

Market Assessment of Immunoglobulins in Rare Disease Segment

By

Annu Mathur

*Dissertation submitted for the partial fulfillment of the
MBA Pharmaceutical Management*

Academic year, 2018-2020



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ABBREVIATIONS

CDSCO	Central Drug and Standard Control Organization
DGFT	Director General of Foreign Trade
DIC	Disseminated Intravascular Coagulation
FFP	Fresh Frozen Plasma
GBS	Guillain Bare Syndrome
HSA	Human Serum Albumin
IPPC	International Plasma Protein Congress
ITP	Idiopathic Thrombocytopenia Purpura
IVIg	Intravenous Immunoglobulin
MRB	Market Research Bureau
NACO	National AIDS Control Organization
NIB	National Institute of Biologicals
PCV	Packed Cell Volume
PPTA	Plasma Protein Therapeutic Association
SCID	Severe Combined Immunodeficiency
VWF	Von Willebrand Factor
WFH	World Federation of Hemophilia

EXECUTIVE SUMMARY

Plasma therapy have a decent scope of remedial applications in different illnesses for all age gatherings, with over a million people overall accepting plasma therapeutics per annum, under different helpful purposes, viz. consume, stun and injury, lung and liver issue, resistant insufficiencies and so on.

A related improvement has been the presentation of therapy as a substitute to Plasma-determined proteins, for remedial purposes. (For items like antihemophilic factor and Factor IX) Currently the marked results of Albumin, Intravenous Immunoglobulin (IVIg) and coagulation factor VIII is out there inside the Indian market.

From Research

Global immunoglobulin market is estimated to be \$11 billion in 2020, with growth of 6.8%, primarily thanks to improved diagnosis and more off-label indications.

- By region, the most important share of immunoglobulin market is in North America at the present, US, immediately followed by Europe.
- In 2014, global immunoglobulin market was dominated by CSL and Grifols with high percentage of market share thanks to each one's higher capacity to serve the increased demand for immunoglobulin products.
- Despite the high cost of IVIG therapies, the demand for these products has increased in every region, and it's expected to still grow within the years to return.
- Also, the usage of plasma products (IVIG, etc.) varies widely from country to country
- For Instance, in India SSR is sort of low (46%) which shows the presence of untapped opportunities in IVIG segment which may be catered to.
- Especially in diseases like Kawasaki although having lower market at the present comparatively but show a better forecasted CAGR of 11.7% necessitating the necessity to serve the segment in future.
- GBS on the opposite hand seems to possess a low market price and a forecasted CAGR of mere 3%.

Plasma products have shown remarkable growth in the past year. Although the discovery of recombinant products leads to naturally occurring plasma protein preparations, plasma products are still gaining popularity in developing countries like India because of higher acceptance among parents. The reason for the growth of plasma products lies in the use of new indications, higher cleaning processes and increasing concern for the Indian biopharmaceutical industry such as PlasmaGenBiosciences, Reliance, Intasetc.

The common denominator of rare diseases is the frequency of occurrence in the human population. The World Health Organization (WHO) often defines a life-threatening disease or condition with a prevalence of 1 or less per 1,000 people as a rare disease. However, some developed and developing countries have their own definitions to meet their needs. This has led to heterogeneity in the definition of rare diseases, which is why there is no consensus among countries. However, it is generally accepted that a disease with less than 100 patients per 100,000 population is described as a rare disease and less than 2 patients per 100,000 as a rare disease. A rare disease is the most rare disease. Rare and very rare diseases are sometimes referred to as orphans or ultra-orphans.

"This is why many biopharmaceutical companies are entering this segment. To market their products effectively and get maximum market share, marketers are trying to identify prescription habits and physician models. Many market research organizations have provided useful data on this segment.

A BRIEF INTRODUCTION ABOUT HUMAN BLOOD/PLASMA

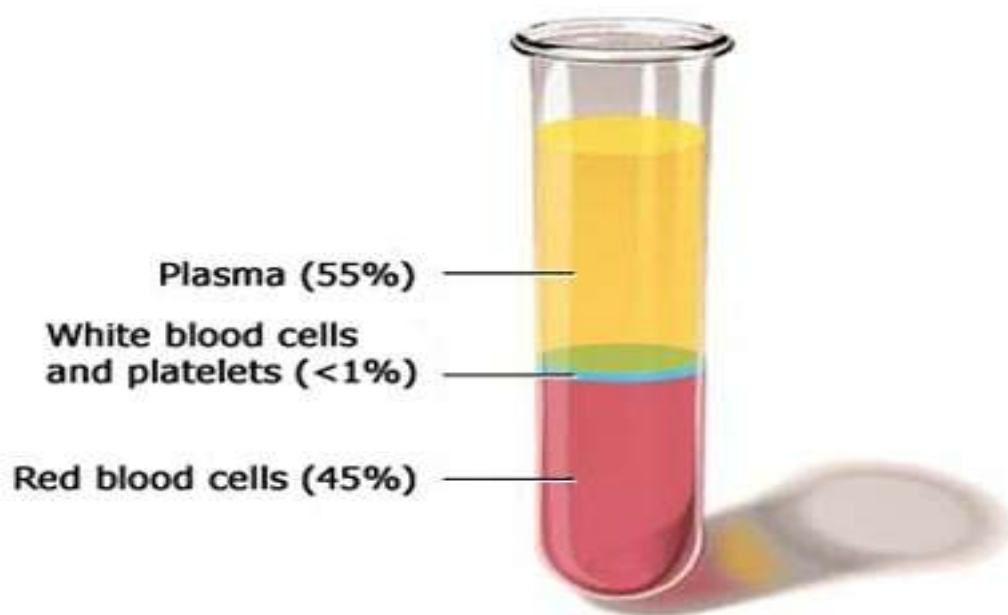


Figure 1;Components of Blood,Wikipedia

Whole blood consists of two main components; red blood cells which represent about 45% of the quantity of a unit of blood, and plasma, which is that the liquid portion of blood, making up the remaining 55%. blood collected from a donor are often separated into these two components by centrifugation.

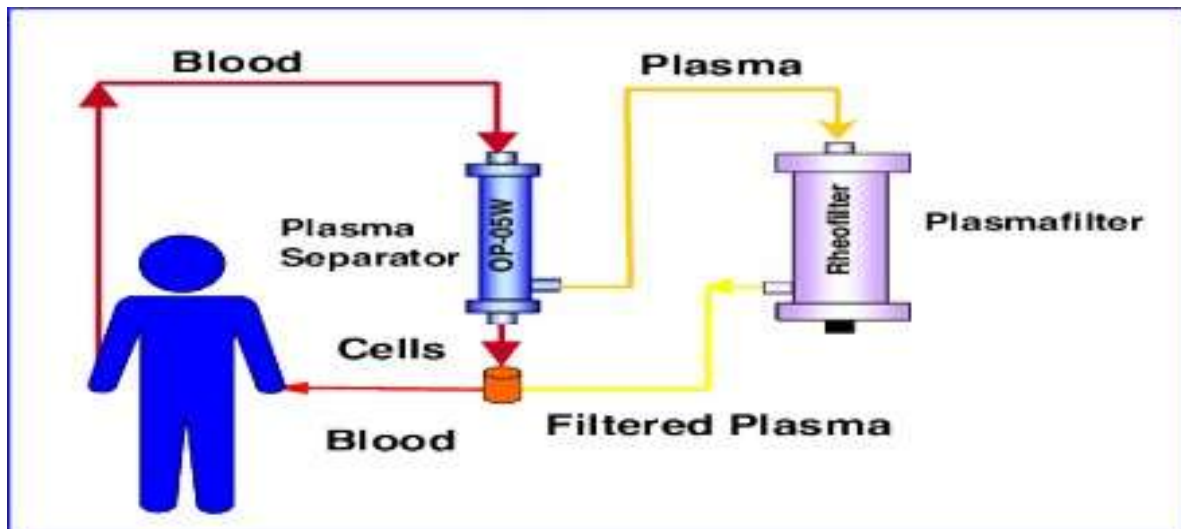


Figure 2;Plasmapheresis,plasmapheresis.html

Once the red cells are separated from the plasma, they're returned to the donor using an equivalent vein or a special one, counting on the machine used. The physical body regenerates plasma within a couple of days, unlike red blood cells, which require a couple of weeks. For this reason, a donor can donate plasma more frequently – up to twice every week within the us – than whole blood.

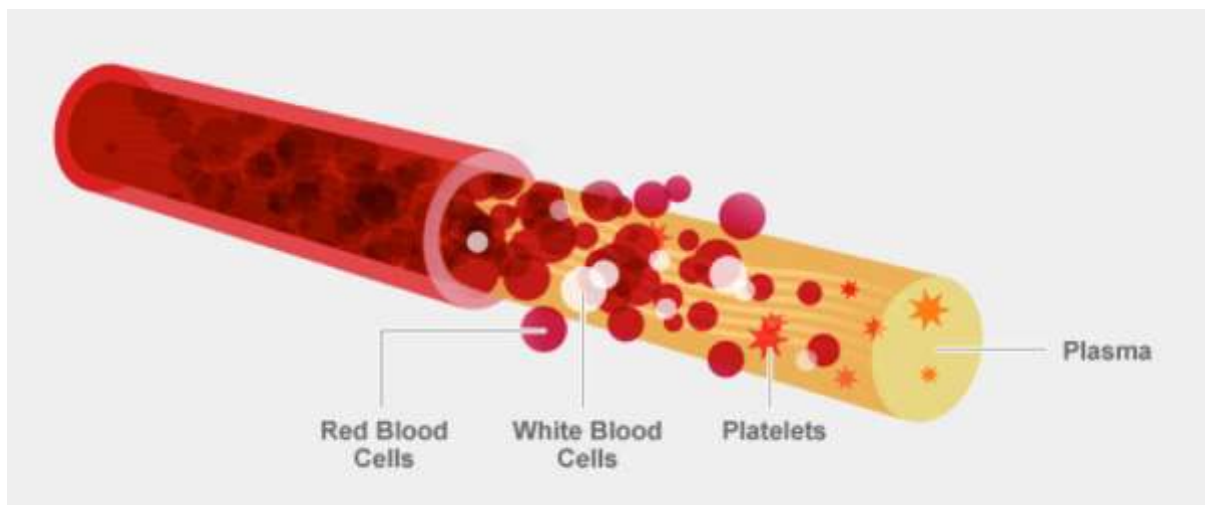


Figure 3;Elements of blood,pmc articles

Erythrocytes

Red platelets (RBCs), likewise called erythrocytes, are the preeminent regular kind of blood corpuscle and accordingly the vertebrate's chief methods for conveying oxygen (O₂) to the body tissues—by means of blood course through the cardiovascular framework. RBCs take up oxygen inside the lungs, or gills of fish, and discharge it into tissues while just barely getting through the body's vessels.

