)

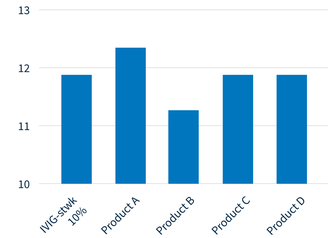

Figure 3. The particle sizes (Z-average) as measured by DLS for the six lots of IVIG-stwk 10% compared to one lot each of four other commercially available 10% IVIG products.

Polydispersity Index

Product	Polydispersity Index
IVIG-stwk 10% (6 lots)	0.080
Product A	0.130
Product B	0.100
Product C	0.070
Product D	0.080

Figure 4. The polydispersity index indicating particle size dispersion measured the average of 6 lots of IVIG-stwk 10% and one lot each of four other commercially available 10% IVIG products.

RESULTS, CONT.

Product	Monomer + Dimer (%)	Polymer (%)	Fragment (%)	Particle Size, Z-average (nm)
IVIG-stwk 10% (n=6)	99.58	0.087	0.335	11.9
Product A	99.43	0.249	0.326	12.3
Product B	99.11	0.107	0.784	11.2
Product C	99.47	0.052	0.478	11.9
Product D	99.14	0.058	0.797	11.9

Table 1. Product composition and particle characterization for 6 lots of IVIG- stwk 10% compared to one lot each of four 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 enhanced purification process developed for IVIG-stwk 10% may contribute to reduced aggregate and fragment levels, which can be associated with IVIG-related adverse events
- Interpretation is constrained by the inclusion of only one lot for four of the commercially available IVIG products, which is a limitation given that there is known variability between lots for IVIG products
- Further multi-lot comparative studies are warranted to confirm these observations and detect any differences that might exist across IVIG products

CONCLUSION

- IVIG-stwk 10% showed a favorable aggregation profile, with high levels of monomers and dimers and low levels of polymers and fragments
- Particle size measurements and the polydispersity index were comparable to those of other commercially available IVIG products
- 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

REFERENCES

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DISCLOSURES AND ACKNOWLEDGEMENTS

GBK and JL are employees of GC Biopharma. SN, AH, SS, LRM are employees of GC Biopharma USA.