A study on competitive Market Analysis of the Plasma Industry for strategic decision making

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Under the guidance of Dr. Dhirendra Kumar

- **AIM:**
- To analyse the competitive market of Plasma Industry for Strategic decision making

- **OBJECTIVE:**

i. To study the Competitive Landscape of plasma industry
ii. To analyze the Opportunities in Plasma industry
iii. To determine the key products and players in the Plasma Industry

- **METHODOLOGY:**
- Study design- Descriptive and Exploratory research
- Study type- Secondary research
- Period of Study – February 2020 to May 2020
- Study Area- Global plasma industry
- Data-collection- Secondary data: A rigorous secondary research was done with inference concluded from different databanks, research papers, books, journals, and websites to collect the data. Plasma industry market was assessed, and the data was extracted and analysed to arrive at conclusions.

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The Blood Plasma Market is expected to exceed more than US$44.0 billion by 2024 at a CAGR of 9.3% in the given period as the need for plasma products will continue to grow

Plasma-Collection & Fractionation

- Plasma is moving from nascency towards a whole therapeutic expertise, and is going to positively affect both the pharma industry and the recipients
- **U.S. commercial blood establishments supply the largest proportion of source plasma used for fractionation**
- Source plasma is also collected in significant quantities in China, Germany, Austria, Czech Republic and Hungary
- The south-east Asian region is also making progress in terms of plasma fractionation and might assume a significant role in plasma production in the coming years

Economics & Key Players

- The Blood Plasma Market which includes product, application and regional **segments is expected to exceed more than US$44.0 billion by 2024 at a CAGR of 9.3% in the given period**
- The key players according to market share in 2019 are:
  CSL Behring (~37%); Grifols (~22%); Octapharma (~12%); Takeda (~11%)
- The commercial sale of all the major products obtained from 1 liter of plasma generates around US$ 696 in 2019

Regulations & Remunerations

- The leading nations **allowing remunerations are USA ($30-50), Germany ($30), China (ranging from several dollars, along with paid leaves for employees and credits for college students), Austria ($28), certain provinces of Canada ($30-50) and Russia ($5.5/plasma donation if donated 60 times annually)**
- Countries that are in the process of developing a national blood program could benefit from taking some aspects of the U.S. regulatory approach to expand their donor base of source plasma for manufacturing, beyond aiming to accept plasma only from voluntary unpaid donors

Challenges & Hurdles

- The amount of domain expertise and capital required, are the major hurdles for a new player or competition to venture into this industry
- The regulatory scenario of the industry will keep on tightening because of the abusable nature of the raw material and new mutated viral infections coming into play
- Due to the increasing number of patients who are suffering from diseases that can effectively be treated with plasma products, **the need for these products will continue to grow and the demand for plasma will increase equally**

Source : WHO, Market watch reports

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More than 3,000 plasma proteins control balance in a human body, some with health promoting effects and others with disease associated effects

What's Plasma?

- Blood is made up of four main components: Red blood cells, white blood cells, platelets, and plasma
- Plasma, also known as blood plasma, appears light-yellowish or straw-colored. It serves as the liquid base for whole blood
- Plasma contains 92% of water and 8% to 9% of solids
- Plasma mainly comprises:
    - Coagulants, mainly fibrinogen, aid in blood clotting
    - Plasma proteins, such as albumin and globulin, that help maintain the colloidal osmotic pressure at about 25 mmHg
    - Electrolytes like sodium, potassium, bicarbonate, chloride, and calcium help maintain blood pH
    - Immunoglobulins help fight infection and various other small amounts of enzymes, hormones, and vitamins