The cytoplasm of erythrocytes is wealthy in haemoglobin, an iron-containing biomolecule which will tie oxygen and is at risk for the red shade of the cells. The phone divider comprises of proteins and

lipids and this structure gives properties basic to physiological cell work like deformability and steadiness while navigating the cardiovascular framework and explicitly the narrow system. In people, develop red platelets are adaptable and oval biconcave circles. They come up short on a core and most organelles, to oblige greatest space for haemoglobin; they will be seen as sacks of haemoglobin, with a cell divider in light of the fact that the sack. Roughly 2.4 million new erythrocytes are created every second in human grown-ups. The cells create inside the bone marrow and flow for around 100–120 days inside the body before their parts are reused by macrophages. Every dissemination takes around 60 seconds (one moment). Around 1/4 of the cells inside the physical body are red platelets. About a large portion of the blood's volume (40% to 45%) is red platelets.

Leukocytes

White platelets (WBCs), likewise called leukocytes or leucocytes, are the phones of the framework that are associated with ensuring the body against both transferable malady and remote trespassers. All white platelets are created and gotten from multipotent cells inside the bone marrow alluded to as hematopoietic foundational microorganisms. Leukocytes are found all through the body, including the blood and lymphatic framework.

All white platelets have cores, which recognizes them from the contrary platelets, the anucleate red platelets (RBCs) and platelets. sorts of white platelets are frequently grouped in standard manners. Two sets of broadest classifications group them either by structure (granulocytes or agranulocytes) or by cell division ancestry (myeloid cells or lymphoid cells). These broadest classes are frequently additionally isolated into the five primary sorts: neutrophils, eosinophils (acidophilus), basophils, lymphocytes, and monocytes. These sorts are recognized by their physical and utilitarian attributes. Monocytes and neutrophils are phagocytic. Further subtypes are regularly ordered; for example, among lymphocytes, there are B cells, T cells, and NK cells".

The quantity of leukocytes inside the blood is generally a marker of illness, and accordingly the WBC check is a critical subset of the whole blood tally. the conventional leukocyte check is commonly between $4 \times 10^9/L$ and $11 \times 10^9/L$. inside the US this is regularly normally communicated as 4,000 to 11,000 white platelets for every microliter of blood. they make up around 1% of the whole blood volume during a sound grown-up, making them significantly less various than the RBCs at 40% to 45%. Be that as it may, this 1% of the blood has an outsized effect to wellbeing since insusceptibility depends subsequently. an ascent inside the quantity of leukocytes over as far as possible is named leucocytosis. it is ordinary when it is a piece of solid resistant reactions, which happen regularly. it is periodically strange when it's neoplastic or immune system in source. A reduction underneath as far as possible is named leukopenia. this implies a debilitated insusceptible framework".

Thrombocytes

Platelets, additionally called thrombocytes (thrombo + - cytes, "blood cluster cell"), are a part of blood whose work (alongside the coagulation factors) is to forestall seeping by bunching and thickening vessel wounds. Platelets have not any cell core: they are parts of cytoplasm that are gotten from the megakaryocytes of the bone marrow, at that point enter the course. These inactivated

platelets are biconvex discoid (focal point formed) structures, 2–3 μm in most noteworthy width. Platelets are discovered uniquely in warm blooded creatures, though in different creatures (for example feathered creatures, creatures of land and water) thrombocytes flow as unblemished mononuclear cells. “On a recoloured blood smear, platelets show up as dull purple spots, about 20% the distance across of red platelets. The smear is utilized to take a gander at platelets for size, shape, subjective number, and bunching. The proportion of platelets to red platelets during a solid grown-up extend from 1:10 to 1:20 .

The primary capacity of platelets is to add to haemostasis: the strategy for halting seeping at the area of intruded on endothelium. They accumulate at the area and except if the interference is truly overlarge, they plug the opening. To begin with, platelets join to substances outside the interfered with endothelium: attachment. Second, they adjust shape, actuate receptors and emit substance delivery people: enactment. Third, they connect with each other through receptor spans: conglomeration. Development of this platelet plug (essential haemostasis) is identified with actuation of the coagulation course with resultant fibrin testimony and connecting (auxiliary haemostasis). These procedures may cover: the range is from an overwhelmingly platelet fitting, or "white clump" to a dominantly fibrin cluster, or "red clump" or the more regular blend. The outcome's the coagulation. Some would include the following coagulation withdrawal and platelet restraint as fourth and fifth means to the consummation of the technique and still others a 6th step wound fix.

Plasma

Blood plasma might be a yellowish shaded fluid segment of blood that typically holds the platelets in blood in suspension; this makes plasma the extracellular lattice of platelets. It makes up about 55% of the body's all out blood volume. it's the intravascular liquid of ECF (all fluid body substance outside cells). it's generally water (up to 95% by volume), and contains disintegrated proteins (6–8%) (i.e.—serum albumins, globulins, and fibrinogen), glucose, thickening components, electrolytes (Na^+ , Ca^{2+} , Mg^{2+} , HCO_3^- , Cl^- , and so on.), hormones, carbon dioxide (plasma being the most vehicle for body squander transportation) and oxygen. Plasma likewise is the protein hold of the physical body. It assumes a significant job in an intravascular osmotic impact that keeps electrolytes in adjusted structure and shields the body from disease and other blood issue.

Blood plasma is isolated from the blood by turning a container of new blood containing an anticoagulant during an axis until the platelets tumble to absolute bottom of the cylinder. The plasma is then poured or drawn off. plasma includes a thickness of about 1025 kg/m^3 , or 1.025 g/ml .

Plasma items are made by isolating the plasma into various proteins and different substances. Every plasma item has diverse clinical employments. They serve numerous different capacities, including

- Circulatory transport particles for lipids, hormones, and nutrients
- Enzymes, supplement segments, protease inhibitors and kinin forerunners.
- Regulation of acellular movement and working and inside the framework.
- Protein holds for the body.

Albumin	Von Willebrand factor
Immunoglobulin	Fibrinogen
Factor VIII	Fibrin sealant
Factor IX	Prothrombin complex
Factor VII	Act. Prothrombin complex
Factor VIIa	Antithrombin

Table 1: Therapeutic products from plasma

Figure 4; Giuliano Grazzini,¹ Pier Mannuccio Mannucci,² and Fabrizio Oleari³ Plasma-derived medicinal products

MARKET DATA OF PLASMA PRODUCTS IN INDIA

India is one of the fastest developing nations on the globe. It has made a very impressive progress in various areas of healthcare with world-class hospitals, large number of US-FDA approved pharmaceuticals plants, clinical research organizations, young and talented human resource and change in the regulatory environment. It attracts many patients across the globe for medical tourism because of cost effectiveness, for the same quality of care as anywhere else in the world. Despite this progress and growth pattern it also faces many challenges. About 70% of population still lives in rural area and 30% in urban and semi-urban setting in large cities and towns. This makes India, a country of contrast, where people with highly diverse socio-economic backgrounds live together.

The access to healthcare facilities is one of the very big challenges because of many factors. One of them being less than 5% Indian population has medical coverage and therefore most of the healthcare expenditure is out of pocket and this puts a huge financial burden to the individual or the families of the patients. These 5% population is largely urban based or in regular employment either in private or government sector. Though access to health is a fundamental right of every citizen and government must ensure it, but at present, there is wide disparity in the access and coverage of essential healthcare services to the citizens of India. So, there is a wide gap within the demand and supply of the plasma products and therefore the plasma products are not available on the regular Basis. The market of those products is estimated to about 500 crores annually

INTRAVENOUS IMMUNOGLOBULINS (IVIG)

PRIMARY IMMUNODEFICIENCY:“Immunoglobulin replacement therapy via the IV or SC route is required in patients with certain PI diseases characterized by absent or deficient antibody production and, in most cases, recurrent or unusually severe infection.

Replacement therapy for agammaglobulinemia and hypogammaglobulinemia in well-described immunodeficiencies like X- linked agammaglobulinemia (XLA)or common variable immunodeficiency (CVID) is important and life-saving. Other more genetically complex PIs, however, can also involve defects in antibody function that contribute to an increased susceptibility to infections. Over 250 distinct PIs are described so far , and with the arrival of whole-exome sequencing, new PIs still be discovered at a rapid pace .The effects of those newly described gene defects on the humoral immune system fully understood or qualified with currently commercially available tests of antibody level and performance . Therefore, indications of immunoglobulin therapy in various clinical presentations of immunodeficiency .

