Edition: September 2025 Issue

Plasma जन an

Plasmapheresis

A dire need to address national self-sufficiency in Plasma derived products

Zakir Nadaf.

Plasmapheresis is a medical procedure that separates plasma from whole blood, returning cellular components to the donor while retaining the plasma. This collected plasma serves as the foundational material for plasma fractionation—a process that isolates specific proteins for therapeutic applications.

In India, the collection of plasma specifically for fractionation purposes is subject to stringent regulations. Historically, the country has prohibited the Plasmapheresis i.e collection of source plasma for commercial activities, including plasma fractionation, primarily due to concerns about transfusion-transmitted infections that arose earlier when compensated blood donations were legal.

Human plasma for fractionation may be obtained by separation from whole blood called recovered plasma or directly by plasmapheresis route called source plasma.

- **Recovered plasma** - It is recovered from blood donated by voluntary non-remunerated donors at blood centres. The blood is collected, and plasma is separated from whole blood by centrifugation as per national regulatory guidelines of the country. The cellular components of the blood are utilized for clinical purposes, while plasma is frozen for further use. It can either be used for clinical purposes or for fractionation
- **Source plasma –** It is obtained by a process called Plasmapheresis, where only the plasma is collected from the donor, while the cellular components are returned back to the donor through a closed system in the same cycle. Globally, most of the source plasma is collected from voluntary but remunerated donors. Source plasma can be further classified into either normal source plasma or hyperimmune plasma.

Donor can give recovered plasma 4 to 6 times a year, compared to upto 104 times for source plasma, depending on national regulations. The volume collected is significantly higher in source plasma (450 to 880 ml) than in recovered plasma (100 to 260 ml) in single donation.

In India, till today Plasma derived medicinal product are manufactured using recovered plasma.

To address the growing need for plasma-derived medicinal products (PDMPs), the National AIDS Control Organization (NACO) introduced the “National Policy for Access to Plasma Derived Medicinal Products from Human Plasma for Clinical/Therapeutic Use” in 2014. This policy aims to facilitate the availability of safe and adequate quantities of Plasma Derived Medicinal Products by optimizing the use of surplus plasma from voluntary, non-remunerated blood donations. The policy also emphasizes the establishment of guidelines for plasmapheresis and encourages the development of plasmapheresis centres for the collection of source plasma.

Despite these policy initiatives, the collection of source plasma through plasmapheresis for fractionation remains limited. As a result, India continues to rely heavily on recovered plasma to manufacture of PDM products.

In summary, plasmapheresis will be a dire need for Indian Plasma fractionation industry to produce plasma derived medicinal products.

Thought for the Fortnight

“Heroes don't always wear capes.
Sometimes, they roll up their sleeves.”

Plasma-Derived Products: Market Outlook and Future Trends

By Dr Ankur Jindal , Manipal Hospital, Indiranagar

The global market for plasma-derived medicinal products (PDMPs) is witnessing strong and sustained growth. Valued at approximately $30.3 billion in 2022, with intravenous immunoglobulin (IVIg) accounting for 60% of the total, the market is projected to reach $50 billion by 2032, growing at a compound annual growth rate (CAGR) of 7.2%. This expansion is driven by several key factors, including the rising prevalence of autoimmune and neurological disorders such as chronic inflammatory demyelinating polyneuropathy (CIDP), immune thrombocytopenic purpura (ITP), and primary immunodeficiency diseases (PIDD). Technological advancements in plasma fractionation have improved both yield and safety, while the global expansion of plasma collection centers and increasing regulatory approvals for new indications and formulations have further fueled growth. Additionally, growing awareness and early diagnosis of immune-related conditions are contributing to increased demand.

IVIg continues to be a cornerstone therapy in immunotherapy, currently used to treat a range of conditions including PIDDs, ITP, Guillain-Barré Syndrome (GBS), CIDP, Kawasaki Disease, and in bone marrow transplantation (BMT). Its role is expanding through ongoing research into new indications such as Alzheimer's disease, autoimmune encephalitis, and long COVID. Innovations like subcutaneous immunoglobulin (SCIG) formulations are enabling more flexible, home-based care options, while AI-driven models and biomarkers are paving the way for personalized dosing strategies. Improvements in safety profiles through new stabilizers and purification methods are also reducing adverse effects.