Plasma's Development

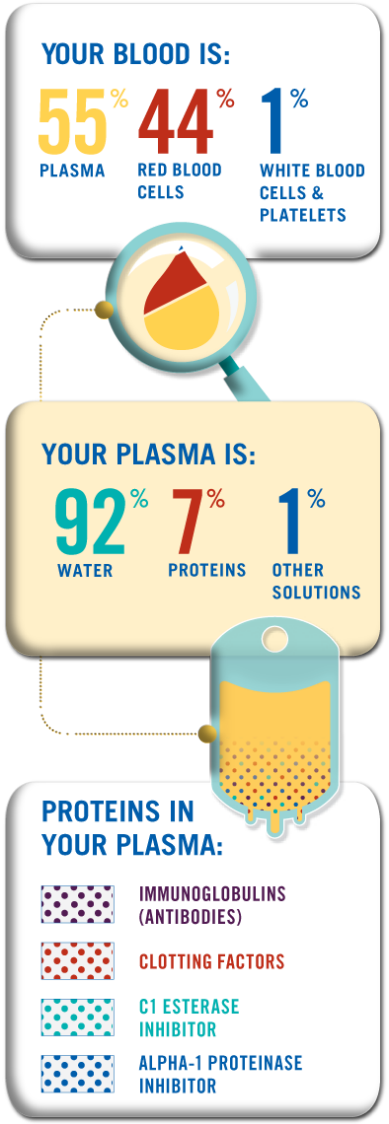
- Plasma is formed from water and salts absorbed through the digestive tract
- Plasma proteins, on the other hand, have distinct organs that produce them based on an individual's stage of development
    - **In Embryo,**

      the mesenchymal cells are responsible for the plasma cell production. The first protein to be synthesized is albumin, followed by globulin and the other plasma proteins
    - **In Adults**,

      the reticuloendothelial cells of the liver oversee plasma protein synthesis. Gamma globulins originate from B lymphocytes, which in turn form immunoglobulins

Role of Plasma

More than 3,000 plasma proteins control balance in a human body, some with health promoting effects and others with disease associated effects. They help to carry out many important functions in the human body, including clotting blood, fighting diseases, and other important jobs

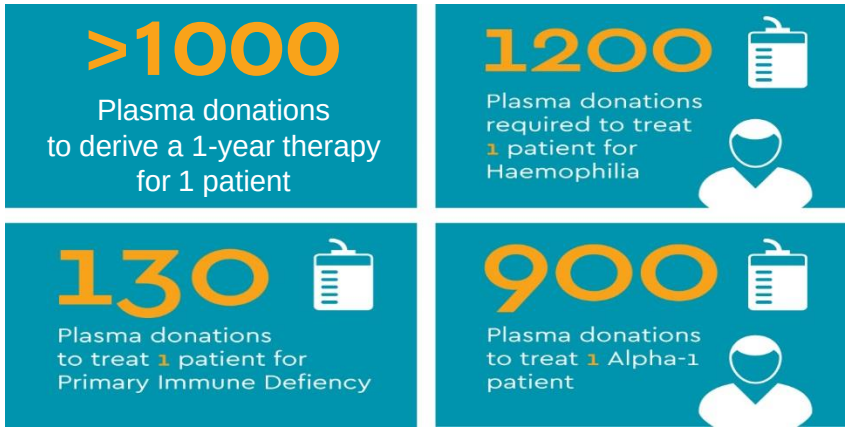


Source : PPTA Report

PharmaACE

The protein concentration in plasma is approximately 60–80 mg/mL and these proteins are isolated to create life saving plasma protein therapies

Plasma Protein	Normal Level	% in plasma	Function
Albumins	3-5 g/dl	60%	Maintains colloid osmotic; transports insoluble molecules
Globulins	2-3 g/dl	38%	Participate in immune system
Fibrinogen	0.3 g/dl	7%	Blood coagulation
Clotting factors		<1%	Conversion of fibrinogen into fibrin
Regulatory proteins		<1%	Regulation of gene expression



Why are plasma proteins therapies important?

- Plasma contains hundreds of proteins covering a myriad of physiological functions
- The protein concentration in plasma is approximately 60–80 mg/mL of which most abundant proteins, albumin and immunoglobulin (Ig) G, are present representing about 80% of all plasma proteins and less abundant proteins include the protease inhibitors, like a1-antitrypsin (AAT) and antithrombin (AT), and the coagulation factors such as factor VIII (FVIII) which exhibit potent physiologic activity
- Plasma proteins are used to treat many conditions including immune deficiencies, autoimmune disorders, neurological & bleeding disorders and shocks and burns
- These proteins are isolated to create life saving plasma protein therapies

Can't these proteins be replicated to treat rare conditions?