IVIG Dosage: single dose of 0.4-0.6gm /Kg every 3-4 weeks

KAWASAKI DISEASE

Kawasaki disease is that the commonest sort of vasculitis in children and if left untreated 1 / 4 will develop serious arteria coronaries aneurysms. the primary successful report of using IVIG for Kawasaki disease in 14 patients came in 1983 and since then meta-analyses have confirmed that high-dose IVIG is very efficacious in reducing arteria coronaries aneurysms when combined with aspirin. More recently, a Cochrane review analysed 59 trials and located that one high dose of IVIG (2g/kg) led to a discount in arteria coronaries aneurysms at 30 days. it is therefore of high priority for Kawasaki patients to be treated with IVIG and aspirin within 10 days of onset.

SIGNS AND SYMPTOMS OF KAWASAKI DISEASE



Figure 5; Signs and Symptoms of Kawasaki disease, Wikipedia

- IVIG Dosage: single dose of 2gm /Kg of body weight

IMMUNE IDIOPATHIC THROMBOCYTOPENIC PURPURA

Immune idiopathic thrombocytopenic purpura (ITP) all ages. Pharmacologic treatment of all children with ITP might not be required because most youngsters will spontaneously recover. Treatment is

typically provided to those children refractory disease. Commonly used therapeutic modalities include systemic corticosteroids, anti-D, IVIG, plasmapheresis, rituximab, and combinations of those. The effectiveness of IVIG in increasing platelet counts has been supported in numerous studies, leading to an FDA-approved indication of its use. Importantly, high-dose IVIG has been compared to systemic corticosteroids in randomized, multicentre trials, and was found to supply a clinically relevant advantage. Thus, at the present, IVIG remains an important presentation of immune-mediated thrombocytopenia. Anti- Rh(D) products have also been used as first-line therapy in patients with primary ITP. However, this product should be avoided in patients with pre-existing haemolysis and other risk factors because the administration of anti-Rh(D) has been rarely related to severe intravascular haemolysis, disseminated intravascular coagulation, and acute kidney failure. Corticosteroids, IVIG, or anti-D immunoglobulin are considered first-line therapies for ITP.

IVIG Dosage: single portion of 0.8-1gm/Kg of weight (youngsters)

IVIG Dosage: single portion of 1gm/Kg of weight (Adult)

GUILLAIN-BARRE' DISORDER

GBS might be a polyradiculopathy described by intense dynamic engine shortcoming of the limits, bulbar and facial musculature, and here and there tactile or autonomic brokenness. It's idea to result from immunologic pulverization of myelin or Schwann cells inside the fringe framework apprehensive. In this manner, it's regularly treated with corticosteroids, PE, and IVIG. Information from the essential enormous scope, randomized, open mark, controlled preliminary of IVIG (0.4g/kg/day for five days) versus PE recommended that the clinical results were at least practically identical. A multicentre, randomized, blinded, controlled preliminary including 383 patients from Europe, Australia, and North America uncovered no huge contrasts in disability grade between patients treated with PE, IVIG, or PE followed by IVIG. The addition of methylprednisolone (0.5g/day for 5 days) after a course of IVIG did during a multicentre, randomized, twofold visually impaired, fake treatment controlled study in 233 patients. Several other studies that have compared indicated comparable discoveries, however patients weren't constantly randomized, and agents weren't blinded to the medicines. A logical audit of information from randomized preliminaries uncovered no huge contrasts in any of the outcome gauges among IVIG and PE. None of the medicines altogether diminished mortality. A few Cochrane surveys have given moderate-quality proof that, in extreme illness, IVIG began inside 2 weeks from onset hastens recovery as much as does PE.

IVIG Dosage: single portion of 0.4gm/Kg/day for five days

CHRONIC IDIOPATHY DEMYELINATING POLYNEUROPATHY

CIDP is portrayed, by, tangible misfortune, and areflexia. In opposition to the intense idea of GBS, indications of movement happen over months, with immunologic harm focusing on the myelin sheaths of fringe nerves. It's been verifiably treated with corticosteroids, PE, or, in RCTs indicated that IVIG improved inability inside 2 a month and a half contrasted and fake treatment and had adequacy practically like that of PE and prednisolone, despite the fact that with an expanded personal satisfaction. The quality portion is 0.4 g/kg/day for five days, however relapsing patients this dose may need to be repeated every 2-8 weeks to deal with progress."

IVIG Dosage: single portion of 0.4gm/Kg/day for five days

MULTIFOCAL MOTOR NEUROPATHY

A few randomized, twofold visually impaired, fake treatment controlled, hybrid clinical preliminaries have demonstrated IVIG to supply adequacy in treating MMN, an interminable incendiary condition that specifically influences the engine nerves (particularly the spiral, ulnar, middle, and standard peroneal). IVIG is presently FDA-affirmed to be utilized in treating MMN. utilizing a dose of 0.4-0.5g/kg/day for 5 consecutive days, >80% of patients had no steady impact on IgM hostile to ganglioside M1 counter acting agent titers.

IVIG Dosage: single portion of 0.4gm/Kg/day for five days

MYASTHENIA GRAVIS

The advantage in MG of IVIG (0.4 g/kg/day for 3-5 days) resembled that of PE in 2 randomized, relative investigations, with a lessening acetylcholine receptor immunizer fixation in one examination and accordingly the evaluated MG clinical score inside the However, Class I proof that IVIG and PE have tantamount adequacy and are comparatively endured in grown-up patients with moderate to serious MG inside about fourteen days of treatment was as of late announced, and in this way the main factor foreseeing reaction to treatment was gauge illness seriousness. In any case, a randomized, fake treatment-controlled investigation did not show a major impact following a month and a half of IVIG treatment. IVIG was considered of conceivable advantage in myasthenic emergencies

IVIG Dosage: single portion of 0.4gm/Kg/day for five days

INDIA MARKET OVERVIEW

India is that the seventh largest country in terms of area and therefore the second most populous country within the world. it's a plethora of natural resources and assets just like the rich agricultural lands, deep gold and gemstone mines, a number of the most important rivers, and, most significantly , its 1.2 billion people, which hold huge potential in additional ways than one Plasma is one such resource, which India could have in abundance, but its potential remains unrealized. Being the youngest and second most populous country, India features a huge blood/plasma donor base which may greatly contribute to the local, also as, global plasma product industry .

Unfortunately for a spread of reasons, this potential is not explored and tapped to its fullest. The challenges within the Indian plasma industry are intense and prevalent in the least the stages right from the beginning until the top. India collects about 10 million of blood at quite 2700 blood banks across the country .“These blood banks are publicly, private, charitable, and hospital settings. As per the Drug and Cosmetic Act, each unit of blood is tested for HIV-I and HIV-II antibodies, Malaria, Syphilis, hepatitis B surface antigen and hepatitis C virus antibody and componentized within 6 hours of collection .

INDIAN OUTLINE

India needs about 900,000 litres of plasma proteins per annum. the general demand of varied plasma derived products is depicted within the table 3 Import of size of those products in year 2014-15 and their cost .

The Indian commercial centre for intravenous immunoglobulin (IVIG) items and treatments is going during a positive course because of a few imaginative systems and focal points it offers to clinicians around the world".

"The rising patient pool influenced by immunological and neurological clutters, mounting geriatric populace, and rising creation of IVIG items additionally are relied upon to have a major positive effect on market's future development possibilities".

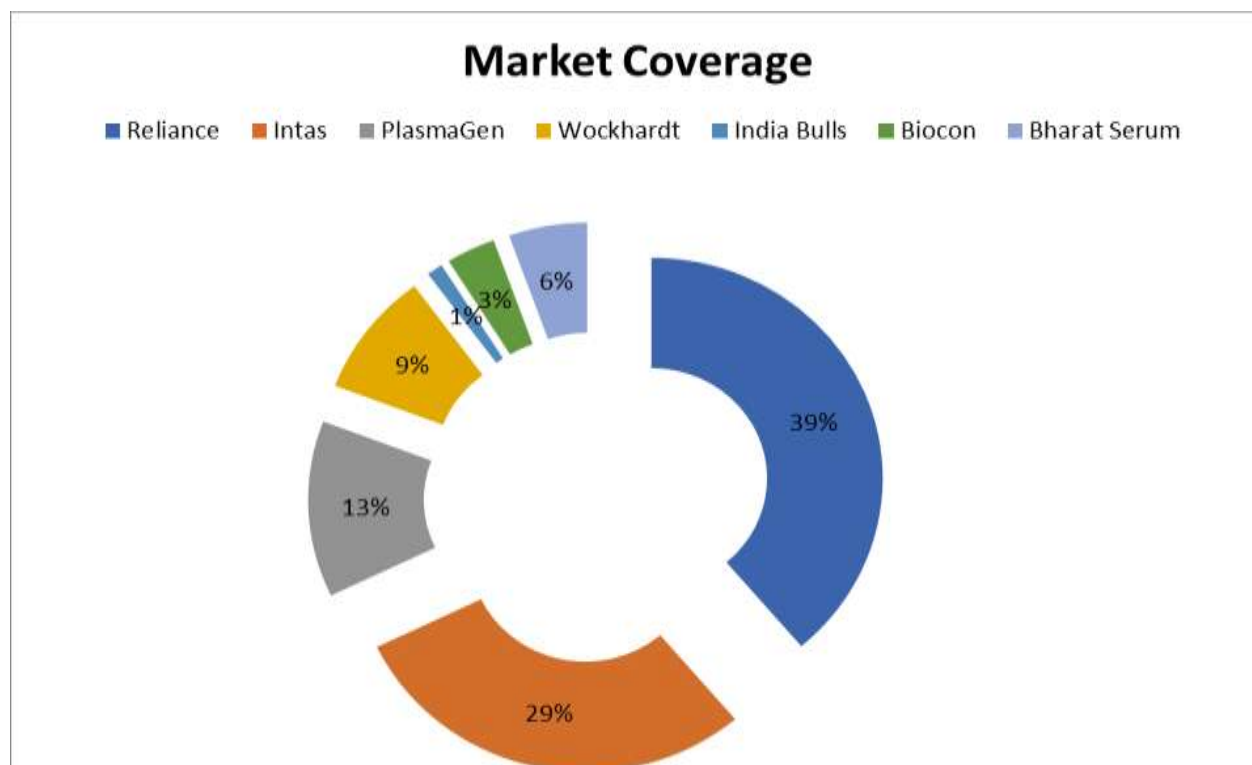


Figure 6; [grandviewresearch.com/industry-analysis](https://www.grandviewresearch.com/industry-analysis)

1. Highest number of market share in terms of percentage is contributed by the Reliance the on subsequently Intas comes on second place which contributes around 29%.
2. PlasmaGen contributes around 13% of market share in immunoglobulins market.
3. Then Wockhardt and subsequently India bulls and Bharat serum are the contributors of the market.
4. 3% of market share is hold by Biocon and the others

LITERATURE REVIEW

Plasma proteins have an honest range of therapeutic applications in various diseases for all age of groups. As many of these therapies are repetitive and have no substitute, the regular availability of plasma therapeutics is essential .“The relatively high cost is said to availability of fantastic quality plasma including relatively high fractionation charges thanks to the state of the art fractionation technologies and quality assurance standards involved, ensures that there exists a high level of correlation between purchasing power parity (and consequently per capita healthcare expenditure) and demand for top end therapeutic product like plasma derived proteins .

