PPTA
Plasma Protein Therapeutics Association

THE FACTS ABOUT...

PLASMA PROTEIN THERAPY MANUFACTURING

Plasma-derived therapies and their recombinant analogs (collectively referred to as plasma protein therapies) are unique among pharmaceuticals and biologics. Their production begins with a biological starting material, human plasma, rather than a synthetic or chemical, which is the starting material for most pharmaceuticals. Each therapy has a unique biochemical profile as a result of differences in production and processing methods that lead to differing clinical responses and efficacy among patients. No two plasma protein therapies are exactly alike and no two patients will respond in precisely the same way to a single therapy. Plasma protein therapies are not interchangeable and have been defined by regulators as sole-source biologic products, therefore no generics or substitutions exist. Further, because of their biological nature and special handling requirements, manufacturers must work with specialty distributors familiar with and able to meet the storage and handling requirements to ensure safety and efficacy. From the starting material, through manufacturing and final distribution to patients, the complexities of producing plasma protein therapies places it in a unique class of biologics.

Plasma-derived Therapies

Human plasma is rich in a number of proteins. Proteins extracted from plasma, including albumin, clotting factors, immunoglobulins and alpha-1 proteinase inhibitors, are used to make therapies that treat rare, chronic, often genetic diseases such as hemophilia, primary immunodeficiencies and alpha-1 antitrypsin deficiency, and acute conditions such as burns and shock.

The production of safe, high-quality, plasma-derived therapies depends on the willingness of people to donate plasma. Source plasma can be given at one of 380 U.S. Food and Drug Administration (FDA) licensed and International Quality Plasma Program (IQPP)-certified plasma collection centers located throughout the U.S through a process called plasmapheresis. In Europe, source plasma can be given at 27 IQPP-certified centers regulated by their appropriate national authorities. During this process, whole blood is separated into cellular and other components by using specialized equipment called a plasmapheresis device. This sterile, self-contained, automated process separates red blood cells and other cellular components in the blood, which are then returned to the donor.

The first plasma donation can take up to three hours and involves completing health screenings, donor education, and the donation process itself. Subsequent plasma donations take approximately one-and-a-half to two hours. In order for the first donation to be used to produce therapies, the donor must make a second donation and both must test negatively for transmissible diseases. Only then can those donations be used to manufacture therapies and does that donor become Qualified. This Qualified Donor Standard is part of the industry's IQPP voluntary standards program for plasma collectors that adds another layer of safety to existing regulatory requirements. U.S. regulations allow a person to donate plasma two times in a seven day period, with at least two days in between donations. The safety and well-being of the donor and the plasma that is donated are the highest priorities for manufacturers of plasma

protein therapies, therefore donor health and plasma safety are assessed at every donation.

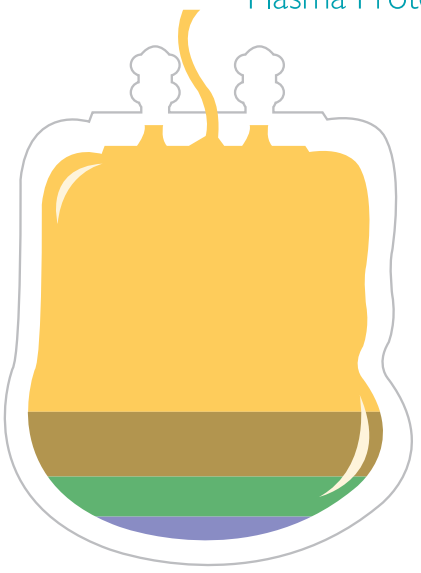
Further, before plasma can enter the manufacturing process, it is held in inventory for 60 days as part of the industry's voluntary international standards program for manufacturers, Quality Standards of Excellence, Assurance and Leadership (QSEAL). This robust standard allows for the identification, retrieval, and destruction of any plasma donation as a result of post-donation information. In light of the comprehensive screening criteria for plasma donors, there could be many reasons for retrieving and destroying a plasma donation. For example, a donor may have received a tattoo or piercing that would have disqualified him/her at the time of the original donation, or perhaps the donor failed to report foreign travel to certain parts of the world that would have disqualified him/her. Regardless of the reason, the QSEAL Inventory Hold Standard offers a strong, important measure of quality control to the production of plasma protein therapies.

Fractionation

The process of producing plasma-derived therapies is called "fractionation." During this process, plasma is pooled, purified, and processed to extract specific plasma proteins that have a proven health benefit. The therapeutic proteins are extracted or "fractioned off" from a plasma production pool of multiple donations in a specific order. As part of the fractionation process, the combination of time, temperature, pH and alcohol concentration allows the extraction of the specific therapeutic proteins. Different purification methods and viral inactivation and removal processes then are used based on the individual properties of the protein classes.

Manufacturers expend substantial research and technology investments to increase the amount of proteins extracted from plasma, known as the "yield," and to identify additional enhancements that can create even more effective therapies. The complex steps and regulations required to collect donated plasma and complete the highly technical, innovative manufacturing processes that ultimately result in a final therapy result in long time interrals between donation and final product release—between seven and nine months. This sets the production of plasma protein therapies apart from chemical pharmaceuticals and other biologics whose manufacturing processes are much more truncated and whose direct manufacturing costs are a significantly smaller portion of the overall cost.

Plasma Proteins and the Diseases They Treat



Albumin (25 grams*)

Shock, Burns, Adult Respiratory Distress Syndrome, Cardiopulmonary Bypass Surgery

IVIG (Intravenous Immunoglobulin) (4 grams*)

Primary Immunodeficiency Diseases, Autoimmune Diseases, Chronic Inflammatory Demyelinating Polyneuropathy, Idiopathic Thrombocytopenic Purpura

Alpha-1 Antitrypsin (.15 to .30 grams*)

Alpha-1 Antitrypsin Deficiency (Genetic COPD)

Coagulation Factors
(Factor VIII: 300 to 450 IUs, Factor IX: 180 to 200 IUs*)

Hemophilia A & B, von Willebrand Disease, Bleeding Disorders

** Plasma Protein Yields Per Liter of Plasma*

Recombinant Biological Therapies

Recombinant therapies for bleeding disorders (antihemophilic factors) are specialized therapies for coagulation deficiencies, including Factor VII, Factor VIII and Factor IX. Recombinant therapies are derived from genetically adapted cell cultures, where an original cell derived is modified (reprogrammed) to produce specific proteins. These proteins are harvested for use in therapies.

For recombinant therapies, manufacturers rely on starter material from special production lines. Facilities harvest a small portion of these original therapy lines from controlled storage and allow the cells to multiply in several stages in order to produce enough proteins for manufacture into finished formulations. The manufacturing process requires massive investments in sophisticated technology to achieve.

Patients throughout the world rely on the critical therapies made from plasma collected from committed and qualified donors and from specialized cell lines. The industry remains steadfast in providing safe, high-quality plasma-derived and recombinant biological therapies that save and improve the lives of the individuals who depend on them.

Information as of May 2009

PLASMA PROTEIN THERAPY MANUFACTURING

Plasma Protein Therapeutics Association (PPTA)
147 Old Solomons Island Road,
Suite 100
Annapolis, MD 21401
Phone: 202-789-3100

PPTA Europe
Boulevard Brand Whitlock 114/5
1200 Brussels, Belgium
Phone: 32-2-705-5811
Fax: 32-2-705-5820

PPTA Japan
4-20-3 Ebisu, Shibuya-ku
Tokyo 150-6018 Japan
Phone: 81-3-5789-5925
Fax: 81-3-5789-5757