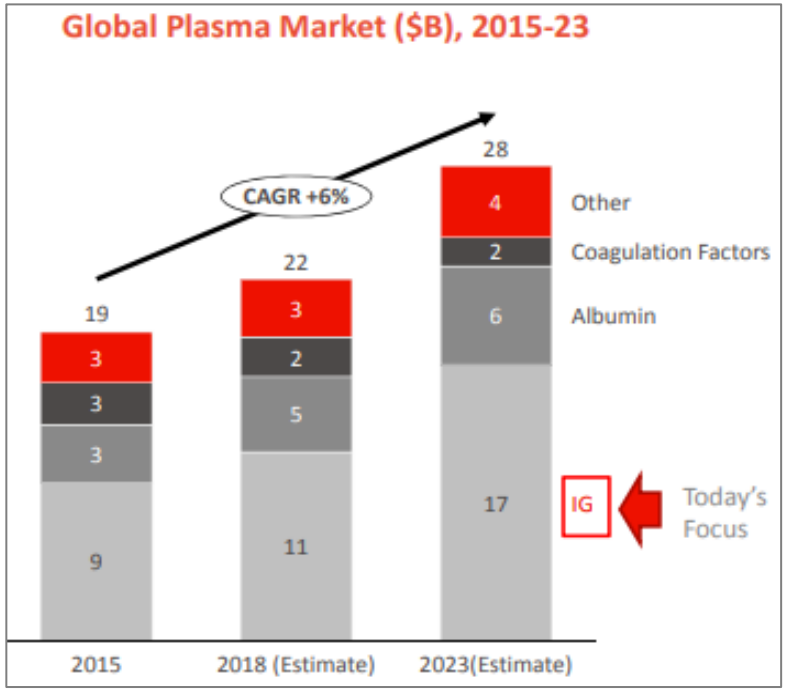
- Due to the specific qualities of some of these proteins, they cannot be replicated by recombinant approaches
- Factors such as histocompatibility or post-translational modifications enforce that these proteins can be considered irreplaceable
- This is the case **in particular with immunoglobulin that, because of its unique structural features and polyvalence, will be very difficult to replicate by recombinant means and therefore plasma therapy is likely to remain the only treatment for immune deficiency or immunomodulation in the foreseeable future**

PharmaACE

Source : PPTA, Grifols Report

Currently there are more than 20 Protein-derived products (PDPs) in the market and Immunoglobulin G (IgG) has been the driver of plasma fractionation volumes for the past twenty years

Immunoglobulin products	Clotting factors and other products	Albumin Products
✓ Intravenous immunoglobulin (IVIG) ✓ Subcutaneous immunoglobulin (SCIG) ✓ Normal human immunoglobulin ✓ Hyperimmune immunoglobulin products	✓ Factor VIII ✓ Factor IX ✓ Factor VIIa ✓ FEIBA ✓ Protein C ✓ Prothrombin complex ✓ Antithrombin III ✓ Fibrogammin ✓ Factor XI and factor XII ✓ C1 esterase inhibitor	✓ 4% human albumin solution ✓ 20% human albumin solution



- PDPs treat well-defined medical conditions, replacing missing or deficient proteins found in plasma, to allow their recipients to lead healthier and more productive lives. The patient populations that rely upon plasma protein therapies generally require regular infusions or injections for the duration of their lives
- The most important biological medicines which can be prepared from human plasma are albumin, Immunoglobulin G (IgG), coagulation factor VIII and IX, α1-antitrypsin, anti thrombin III, ceruloplasmin, and plasminogen
- Today, more than 20 different protein products, and more if one considers the variety of hyperimmune IgG preparations, can be extracted through large-scale fractionation of human plasma
- **IgG has been the driver of plasma fractionation volumes for the past twenty years**
- Prior to that, factor VIII was the driving protein for fractionation. At present, **IgG and albumin are sold from every liter of plasma fractionated**, and factor VIII is still sold from nearly all the liters fractionated