A related development has been the introduction of recombinant product as a substitute to plasma-derived proteins, for therapeutics purposes (for products like antihemophilic factor & Factor IX) recombinant products meet higher safety standards as compared to plasma derived proteins (the former having been cloned synthetically, as against the latter having been sterilized using virus inactivation methods). However, recombinant technology makes these products much more expensive than plasma derived products. Also, future usage of recombinant products has been found to cause certain immunological effects which is proving to be very discouraging of the long run for recombinant substitute for plasma proteins .“According to a study conducted by market research bureau- only developed countries are gradually moving toward usage of recombinant products but the marketplace for plasma-derived proteins is growing continuously within the developing countries like India .

In its 2016 report, blood products and blood testing markets, Kalorama indicates that the strong promotion of blood donations on behalf of collection agencies, in conjunction with synthetic blood products, is scarcely meeting the demand for this industry's products and this continued need is driving up blood prices. Stored and distributed blood, originally developed to treat war casualties, is now used primarily for testing and transfusions. Kalorama finds quite 50% of transfusions occur in patients over the age of 65, and thus attributes the expansion of the blood products market to an aging population, which is inherently driving up prices .

According to John M. Curling (consultant)- The Indian market is simply 0.25% of the worldwide plasma products market. Plasma fractionations in India face a significant challenge with low price imports .

As per PRLog (Press Release)- the worldwide plasma products market has quite doubled over the quantity 2015-22 because of increase in demand and costs of plasma products. The worldwide plasma supply has increased but not at the same pace because the demand for the plasma products. the worldwide plasma products market has been segmented supported plasma proteins like immunoglobulin, albumin, clotting factors and other proteins. The IVIG or Immunoglobulin market is that the most important segment of the plasma products market having quite one-half share of the market. The IVIG and Albumin segment has been real drivers of the worldwide plasma products market as they witnessed double-digit rate of growth over the previous few years .

According to Global plasma Market Report: 2011 Edition-Recent scientific studies are leading to the invention of latest proteins within the plasma and their uses to treat hitherto unresolved medical conditions. The marketplace for plasma products has shown continuous growth within the past years growing at a CAGR of around 10% during 2001-10 and is projected to expand steadily within the years to come .

The use of plasma products in developed countries is well established; however, their demand in emerging countries, like China and India is persistently on the rise. With scientific, technological advances in medical research in developed and developing countries, there's now much room for increased usage of IVIG. New indications are being explored whereby various plasma products are being put to new uses for treatment of old and new diseases. Besides this bleeding disorders and related diseases are growing requiring increased usage of plasma products. Ageing population is on the constant rise worldwide and thus the aged people are vulnerable to develop diseases requiring more demand of blood derivatives. Furthermore, the process is additionally responsible for higher utilization of blood plasma derivatives. Also, new proteins are being discovered in plasma, which are being put to new uses for treatment of various diseases .

when the first plasma-derived clotting factor concentrates were introduced within the late 1960s and 1970s, they revolutionized the treatment of bleeding disorders. People with haemophilia could not

only anticipate to how longer lifespan, apart from the first time they were free to travel, work and set about their everyday lives without the gnawing fear of uncontrolled bleeds .

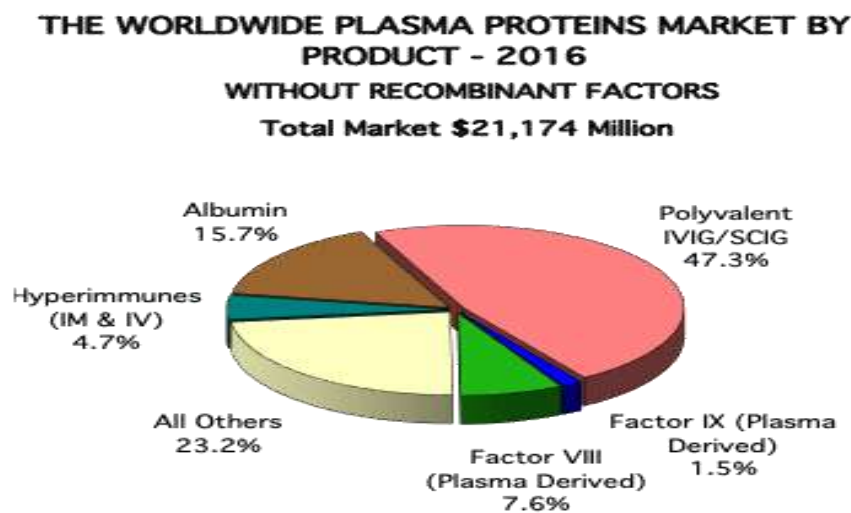


Figure 7;Source:marketingresearchbureau.com/plasma-industry

PLASMA PROCUREMENT AND SAFETY

To acquire enough crude materials to give plasma items, numerous litres of plasma are required yearly. assortment of the plasma is acquired by isolating plasma from red a great many bloods gift, for instance at a Red Cross Blood Drive. This plasma is known as "recuperated plasma" because the objective of the blood assortment association it to encourage red cells and platelets, and plasma could likewise be a result. Another sort of plasma for fractionation, called "source plasma," is created by devoted plasma assortment focuses, which gather plasma from contributors through plasmapheresis machines (these machines extricate blood from the benefactor, keep the plasma and return the red cells to him/her). inside the us and a couple of different nations, plasma benefactors get a money remuneration for their time and endeavours as they will give as often as possible, while blood givers are urged to give by methods for a token non-financial impetus.

It is significant for each organization to have access to an adequate amount of plasma to fulfil its creation goals. to this end, the huge, global plasma organizations (the fractionators) own most the plasma assortment focuses inside the U.S., where they gather most of the plasma they need. Source plasma is furthermore gathered in critical amounts in China, Germany, Austria, Czech Republic, and Hungary. Together, the first significant three organizations (CSL Plasma, Grifols and Bio Life (Shire)) gather over 80% of the entire U.S. source plasma for fractionation.

As of late, the amount of plasma focuses has expanded altogether inside the us , from yet 500 out of 2015 to more than 650 out of 2017, mirroring that the needs for remedial plasma proteins is foreseen to even now develop inside the moving toward years.

A comparative pattern has been seen in Europe in spite of the fact that the guidelines set up inside the area by and large don't permit as enormous volumes of plasma to be given yearly or paid the most extreme sum by an individual contributor as inside the us , constraining the development of plasma

assortments for fractionation.

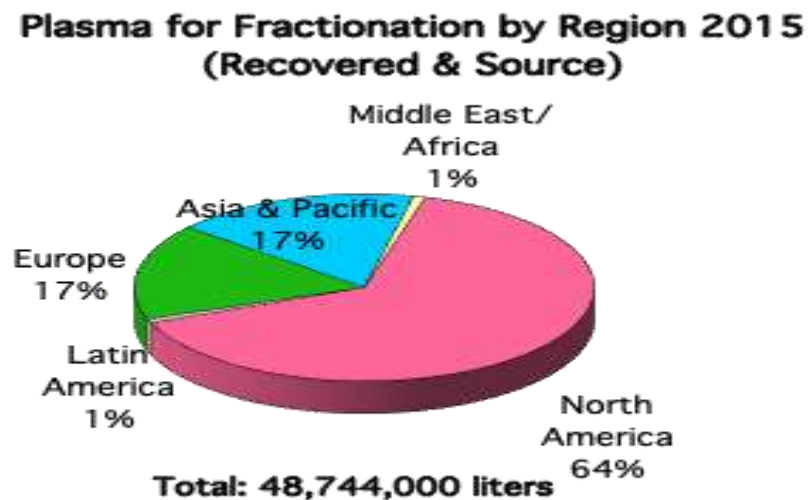


Figure 8; Source: plasma-economics-concept-of-plasma-market-

PLASMA SAFETY AND VIRAL INACTIVATION

Following instances of infection transmission from blood and blood items inside the 1980's, particularly HIV, the plasma business has actualized severe controls to shape sure that lone plasma from non-tainted contributors is utilized to make plasma items. a choice of measures is acquainted with increment the wellbeing of plasma, assortment of them presented by the Plasma Proteins Therapeutics Association (PPTA), the business plasma industry gathering. a gaggle of measures proclaimed by PPTA is that the "Quality Plasma Program" (QPP) which incorporates isolate of givers' first plasma gift, plasma stock holds, contributor determination and gift screening by macromolecule testing (NAT) for HIV, hepatitis B and C.