Despite its promise, the IVIg market faces challenges such as supply constraints due to limited plasma donations, cost pressures, and reimbursement hurdles in certain regions. There is a pressing need for sustainable plasma sourcing and robust donor recruitment strategies. Moreover, innovation in recombinant alternatives may eventually complement or compete with plasma-derived IVIg. Nonetheless, the outlook remains highly promising. With strategic investments in plasma infrastructure, research, and global accessibility, plasma-derived therapies—especially IVIg—are poised to play an increasingly vital role in the future of immunotherapy.

E-mail
editor@plasmajan.in(Editorial team)
reach@plasmajan.in(General Inputs

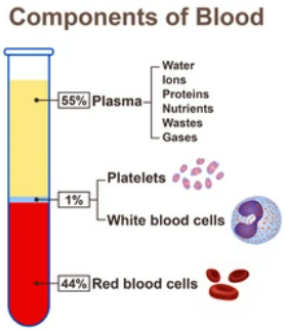
Plasmagen BIOSCIENCES

Plasma जन an

Human Plasma and its derivatives

Bhavesh Agarwal.

Human Plasma:



Human Blood is the source of plasma which is used to manufacture various therapeutic products. Blood comprises of ~55% plasma (light-yellow colour liquid containing proteins), ~44% red blood cells (RBC) and <1% white blood cells (WBC) and platelets. This blood plasma (non-cellular liquid part) will be used to fractionate various proteins such as Albumin, Immunoglobulins, and clotting factors.

Human plasma can be collected from blood banks through two ways –

1) Voluntary donations and

2) Plasmapheresis.

Plasma collected through mode of voluntary donations is called as "Recovered Plasma" whereas Plasma collected through plasmapheresis is called as "Source Plasma." In India commercially pheresis not allowed so plasma is collected only from voluntary donated blood by separating out other cellular components. Blood banks utilize the cellular components (RBC, WBC, and platelets) for various applications as per blood group needs. However, plasma (devoid of cellular components) generally remains unused or surplus in blood banks. These excess or surplus plasma collected from blood banks by plasma fractionators for clinical / therapeutic use as per "National Plasma Policy" of Ministry of health & family welfare.

Human Plasma composed of more than 130 proteins which can be used for various therapeutic indications but only few plasma products are developed at commercial scale and others are in R&D pipeline of many companies. Globally, main plasma proteins extracted so far are listed below with their therapeutic /clinical indications:

Manufacturing Process & Technology:

The technology backbone for plasma fractionation is mainly the Cohn's Process. In late 1940s, Edwin J. Cohn developed the process with series of purification steps to extract the Human Albumin from Blood plasma to save life of soldiers in World War-II. Later it was named as Cohn's Fractionation Technology, still continuous improvements and optimization is happening worldwide to enhance yield and extract new proteins.

Manufacturing processes comprises of series of stages to convert raw plasma into finished products. During processing, various strategies used for separation/ purification which play critical role for product quality, safety, and efficacy. The main stages of manufacturing are Fractionation, Downstream processing, and Fill-Finish.

Generally, there are two methods used for fractionation /purification stages either in combination or separately:

a) Precipitation based method:

This method includes series of precipitation of different proteins of interest using different concentration of solvent, temperature, pH and ionic strength in sub-zero temperature.

b) Chromatography based method:

This method uses typical purification methodology to separate different proteins based on molecular weight cut off or ionic charge of proteins. The yield and quality are two parameters which determine the strategies for further purifications.

Each methodology has its own benefits and challenges in terms of scale up, yield, quality, and safety. All the activities of manufacturing from plasma storage to finished product should be performed under different classified areas and complied to cGMP requirements defined in Annex 1 of the EU-GMP Guide / WHO-GMP Annex 4, TRS No 961.