Source : Annals of Blood reports

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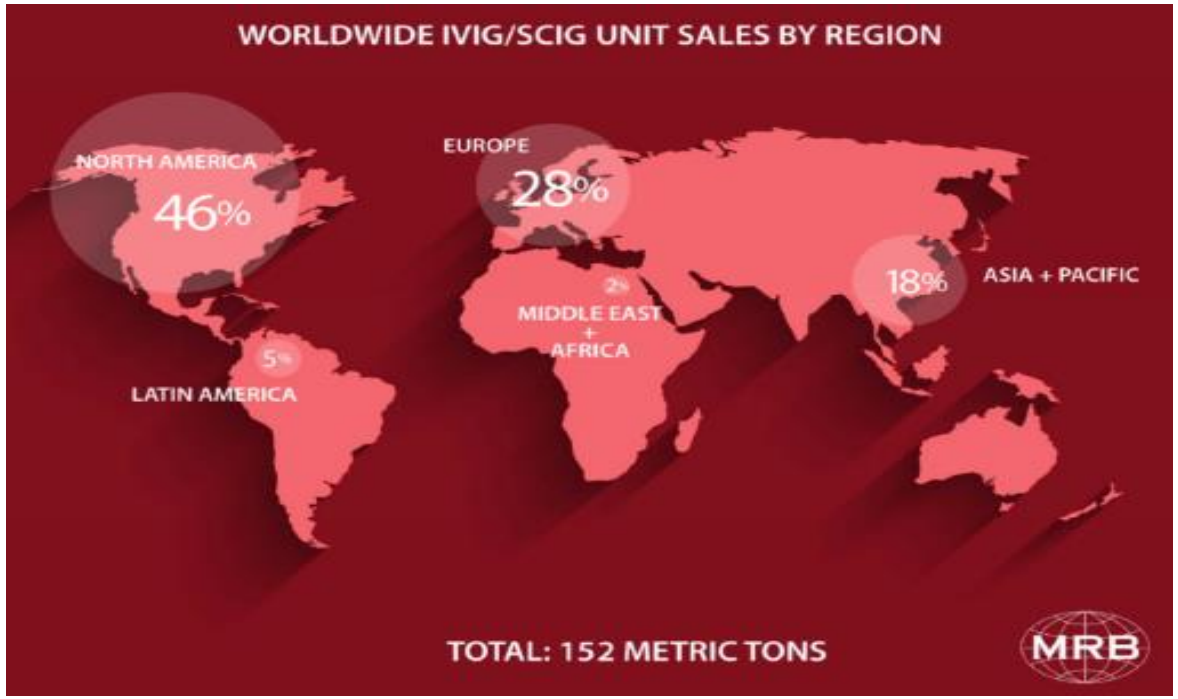
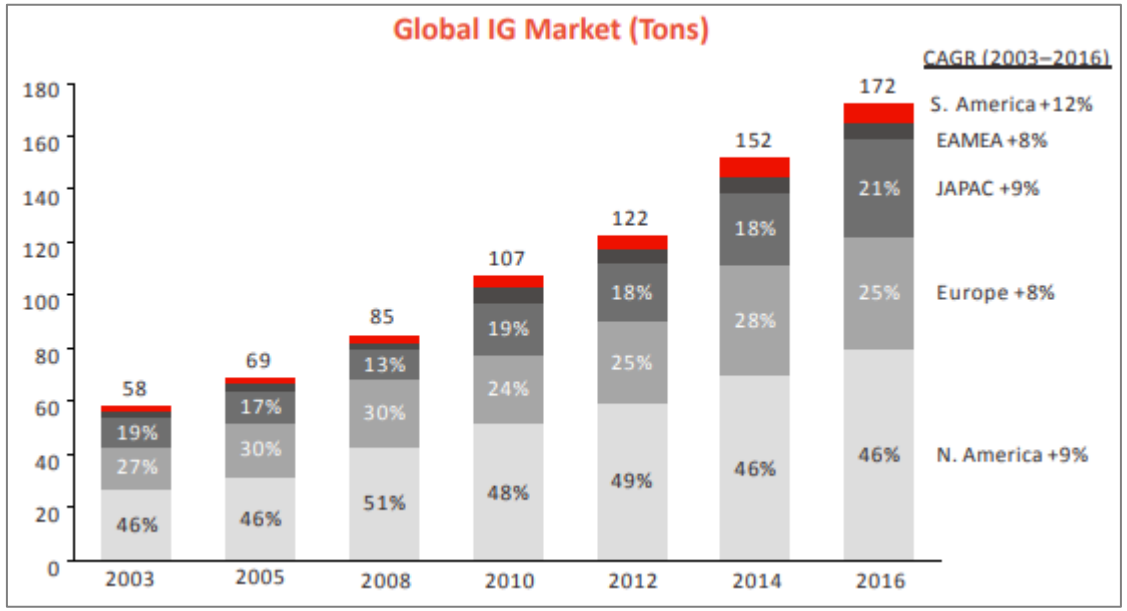
