PROLYTIX
Biotherapeutic Experts
from Discovery to Release

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

A highly efficient method of plasma fractionation that has the potential to address the growing global IG product shortage.

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-CoV-2) and prevent or treat infection. The U.S. intravenous immunoglobulin (IVIG) market size was valued at USD 4.7 billion in 2021.[1] 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 inflict heavy costs on health systems. The current worldwide demand for IVIG products, which is only expected to grow in the future, already exceeds the current plasma collection capacity of most countries. Thus, the need for plasma and plasma-derived products grows each year, but the complex nature of Ig products as biologics means that it takes time to increase the supply. It's not as simple as churning out more pills and faster, or is it?

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 effects of alcohol and low pH has implications for improved protein stability, in vivo half-life, patient tolerability, and reduced

The current worldwide demand for IVIG products, which is only expected to grow in the future, already exceeds the current plasma collection capacity of most countries.

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.

Prolytix was presented with a novel plasma fractionation technology that utilized salt rather than ethanol to precipitate IgG.

Challenge

Prolytix was presented with a novel plasma fractionation technology that utilized salt rather than ethanol to precipitate IgG. This technology was purported to not only take significantly less time (48–72 hours) than the Cohn process, but it was also apparently capable of producing a significantly higher yield of IgG (>90%). Prolytix was charged with validating this novel fractionation process and developing a complete scalable process for IVIG production.

Solution

Plasma Base Fractionation Technology

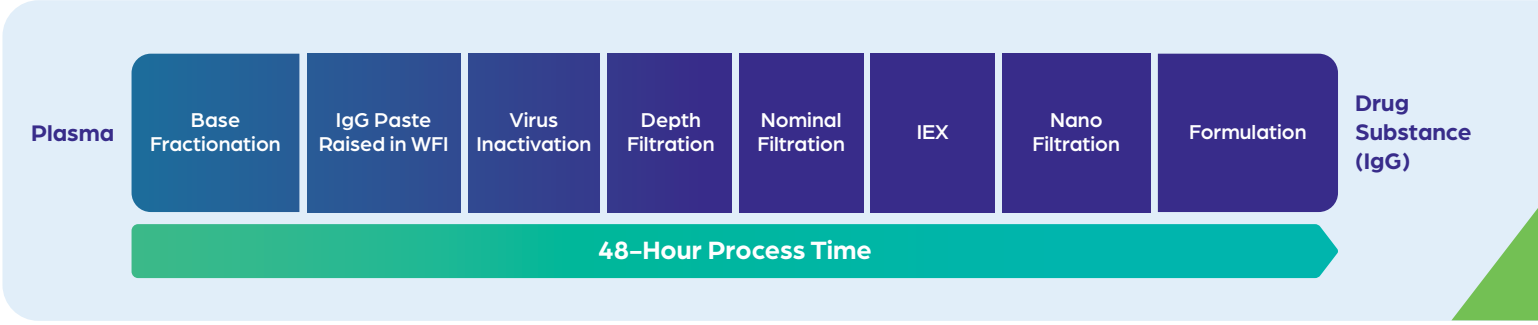
The principal technology resides in the base fractionation of plasma with two salt precipitations followed by a centrifugation step. The product of the second precipitation/centrifugation step is a protein paste that is approximately 50% IgG. Prolytix first sought to optimize the process with a focus on the robustness of this base fractionation technology. To accomplish this, a multi-donor (N=120) plasma pool was created, and an experimental matrix was constructed to stratify the salt percentage in the first and second salt precipitation steps. IgG levels were monitored with a total IgG ELISA, and the results indicated that the salt precipitation scheme produced the optimal combination of IgG yield and purity in the final paste.

Process Development

Once validation of the novel base fractionation technology was established, process development for the downstream purification and formulation of IgG could begin. The following process/protocol is the product of 9 months of rigorous scientific examination and experimentation. Paste from base fractionation was raised in water for injection, and this material was subjected to its first virus removal step. Due to the turbid nature of the resuspended pellet, depth and nominal filtration were necessary to clarify the solution prior to IEX. Chromatography consisted of both anion and cation exchange steps. Prior to the cation exchanger, the IgG material was already at >98% purity, and the cation exchange step was essentially used to polish the final product, which was 99.7% pure IgG.

Results

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 75% IgG as compared to the starting cryo-poor plasma. 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%. As shown below in Figure 1, the new process consists of 8 steps and takes only 48 hours to complete. Compared to the Cohn process's 7–10-day cycle time, the cost savings combined with improved yields make this new technology revolutionary in the field of plasma fractionation. In a period of 18 months, Prolytix was able to harness this new technology and use it to create a scalable process for industrial production of an IVIG product that passes all EP standards for safety and purity. These benefits combined with the marked increase in IgG yield should place this new technology at the forefront of this multibillion-dollar industry.



References

[1] Grand View Research. Market Analysis Report: Intravenous Immunoglobulin Market Size, Share & Trends Analysis Report By Application (Immunodeficiency Diseases, Hypogammaglobulinemia, CIDP), By Type, By Distribution Channel, By Region, And Segment Forecasts, 2022–2030. www.grandviewresearch.com. Published 2022.