Plasma Proteins	Therapeutic / Clinical uses
Fibrinogen	Treat bleeding episodes in people with a congenital fibrinogen deficiency.
Thrombin (Factor IIa)	It is topical haemostatic agent used to control and minimize blood loss during surgical procedures
Factor II	Factor II deficiency
Factor V	Factor V deficiency
Factor VII	Factor VII deficiency
Factor VIII	Haemophilia A
Factor IX	Haemophilia B
Factor X	Factor X deficiency
Factor XI	Haemophilia C (factor XI deficiency)
Factor XIII	Factor XIII deficiency
Albumin	Treat or prevent shock in serious injury, bleeding, surgery, or burns and act as blood Volume replacement/ expander
Polyvalent IgG (normal)	Used for prevention of infections in immunodeficient patients; Immune modulation in various immunological disorders
Hyperimmune IgG: a) Hepatitis B, b) Hepatitis A, c) Tetanus, d) Rabies, e) Varicella/zoster	Prevention or treatment of in certain immunodeficiency states (specific type of infection)
Prothrombin Complex Concentrate (PCC)	Treatment of bleeding events associated with haemophilia B, congenital deficiencies of the other vitamin K–dependent clotting disorders, or in case of severe liver disease.
Fibrin sealant or Fibrin glue (combination of fibrinogen and thrombin)	Topical tissue haemostatic healing and sealing agent for surgical applications
Antithrombin	Congenital (or acquired) deficiency leading to thrombosis
Alpha 1-antitrypsin	It is a protease inhibitor, used to protect from proteolytic damage. Indicated for treatment of congenital deficiency associated with panacinar pulmonary emphysema
C1-esterase inhibitor	Treat or prevent hereditary angioedema (HAE). HAE is a rare disease that causes swelling of the face, hands, feet, throat, stomach, bowels, or genitals.
Anti-Rho (D)	Prevention of haemolytic disorders in new-born

References:

https://www.crbgroup.com/insights/pharmaceuticals/trends-plasma-manufacturing-industry
https://www.fortunebusinessinsights.com/india-plasma-fractionation-market-106442
https://aob.amegroups.com/article/view/4496/5240

Plasmagen BIOSCIENCES

Blood centres: On-field Challenges

India's Missed Heartbeat: The App That Could Have Saved Thousands

The Echo of a Selfless Mission

In a nation bursting with digital prowess, the shutdown of 'Simply Blood' is a sobering reminder that technological solutions mean little without cultural resonance and civic empathy. Here was a platform built not to profit, but to save lives—yet in its death, it reveals a paradox: we celebrate heroes in hashtags, but hesitate to become one in real life.

'Simply blood' s founder's vision—"Nobody will die waiting for blood in India"—was not flawed in ambition but unmet in action. Public apathy, governmental disinterest, regulatory roadblocks, and inadequate infrastructure form a cocktail that even the most determined changemakers cannot always overcome.

India has the talent to launch satellites and engineer billion-dollar start-ups yet struggles to maintain a network that could connect one donor to one receiver in time. Why?

Maybe we need to market empathy the way we market shampoo. Maybe life-saving platforms deserve prime-time slots, corporate sponsorships, and regulatory incentives. And maybe, just maybe, innovation should be rewarded not only when it makes money, but when it saves lives.

So the platform fades... but the questions remain:

- Why do selfless endeavors lack sustainable funding?
- Can technology ever overcome behavioral barriers?
- Is a centralized national blood registry still a pipe dream?
- Should blood availability updates be mandatory like nutritional labels?
- Will we wait until someone we love needs blood?

If 'Simply Blood' taught us anything, it's that one visionary can light a lamp—but it takes collective will to make the flame burn bright.

Knowledge Centre

MAT vs RPT: Journey from rabbits to cell in advancing ethical pyrogen testing method

Dr. Mahammad Sadique.