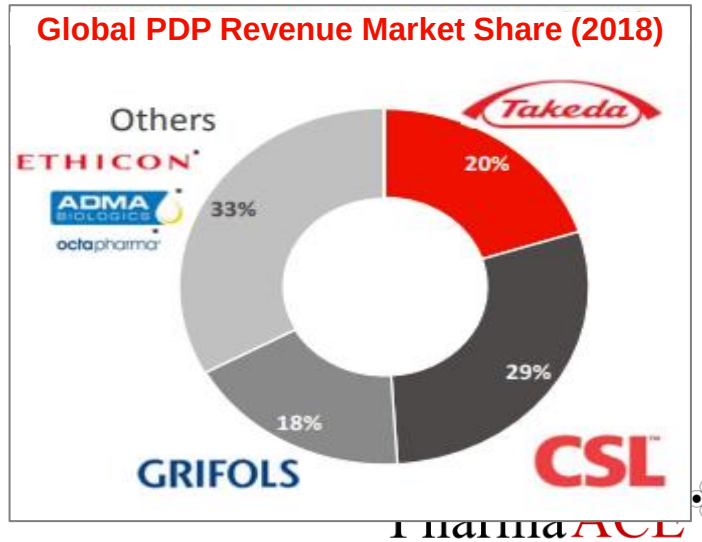
There is a growing need for Plasma derived products led by Immunoglobin and by 2018, CSL, Takeda and Grifols are the top 3 companies in terms of product revenues