Notwithstanding choosing benefactors and testing plasma for explicit infections, the plasma business has built up a few viral inactivation procedures to ask to forestall known and obscure infections and microscopic organisms inside the fractionation and sanitization forms. These methods incorporate dissolvable/cleanser washes, low pH, warmth, nanofiltration, and chromatography. These strategies lessen the threat of any infection transmission from a plasma item by a few sets of size. Organizations and scholastic specialists despite everything look for new strategies for viral inactivation to additionally improve the security of plasma-inferred items.

ITEM PRICING AND VALUE STRUCTURE

The plasma business' cost structure contrasts from the customary pharmaceutical or biotechnology enterprises. the value of plasma – the plasma business' staple – is commonly over the value of the staple s used inside the typical pharmaceutical or biotechnology ventures. Plasma is cherished on the grounds that gathering plasma could likewise be a complex and sensitive activity, including an outsized labour because of the need to gather plasma from a huge number of individuals. Segments of this expense incorporate plasmapheresis hardware and exceptionally qualified staff, givers got the chance to give plasma as often as possible and a lot of givers are required by the organizations, complex coordination's, severe guidelines, and contributor remuneration. As referenced, it is by and large evaluated that plasma, the staple, speaks to generally half of the entire expense to give plasma-based remedial proteins.

For a patient, the yearly expense of treatment utilizing a plasma-based item may surpass \$200,000, speaking to an impediment to their acknowledgment in numerous nations albeit noteworthy advancement has been of late. As medicinal services spending plans despite everything be feeling the squeeze, support and mindfulness are utilized to affirm that patients needing these treatments approach them.

RIVALRY FROM NEW TECHNOLOGIES

In the previous four years assortment of most recent recombinant and non-factor items are presented inside the zone of haemophilia treatment, speaking to expanded rivalry to plasma-determined coagulation factors.

In the mid 1990's, the essential recombinant antihemophilic factor was presented. From that point forward, numerous recombinant proteins are created, including recombinant factor VIIa, factor IX, fibrines, Willebrand factor, egg whites, antithrombin-III, C1 esterase inhibitor (C1-INH) and thrombin. Extra recombinant proteins are a work in progress including recombinant fibrinogen, alpha-1 antitrypsin, et al

In 2014, the essential expanded half-life recombinant antihemophilic factor and IX items were affirmed inside the U.S. With an improved bioavailability over their plasma-inferred rivals, these items gave higher trough levels in hemophilia patients, permitting them to implant the product less much of the time, which upgraded the patients comfort, decreasing their reliance on visit factor imbuelements. the stockpile of those new recombinant items expanded the quantity of items accessible for hemophilia A and B treatment, bringing about value disintegration of the less propelled items, including the plasma-inferred, especially outside the us

In late 2017, Roche's Hemlibra, a bi-explicit neutralizer, was affirmed by the FDA and consequently the EMA (February 2018) for the treatment of hemophilia A patients with inhibitors antibodies to antihemophilic factor. In October 2018, Hemlibra was endorsed inside the U.S. for the treatment of all hemophilia A patients. since it just requires one subcutaneous medication mixture week by week every other week, or month to month, relying on the patients seriousness, it's relied upon to acknowledge quick acknowledgment, as proposed by its ubiquity inside the initial scarcely any months of its accessibility inside the inhibitor sub-section inside the U.S. Regardless, Hemlibra will without a doubt cause significant moves in hemophilia treatment inside the following scarcely any years. furthermore, quality treatment for hemophilia A and B is likely going to be economically accessible inside the mid-2020s, speaking to a "fix" for the illness after just a single implantation. the common toughness of quality treatment stays obscure, yet signs are that it'll last at least two or three years and perhaps a significant decade. Quality treatment will in the end cause an interference inside the commercial centre for hemophilia treatment, however its take-up will be at first be ease back and be limited to grown-ups' extreme patients at first.

As coagulation factors made up of plasma have now been consigned to an optional situation inside the hemophilia care showcase, immunoglobulin has gotten always critical to continue the financial reasonability of the plasma business, close by egg whites. to the current day, the market pre-prominence of intravenous and subcutaneous immunoglobulin (IgG) in treating assortment of immune system maladies was fantastic. Be that as it may, a few biotechnology organizations (Argenx, UCB, Momenta, and so on.) have as of late grew new monoclonal antibodies (against FcRn specialists) or recombinant items (recombinant trivalent IgG1 Fc multimers)that impersonate the resistant modulatory method of activity of IgG inside the treatment of certain maladies, as ITP, Pemphigus Vulgaris, MMN, CIDP and myasthenia . though these items are at a beginning period of advancement they may start to affect the IgG advertise inside five years on the off chance that they persuade be protected, useful, and cost serious. At first, they're relied upon to advance IgG, rather than ripping

apart it, even as the recombinant components did inside the zone of hemophilia care inside the previous 20 years.

Recombinant egg whites were just popularized in Japan and didn't increase huge piece of the overall industry since its restrictive cost and nonappearance of clinical prevalence looked at over plasma-inferred egg whites. Therefore, it had been in the end pulled back from the market and has not been re-presented since. Non-plasma-based, non-biotech plasma volume substitution arrangements, similar to starches are on the commercial centre for assortment of decades at much lower costs than human egg whites. While they speak to significant modest choices for spending plan compelled clients, their adequacy and especially their wellbeing don't coordinate human egg whites in most clinical signs.

NEW PRODUCTS FRACTIONATED FROM PLASMA

Following a decades-in length break, the industry is on the cusp of presenting new plasma proteins. Plasminogen is in late stage improvement by Kedrion and Prometic, CSL Behring is investigating reconstituted HDL from plasma, and partnerships looking to market novel proteins are investigating new plans of action. very 2,000 proteins exist in plasma, with just 15-20 marketed, leaving the greater part of potential proteins unexploited for commercialization. it's impossible that a substitution protein will override IgG in light of the fact that the plasma business driver, yet extra proteins will add to the business' financial suitability and advantage new patients with sheltered and effective plasma treatments, except if prevalent biotechnology-determined medications and quality treatment choices are regularly evolved. Until such time, giver plasma will in any case be required in developing amounts.

NEW INDICATIONS FOR PLASMA-BASED PRODUCTS

- Other plasma-based items are under scrutiny for additional infections or signs, including:
- IVIG in different neurological infections (Myasthenia Gravis, Neuropathic Pain, Chronic Fatigue Syndrome, Post-Polio Syndrome, Dermatomyositis, and so on.),
- Albumin in Cirrhosis, infection, Alzheimer's Disease, Malaria and Sepsis,
- Alpha-1 antitrypsin in lung Graft-versus Host Disease (GVHD), Lung wounds, and sort 1 Diabetes, and
- Fibrinogen in aneurysm medical procedure with fibrinogen lack,
- C1 INH for counter acting agent intervened dismissal in organ transplantation.

OBJECTIVE

1. To review the worldwide growth pattern of the products supported plasma derived therapy

Extent of study:

- To comprehend development of the product bolstered plasma determined restorative proteins and its signs.
- To study the current situation of item bolstered plasma inferred restorative proteins and its future markets.

2. To study the Indian scenario on protein treatments and new headways during this remedial zone.

Extent of study:

- To comprehend the market chiefs and their piece of the overall industry in local market.
- To study the new advancements in the immunoglobulin therapy areas.

RESEARCH METHODOLOGY

Study span: 3 Months

Data types: Quantitative and Qualitative data

Information Collection Tool: Secondary Data gathered (Company Annual Reports, different research articles and distributions). Information was triangulated utilizing auxiliary methodology.

Secondary Data: the ensuing are a few different ways of gathering optional information –

- Books
- Records • Biographies
- Newspapers
- Published censuses or other measurable information
- Data files
- Internet articles
- Research articles by different scientists (diaries)
- Databases, and so on.

Limitations of Secondary Research.

It is easy to find and collect secondary data., However there is some limitations also that are below.

- Secondary data can be general and vague
- The information and data may not be accurate. The source of the data must always be checked
- The data maybe old and out of date
- The sample used to generate the secondary data may be small

Ethical Consideration

- This research was completed with the appropriate research guidelines.

- Enough time was given to the respondent of the study so that they can depict their true view on research questions.
- Data was not manipulated from the secondary research, I had taken the exact figures from the resources
- The disclosure of respondent identity was based on their permission where if they are not willing to disclose identity, their identity was exhibited.

