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Development of a Novel Plasma Fractionation Process for the Production of Immune Globulin

BACKGROUND: Immune globulin (IgG) is a protein product prepared from human blood plasma for the treatment of primary immunodeficiency and a wide variety of other immunological disease conditions. In addition, IgG can be used for passive immune transfer to accelerate the clearance of pathogens (e.g., SARS-CoV2) and prevent or treat infection. The U.S. intravenous immunoglobulin (IVIG) market size was valued at USD 3.13 billion in 2017. A rise in demand for immunoglobulin replacement therapies for the treatment of primary immunodeficiency diseases is a high impact-rendering driver for the market. According to the American Board of Internal Medicine Foundation, at least 1 in 1,200 persons in the U.S. had primary immunodeficiency in 2017. Moreover, according to the Immune Deficiency Foundation, more than 350 rare immune disorders are representing primary immunodeficiency disorders. Shortages of IG occur whenever the demand for the product outstrips the supply. Current shortages, following other historical periods of shortage, threaten the well-being of patients dependent on these products and incur heavy costs on health systems. The current worldwide demand for IVIG products and forecasted growth exceeds the current plasma collection capacity of most countries.

PROBLEM: For over 70 years, IgG has been produced with the Cohn process, which separates, or fractionates, plasma proteins based on their differential solubility in ethanol with variances in temperature, pH, ionic strength, and protein concentration. While the exact overall IgG yield from the Cohn process is a closely guarded secret of each plasma fractionator, the modern Cohn process is widely known to achieve yields of only 50-60% of the starting IgG, and the process takes between 7-10 days to complete. Aside from the obvious environmental concerns of working with large volumes of ethanol, IgG produced by Cohn fractionation carries an inherent risk of protein denaturation since it is produced with the combination of alcohol and extreme pH changes. The avoidance of the combined effect of alcohol and low pH has implications for improved protein stability, *in vivo* half-life, patient tolerability and reduced immunogenicity of the protein therapeutics. With the ongoing shortage of IgG products and the inability of plasma collections to satisfy patient demands for IgG, any new process that addresses the shortcomings of the Cohn fractionation process is poised to displace it as the new industry standard to produce IgG (and other plasma proteins) for patients who rely on these lifesaving treatments.

CHALLENGE: Over the past year, Haemtech has collaborated with the inventors of a technologically-advanced and transformative process for the extraction of therapeutically useful proteins from plasma. This technology replaces the denaturing and low yielding 80-year-old Cohn Cold Ethanol Process by combining salt precipitation with purification by advanced precision membrane filtration and chromatographic techniques. This technology was purported to not only take significantly less time than the Cohn process, but it was also apparently capable of producing a significantly higher yield of IgG (>75%). Haemtech was charged with validating this novel fractionation process and developing a complete process for IVIG production.

APPROACH: The principal technology resides in the novel base fractionation of plasma with a salt as the precipitant rather than ethanol. The resulting product of the second precipitation process is a protein paste that is approximately 50% IgG. Haemtech first sought to optimize the process with a focus on the robustness of this base fractionation technology. To accomplish this, a multi-donor plasma pool was created and an experimental matrix was constructed to stratify the salt percentage in the precipitation steps. IgG levels were monitored with a total IgG ELISA and the results indicated the optimal salt precipitation scheme to produce the best possible combination of IgG yield and purity in the final product. Once validation of the novel base fractionation technology was established, process development for the downstream purification and formulation of IgG began in earnest.

SUCCESS: The finished drug substance was tested in and passed all assays specified by the European Pharmacopoeia (EP) standard for IVIG. The final yield of the process at bench scale was reliably 74% IgG as compared to the starting cryo-poor plasma with further known optimization and scale-up opportunities to improve upon the yield. Furthermore, this process was developed to be infinitely scalable with state-of-the art technology which is expected to produce yield gains of 5-10%. The new process consists of 10 process steps and takes approximately 48 hours to complete. Compared to the Cohn process's 7-10 day cycle time, the cost savings combined with improved yields makes this new technology revolutionary in the field of plasma fractionation. Thus, in the timespan of approximately 18 months, Haemtech was able to harness this new technology and use it it to create a scalable process for industrial production of an IVIG product that producted an IgG yield of 74.1% in the bulk formulation and passed all EP standards for safety and purity. We are confident that the yield can be increased with further known optimization opportunities that were recognized during R&D. Also, a yield increase can be expected when the process is scaled from our 2L R&D pilot runs. The other proteins are present in remarkably low amounts (e.g., IgA 1.57ug/mL) for such a high-yielding IgG fractionation process. These benefits combined with the marked increase in IgG yield should place this new technology at the forefront of this growing multi-billion-dollar industry and benefit patients worldwide.