The Monocyte Activation Test (MAT) is a viable in vitro alternative to the traditional Rabbit Pyrogen Test (RPT) for detecting pyrogens in parenteral products. It offers advantages like broader applicability and better reflection of human immune responses. While the Rabbit Pyrogen Test has been the go-to for pyrogen testing for over a century, regulatory agencies such as the European Pharmacopeia (Ph. Eur.) are now pushing for in-vitro alternatives, with the MAT being a top recommended choice.

The Monocyte Activation Test (MAT) is a cutting-edge in-vitro assay that employs human blood to replicate the early stages of the human immune system. This innovative test is designed to detect all types of pyrogens in parenteral drugs, biologics, and medical devices. The monocyte activation test (MAT) is used to detect or quantify substances that activate human monocytes or monocytic cells to release endogenous mediators: such as pro-inflammatory cytokines, for example tumour necrosis factor alpha (TNF α), interleukin-1 beta (IL-1 β) and interleukin-6 (IL-6). These cytokines have a role in fever pathogenesis. Consequently, the MAT will detect the presence of pyrogens in the test sample. The MAT is suitable, after a product-specific validation, as a replacement for the rabbit pyrogen test.

Pyrogen detection is crucial for quality assurance and product safety in the production of parenteral pharmaceuticals, and for decades, the rabbit pyrogen test (RPT) was the traditional method for pyrogenicity testing. While this classic in vivo assay can potentially detect all pyrogenic contamination, it was never formally validated, and its results are not directly transferable to humans [1].

The monocyte-activation test (MAT) was introduced in the European Pharmacopoeia (Ph. Eur.) in 2009 as an official method that could be used as an in vitro alternative to the RPT. The MAT is human-specific, has high sensitivity, can detect both endotoxin and non-endotoxin pyrogens, and is more readily transferable to human in vivo reactions. Thus, a significant step for patient safety. The introduction was also an important step for animal welfare, in accordance with the 3Rs concept of Reduction, Replacement and Refinement of laboratory animal use.

However, despite the publication of the MAT chapter and multiple efforts since then to encourage developers to apply MAT instead of the RPT, rabbits continued to be used extensively to detect pyrogenic substances. Therefore, the complete removal of the RPT from the Ph. Eur. is necessary if the aim is to move towards the exclusive use of in vitro tests to control pyrogenicity.

To expedite the transition from MAT being viewed as an alternative method to being viewed as the best possible test option, the European Directorate for the Quality of Medicines & HealthCare (EDQM), Council of Europe and the European Partnership for Alternative Approaches to Animal Testing (EPAA) organised an international conference - The future of pyrogenicity testing: phasing out the rabbit pyrogen test. The event was held in Brussels, Belgium, on 14–15 February 2023 and presented the Ph. Eur.'s strategy for phasing out the RPT, the use of the MAT, the viewpoints of regulators and industry representatives, and perspectives from outside Europe on animal-free pyrogenicity testing.

Why MAT is an Alternative:

In vitro:

- The Monocyte Activation Test (MAT) is a progressive and ethical method in pyrogen testing, which is designed to detect substances that might cause fevers when introduced into the body. Instead of relying on traditional tests like the Rabbit Pyrogen Test (RPT), MAT harnesses the power of human biology to provide accurate and reliable results.
  MAT specifically utilizes human peripheral blood mononuclear cells (PBMCs), a subset of white blood cells that play a critical role in our immune system. PBMCs are instrumental in detecting foreign substances and initiating immune responses. In MAT, these cells are exposed to test substances to observe their reaction, particularly whether they release specific cytokines—proteins that signal an immune response. By replicating the initial stages of the human immune response, MAT gives researchers insight into how a substance might behave inside the human body. This approach is especially valuable as it eliminates the need for animal testing, aligning with modern ethical standards and reducing reliance on animal models like the RPT. Moreover, because MAT uses human-derived cells, it provides results that are more directly relevant to human health, thereby enhancing the accuracy and reliability of pyrogen detection.

Broader applicability.