Global Trends: Intravenous Immunoglobulin usage

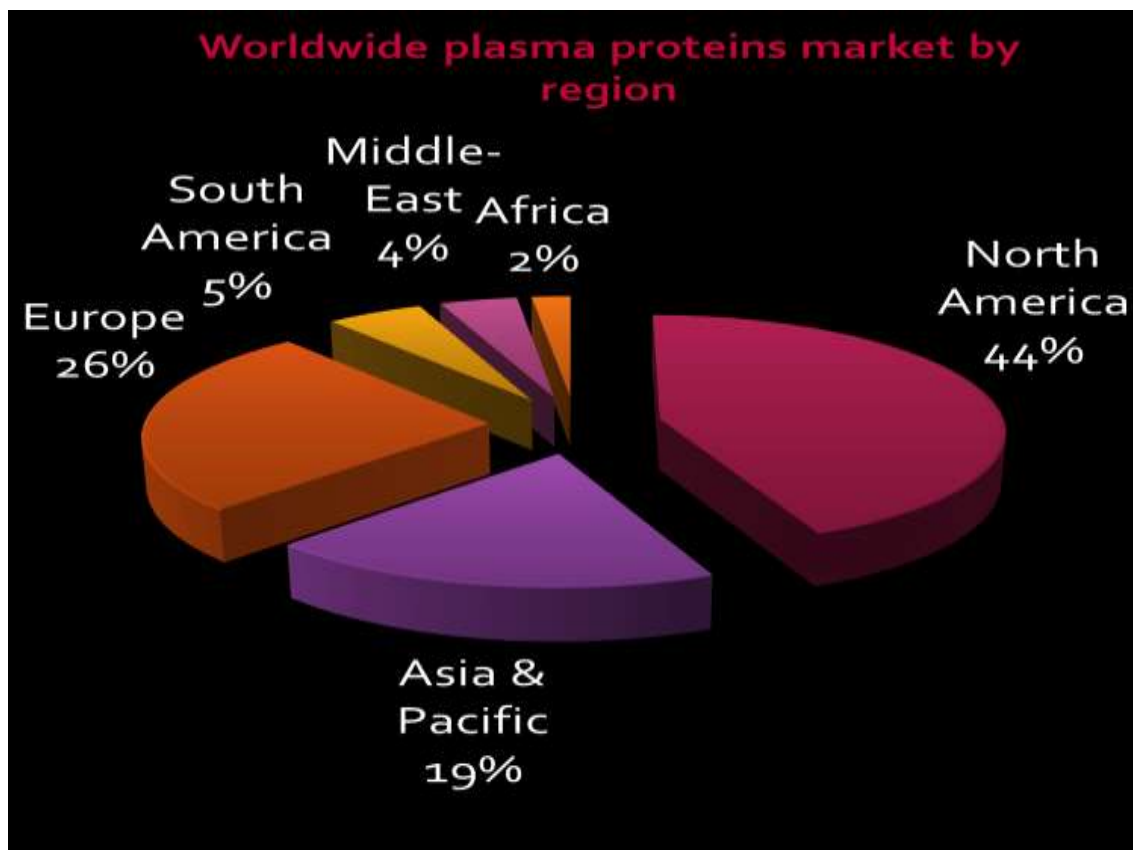


Figure 9; Worldwide plasma proteins market by region/Industry Source

Interpretation

- Different Proteins of plasma are used for treatment of various diseases like Haemophilia, Immunodeficiency etc.
- Intravenous immunoglobulin (IVIG) is one such plasma derivative comprising polyvalent IgG (immunoglobulin G)
- The global demand of plasma products varies geographically due to factors like Product awareness, Availability, Demographic trends.

IVIG usage portfolio

Global IVIG market by Indication(\$ million)-2015

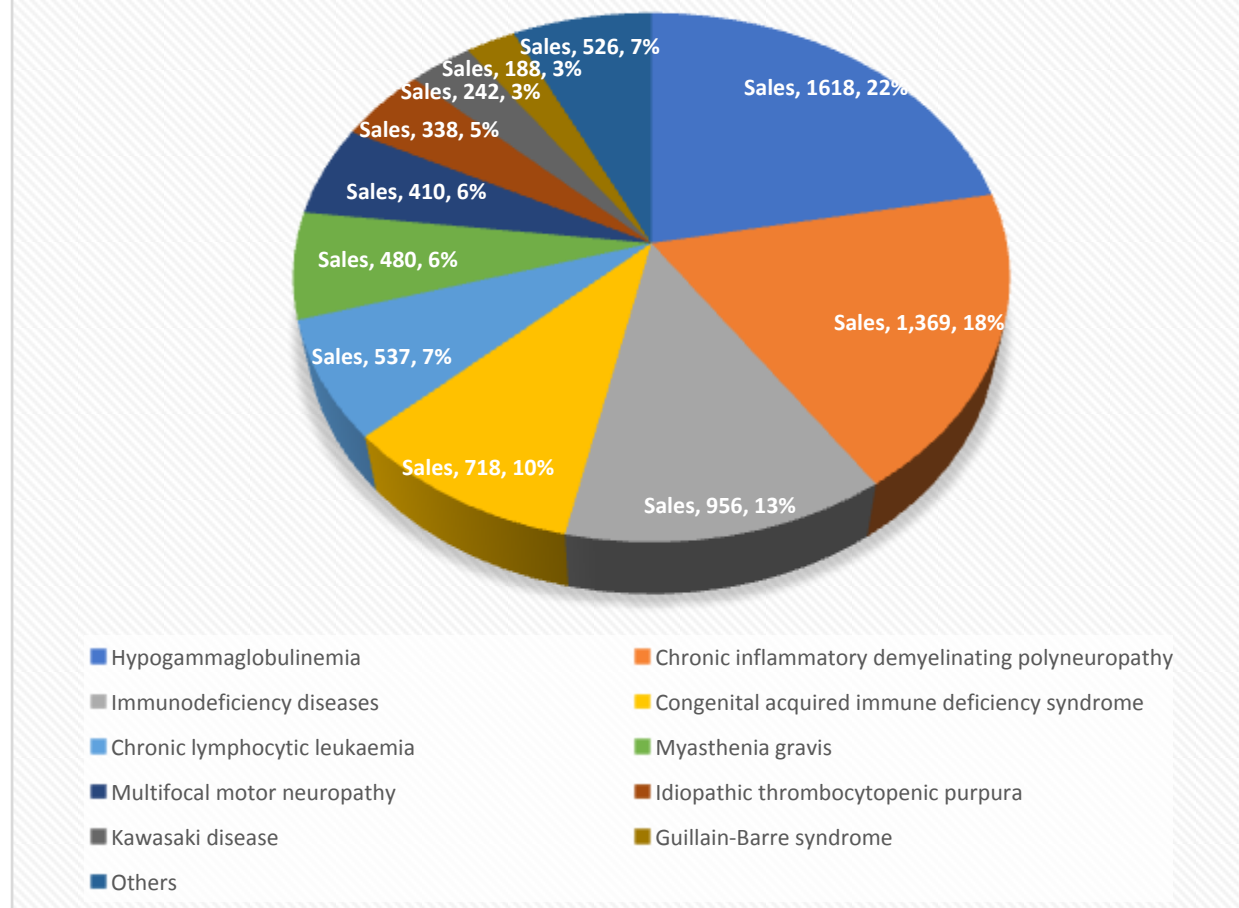


Figure 10; Global IVIG Market by indications and Industry Source.

Interpretation:

- Hypogammaglobulinemia and chronic inflammatory demyelinating polyneurathy has covered the highest market share in comparison to the other ones.
- Congenital acquired immune deficiency syndromes takes the third place in terms of acquired disease pattern globally.
- While Myasthenia gravis and Idiopathic thrombocytopenic purpura holds the subsequent ranks.

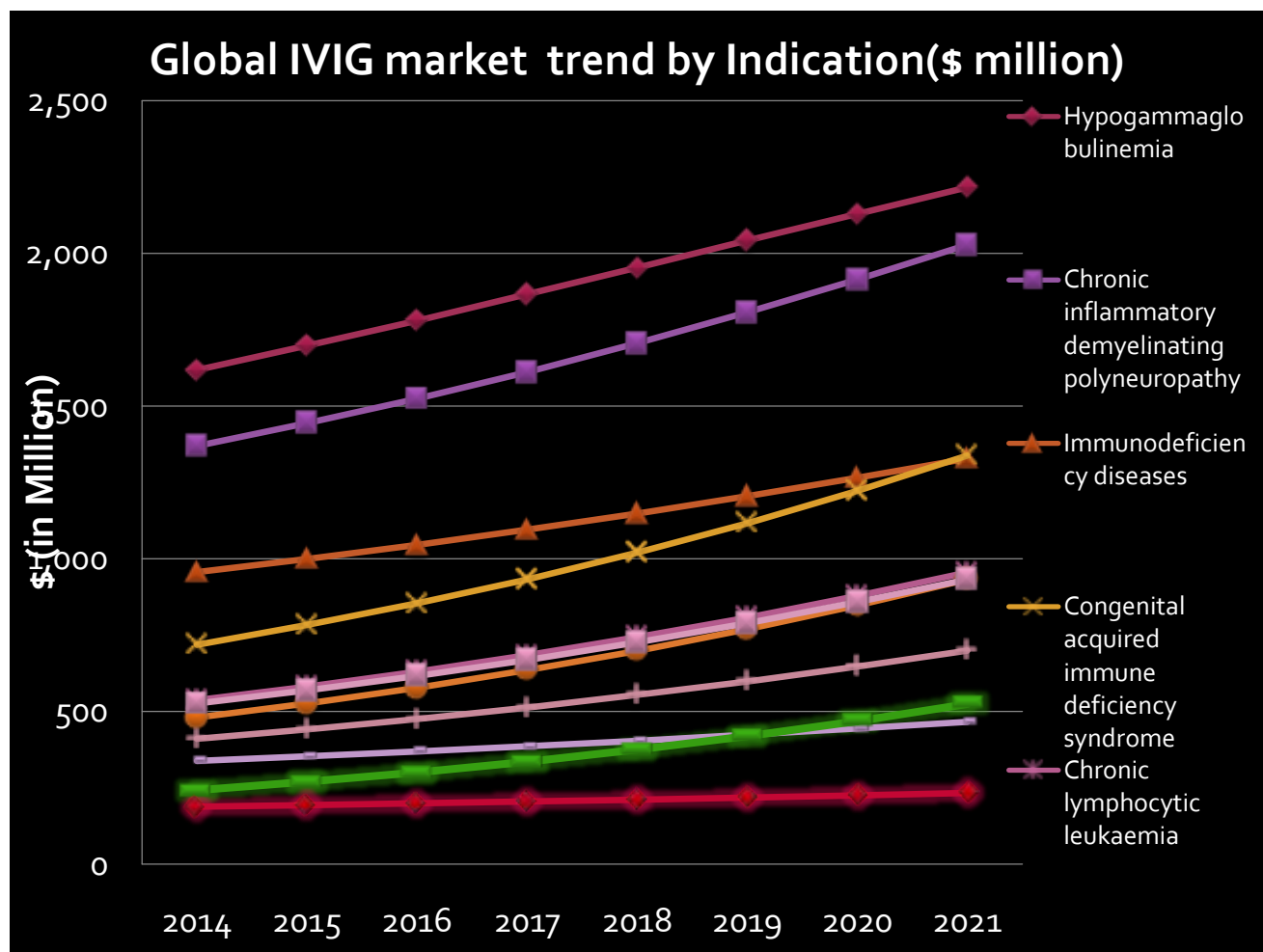


Figure 11; Global IVIG Market trend by indication, Industry source

Interpretation:

- Trends of different indications are shown world wise year wise in millions, whereas hypogammaglobulinemia and chronic inflammatory demyelinating polyneuropathy are high in comparison to other indications.
- Chronic lymphocytic leukemia shows the trends slightly fluctuating in comparison to the congenital acquired immune deficiency syndrome in the subsequent years

Global IVIG market by Indication(\$ million)-2021

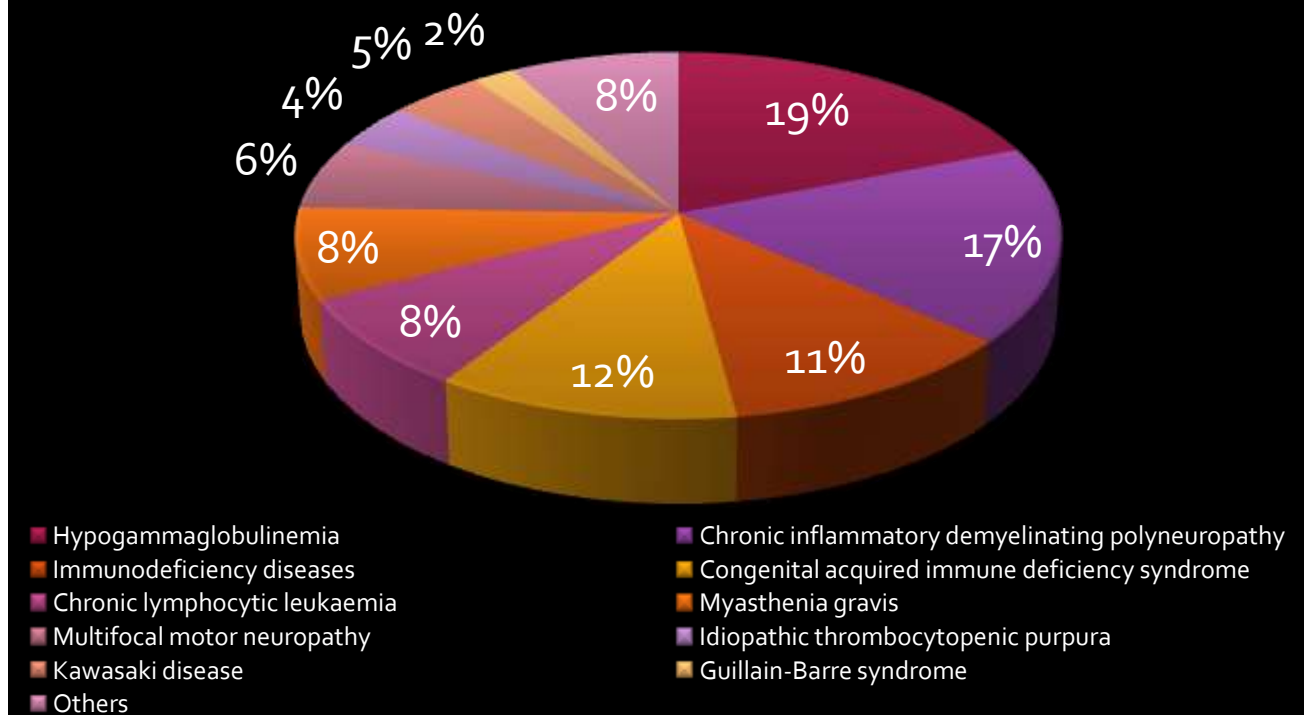


Figure 12;Global IVIG market by indications2021-

Global IVIG market by indications -2021

Interpretation:

- The graphs indicate the global IVIG market by indications in the upcoming year. Major part 19% has been occupied by the hypogammaglobulinemia and 17% contributes chronic inflammatory demyelinating polyneuropathy. whereas 12% contributes to the congenital acquired immune deficiency syndrome.

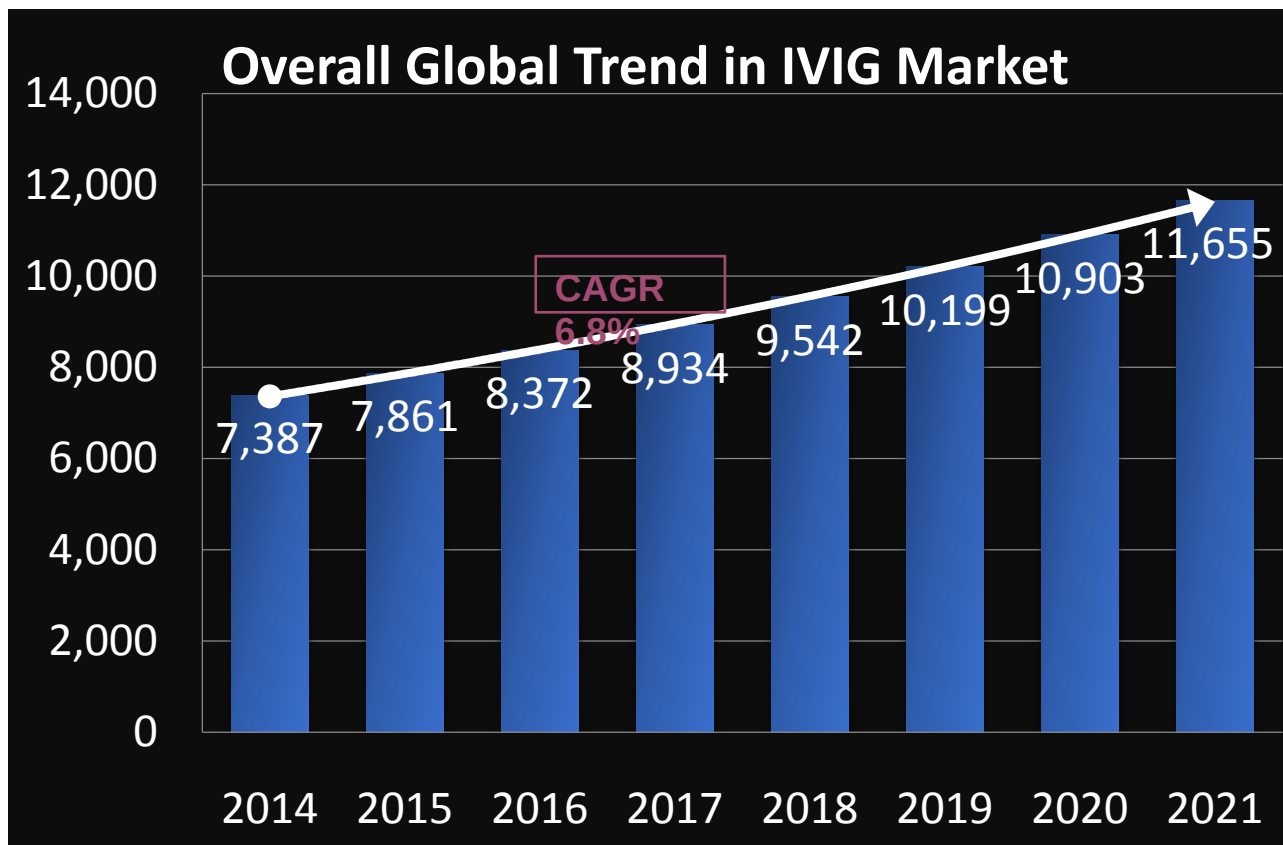


Figure 13:global-market-share-ivig-by-leading-companies/global report

Overall global trend in IVIG market

Interpretation:

- The CAGR market of IVIG is 6.0% and around 11,665 million market is projected in year 2021. Whereas current market is projected as 10,903 million in 2020 year.
- From 2014 to the upcoming year 2021 Or the current year, there is a tremendously growth in the overall market of the IVIG. The reason behind this is the increase in the awareness regarding to the rare diseases as well increase in the prevalence of these numbers.