- The Monocyte Activation Test (MAT) is a versatile tool in the realm of pyrogen testing, offering capabilities that surpass those of the Rabbit Pyrogen Test (RPT). One of MAT's major advantages is its ability to evaluate a wide range of products across various industries.
- Unlike the RPT, which is primarily limited to injectable pharmaceuticals and certain types of medical devices, MAT has the flexibility to test other types of products, including. Biopharmaceuticals: Complex biologics such as vaccines, monoclonal antibodies, and cell-based therapies can be assessed effectively using MAT.
- Dialysis Solutions: MAT can determine the safety of fluids used in critical care.
- Nutritional Products: It is suitable for pyrogen detection in parenteral nutrition solutions.
- Blood Products: This includes plasma, platelet concentrates, and other blood-derived products.
- Medical Devices and Implants: MAT is capable of testing devices that come into contact with the bloodstream or sterile tissues.
- Cosmetics and Personal Care Products: Some of these products, especially those that interact with sensitive areas of the body, can also undergo pyrogen testing using MAT.

Better human-specific response:

- The reason MAT is so adaptable lies in its mechanism—it uses human immune cells, which are designed to simulate the human immune response. This human-relevant approach makes it applicable to products where traditional animal tests, like the RPT, might fail to provide reliable insights due to species differences or ethical concerns.

Benefits of MAT:

- **Animal-free:** Reduces the use of laboratory animals.
- **Higher sensitivity:** MAT is generally more sensitive than RPT and can detect a wider range of pyrogens.
- **More representative of human response:** Mimics the human immune reaction more closely than RPT.

GMP: Bridging Philosophy and Practice

Birendra Kumar.

Blood plasma-derived medicinal products (PDMPs) play a critical role in modern healthcare, offering life-saving solutions for individuals battling complex and severe health conditions. These therapies, including immunoglobulins, clotting factors, and albumin, are indispensable in treating a range of medical disorders. Immunoglobulins strengthen the immune system in patients with immune deficiencies, protecting them from potentially life-threatening infections. Clotting factors are essential for managing haemophilia, allowing individuals with clotting disorders to lead healthier lives, while albumin is widely used for maintaining proper fluid balance and addressing protein deficiencies, particularly in cases of critical illnesses.

What sets these products apart is their unique origin: they are derived from human plasma donated by individuals. This reliance on human donors underscores the need for rigorous safety measures and robust screening processes to ensure the efficacy and integrity of these treatments. As PDMPs are directly administered into vulnerable populations, including patients with weakened immune systems, safety becomes paramount in every step of their development—from plasma collection and processing to quality control and distribution.

By addressing conditions such as autoimmune diseases, haemophilia, and immune deficiencies, PDMPs not only save lives but also contribute to improved quality of life for countless patients worldwide. The advancements in safety protocols and testing methods continue to elevate the reliability of these products, ensuring that they remain a cornerstone of therapeutic medicine.

Risk and safety concerns:

The primary safety challenge associated with plasma-derived medicinal products (PDMPs) is the risk of transmitting infectious agents, which include dangerous viruses such as HIV and hepatitis B and C, as well as prions responsible for diseases like variant Creutzfeldt-Jakob disease (vCJD). Since PDMPs are produced from plasma donated by human donors, they carry an inherent risk of contamination by pathogens present in the donor's blood. This potential threat has historically led to devastating public health crises, underscoring the critical importance of rigorous safety measures.

For instance, during the 1980s and 1990s, large-scale transmission of HIV and hepatitis C through contaminated blood products caused widespread concern, leaving countless patients, including haemophiliacs, vulnerable to these life-threatening

infections. Such incidents not only resulted in tragic loss of life but also eroded public confidence in the safety of plasma-derived products. These crises acted as a wake-up call for the pharmaceutical and healthcare industries, prompting a paradigm shift toward adopting stricter safety and testing protocols.

Plasmagen: Setting the Benchmark for Plasma Product Safety:

Donor Screening and Selection: Rigorous screening processes have been implemented to identify and exclude high-risk donors, reducing the likelihood of contaminated plasma entering the supply chain. This includes detailed medical histories, physical examinations, and laboratory testing for known infectious agents.

Pathogen Inactivation and Removal: Advanced manufacturing processes at plasmagen having integrated methods such as heat treatment, solvent/detergent treatment, and filtration to effectively inactivate or remove pathogens from plasma-derived products. These techniques are meticulously validated to ensure their effectiveness without compromising the integrity of the final product.

Nucleic Acid Testing (NAT): Highly sensitive molecular testing methods, such as NAT, are employed to detect minute traces of viral RNA or DNA in plasma donations. This allows for the early detection of infectious agents, even in cases of low viral loads or during the "window period" when traditional antibody tests may not detect an infection. Fully automated closed system from ROCHE has been in place for NAT testing.

Continuous Monitoring and Quality Assurance: Comprehensive quality management systems (QMS) have been established to monitor and validate every step of the production process. This includes regular audits, stringent compliance with regulatory guidelines, and post-market surveillance to identify and address potential risks.

Post marketing surveillance: Plasmagen has a well-established and robust pharmacovigilance department dedicated to ensuring the safety and effectiveness of its plasma-derived medicinal products during the post-marketing phase. This department plays a crucial role in monitoring and managing any potential risks associated with the use of these products in real-world settings, thereby upholding high safety standards. To facilitate seamless communication and reporting, Plasmagen provides a dedicated helpline number and email address, prominently displayed on its official website. These channels are operational 24/7, ensuring that healthcare professionals, patients, and other stakeholders can report any adverse drug reactions (ADRs) or product-related concerns promptly and conveniently.

The pharmacovigilance team at Plasmagen comprises highly trained and experienced professionals who specialize in handling ADR reports with precision and urgency. Upon receiving a report, the team conducts thorough investigations to identify the root cause and assess any associated risks. This meticulous approach ensures that appropriate corrective actions are taken swiftly, thereby maintaining the safety and trustworthiness of Plasmagen's products. In addition, the department actively analyzes data from reported cases to identify trends or potential safety signals, contributing to the continuous improvement of product safety. By integrating advanced monitoring systems and a proactive response framework, Plasmagen demonstrates its unwavering commitment to safeguarding patient health and enhancing public confidence in its therapies

Environmental control: All critical manufacturing processes at Plasmagen take place in cleanrooms, which are controlled environments meticulously designed to minimize airborne particles and ensure product quality and safety. High-Efficiency Particulate Air (HEPA) filters are essential in maintaining air cleanliness. These filters can trap particles as small as 0.3 microns with an efficiency of 99.97% or higher. Air within the cleanroom undergoes continuous recirculation to ensure a consistent reduction in particle levels. Parameters such as temperature, humidity, and pressure are stringently controlled and constantly monitored. Strict protocols ensure that personnel entering the cleanroom do not introduce contaminants. This includes wearing specialized clothing such as coveralls, hoods, gloves, masks, and shoe covers.

Conclusion:

Advancements in donor screening, sophisticated testing methods, and cutting-edge manufacturing technologies have significantly enhanced the safety of plasma-derived medicinal products (PDMPs). These measures, combined with ongoing research efforts and stringent regulatory oversight, have strengthened the safety profile of these critical therapies, ensuring that patients receive life-saving treatments with minimal risk.

Additionally, Good Manufacturing Practices (GMP) play a pivotal role in safeguarding the production process of PDMPs. By enforcing rigorous standards for cleanliness, quality control, and operational precision, GMP creates a robust framework that guarantees both the efficacy of the products and the safety of the patients who rely on them. Together, these advancements and precautions uphold the highest standards of quality and reliability in plasma-based therapies.

PlasmaJan Team
Newsletter Champion: **Dr. Mahammad Sadique**
Editor: **Dr. Chandra V**
Co-editor: **Alok Chandrashear**
Creative Team: **Graphicwiz**

You are invited to make your contributions for the next issue of PlasmaJan. Please feel free to share your feedback and suggestions to make PlasmaJan more interesting.