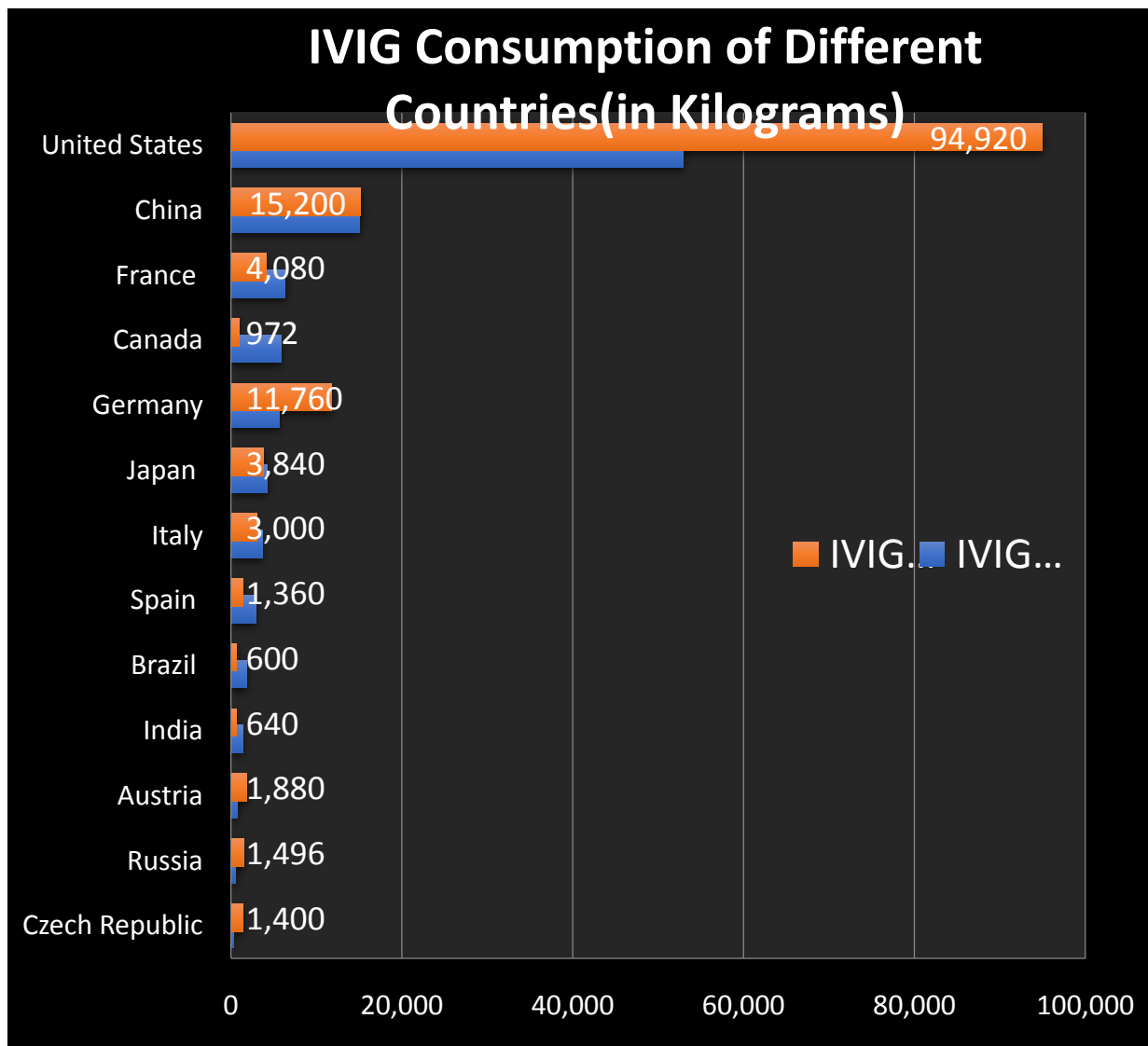


Figure 14: <https://www.statista.com/statistics/758041/global-market-share-ivig-by-leading-companies>

Consumption > Production

Self Sufficiency Ratio = 46%

International variations intake of IVIG may be explained by means of:

- Market penetration of IVIG remedy, physician's consciousness & prognosis
- Use for chronic illnesses remedy vs. Acute conditions
- Competitive remedies and pharmaceutical tablets
- Absence of regulations for and repayment of off-label IVIG use
- Product advertising, logo opposition
- Influence of patient's advocacy organizations & Funding

The worldwide marketplace for Intravenous Immunoglobulin (IVIg) is projected to exceed US\$eleven.1 billion by way of 2020, pushed via the rise in the superiority of immunoglobulin deficiency. The United States represents the most important market global, followed with the aid of Europe. Asia-Pacific, led by using China, is forecast to witness sturdy boom pushed by favourable demographics, rising consciousness over the efficacy of plasma protein treatment options, and increasing investments in healthcare infrastructure improvement. China, with its great unmet clinical wishes, offers robust opportunities for growth

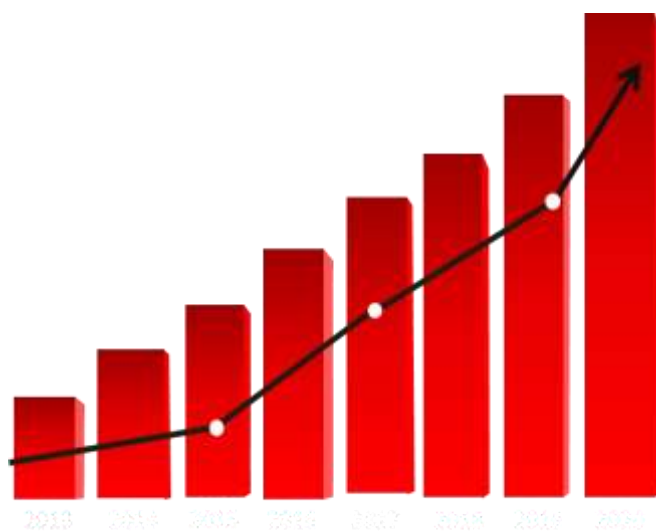


Figure 15; Source: The Marketing Research Bureau, Inc. (Orange, CT)

- CSL Limited
- Grifols
- Baxter
- Bharat Serums and Vaccines Limited
- Biotest AG
- Kedrion S.p.A
- LFB Group

CONCLUSION

MARKET DRIVERS & CHALLENGES

DRIVERS CHALLENGES

- Growing Incidences of Bleeding Disarranges
- Use of IVIG in Therapies for Neurological Disorders
- Approval for Use in New Disease Signs
- Subcutaneous IG Formulations Addition Therapeutic Foothold
- Strong Capital Spending in Human services in Developing Countries
- High Treatment Cost
- Stringent Government Regulations
- Risk of Side Effects

INTERPRETATION

The global immunoglobulin market is estimated to be \$11 billion in 2020, with growth of 6.8%, primarily thanks to improved diagnosis and more off-label indications.

- By region, the most important share of immunoglobulin market is in North America at the present, US, immediately followed by Europe.
- In 2014, global immunoglobulin market was dominated by CSL and Grifols with high percentage of market share thanks to each one's higher capacity to serve the increased demand for immunoglobulin products.
- Despite the high cost of IVIG therapies, the demand for these products has increased in every region, and it is expected to still grow within the years to return.
- Also, the usage of plasma products (IVIG, etc.) varies widely from country to country
- For Instance, in India SSR is sort of low (46%) which shows the presence of untapped opportunities in IVIG segment which may be catered to.
- Especially in diseases like Kawasaki although having lower market at the present comparatively but show a better forecasted CAGR of 11.7% necessitating the necessity to serve the segment in future.
- GBS on the opposite hand seems to possess a low market price and a coffee forecasted CAGR of mere 3%.

OUTCOMES OF THE STUDY

- Highest number of market share in terms of percentage is contributed by the Reliance the on subsequently Intas comes on second place which contributes around 29%.
- PlasmaGen contributes around 13% of market share in immunoglobulins market.
- Then Wockhardt and subsequently India bulls and Bharat serum are the contributors of the market.
- 3% of market share is hold by Biocon and the others
- The CAGR market of IVIG is 6.0% and around 11,665 million market is projected in year 2021. Whereas current market is projected as 10,903 million in 2020 year.
- From 2014 to the upcoming year 2021 Or the current year, there is a tremendously growth in the overall market of the IVIG. The reason behind this is the increase in the awareness regarding to the rare diseases as well increase in the prevalence of these numbers.
- The global IVIG market by indications in the upcoming year. Major part 19% has been occupied by the hypogammaglobulinemia and 17% contributes chronic inflammatory demyelinating polyneuropathy. whereas 12% contributes to the congenital acquired immune deficiency syndrome.
- Trends of different indications are shown world wise year wise in millions, whereas hypogammaglobulinemia and chronic inflammatory demyelinating polyneuropathy are high in comparison to other indications.
- Chronic lymphocytic leukemia shows the trends slightly fluctuating in comparison to the congenital acquired immune deficiency syndrome in the subsequent years
- Hypogammaglobulinemia and chronic inflammatory demyelinating polyneurathy has covered the highest market share in comparison to the other ones.

- Congenital acquired immune deficiency syndromes takes the third place in terms of acquired disease pattern globally.
- While Myasthenia gravis and Idiopathic thrombocytopenic purpura holds the subsequent ranks.
- Different Proteins of plasma are used for treatment of various diseases like Haemophilia, Immunodeficiency etc.
- Intravenous immunoglobulin (IVIG) is one such plasma derivative comprising polyvalent IgG (immunoglobulin G)
- The global demand of plasma products varies geographically due to factors like Product awareness, Availability, Demographic trends.
- Hypogammaglobulinemia and chronic inflammatory demyelinating polyneurathy has covered the highest market share in comparison to the other ones.
- Congenital acquired immune deficiency syndromes takes the third place in terms of acquired disease pattern globally.
- While Myasthenia gravis and Idiopathic thrombocytopenic purpura holds the subsequent ranks.

LIMITATIONS

- Difficulty for those with poor venous access
- Patients with recurrent systemic reactions
- Requires hospitalization or a good homecare programme

CONCLUSION

- Price of the Product
- Lack of data availability
- Lack of diseases diagnosis

RECOMMENDATION

- This study shows that paediatricians, obstetricians and general surgeons now prescribe plasma products more often. There is more room to shoot in this segment because there is less competition in this segment so we can create our own market.
- An appropriate advertising plan must be developed to increase awareness of the use of plasma products. The advertising plan must be focused; and must address the main problem of the target customer through the organization of seminars, conferences etc. Target customers need to be aware of the benefits of plasma products.
- Brand are one of the most important components of positioning and it must be remembered that doctors can easily call them. An effective positioning strategy must be designed so that doctors can be drawn on behalf of the brand.
- Haematologists, neurologists and oncologists use this product in newer and less frequent indications. Therefore, plasma products must be actively promoted for this area of specialist doctors. Medical literature must be available for doctors to inform them of the latest advances in the use of plasma products in more recent indications.

- Target customers must be correctly identified and characterized based on heavy, moderate and low users.
- Price is an important criterion for the success of a brand, so the price must also be economical because many doctors depend on the price factor when prescribing drugs, especially in public hospitals.

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