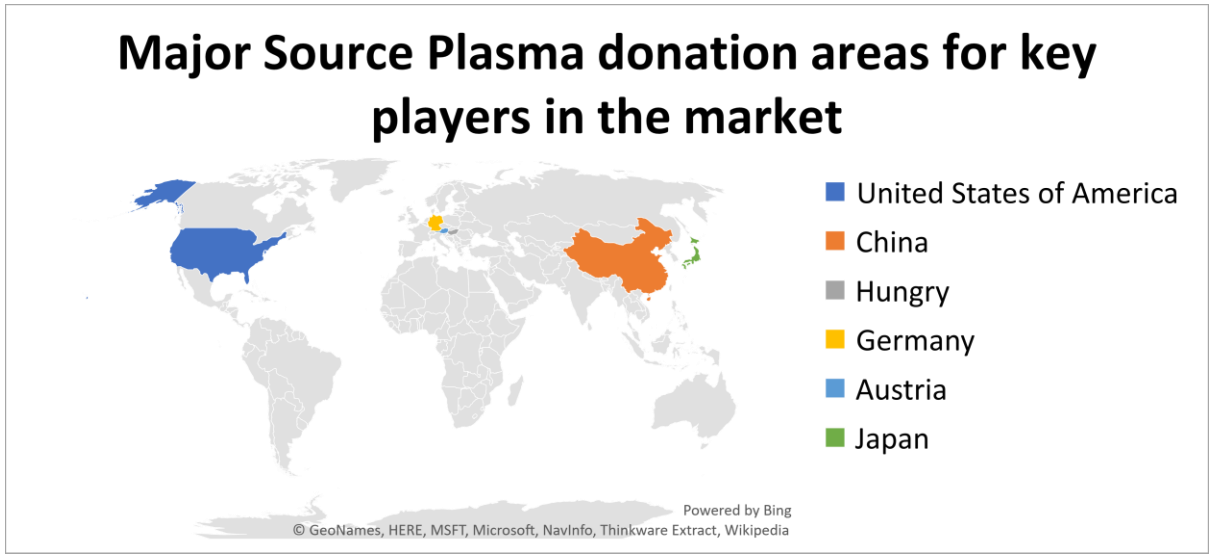


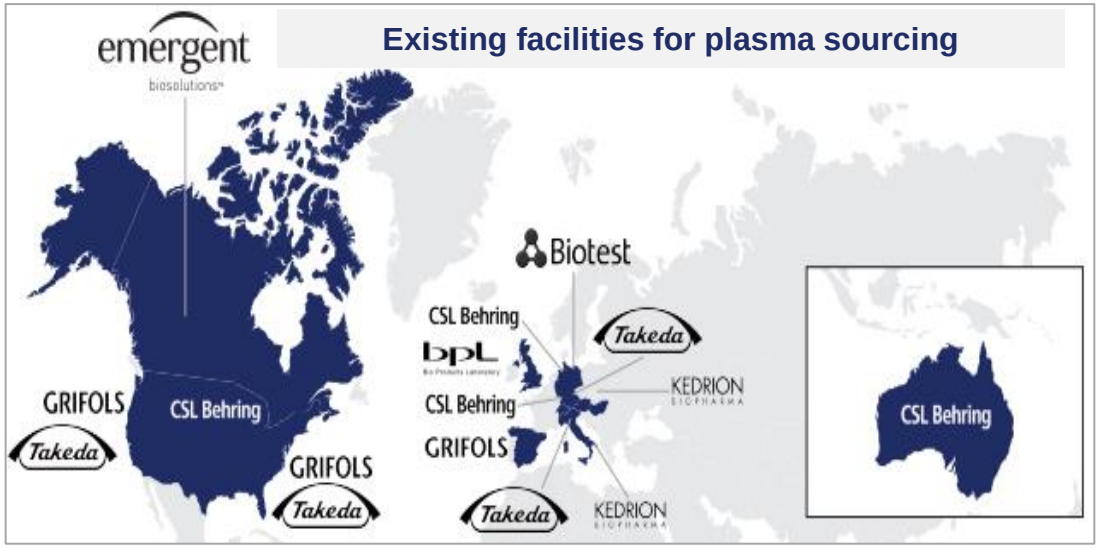
- Large amounts of plasma derived products are exported from the U.S. and Europe to countries in Asia Pacific, South America, Middle East and Africa
- **IgG has been the driver of plasma fractionation volumes for the past twenty years due to improved diagnosis rate and disease awareness**
- There is a growing need for Plasma derived products led by Immunoglobin and by 2018, CSL, Takeda and Grifols were the top 3 companies in terms of product revenues
- North America and Europe hold major worldwide IVIG/SCIG unit sales for the year 2017
- Prior to that, factor VIII was the driving protein for fractionation. At present, **IgG and albumin are sold from every liter of plasma fractionated**, and factor VIII is still sold from nearly all the liters fractionated



Source : Annals of Blood, Takeda and Edqm reports

The U.S. PDPs market represents close to half of the world's total in value, as well as in volume for some products





Plasma Sourcing

- US is the major exporter responsible for more than 40% of world's source plasma feed, which is worth more than $2bn in terms of plasma and related products
- **China has begun to impact the global plasma proteins industry through its mergers and acquisitions of plasma companies outside China**
- **In order to operate multiple production sites, about half of the plasma collected in the U.S. for fractionation is shipped abroad, mainly to Europe**
- In 2018, 22 million liters of U.S. plasma transfers to foreign countries were recorded by the U.S. Department of Commerce and 144,000 liters came from 24 countries into the U.S.
- **Much of the plasma that left the U.S. for Europe comes back about 10 months later in the form of various PDPs**
- **The U.S. PDPs market represents close to half of the world's total in value, as well as in volume for some products**
- Throughout South-East Asia, there is certainly a strong regional will to contribute to the world's supply of plasma for fractionation and could even be a more active contributor

Source : Grifols, Takeda, PPTA reports

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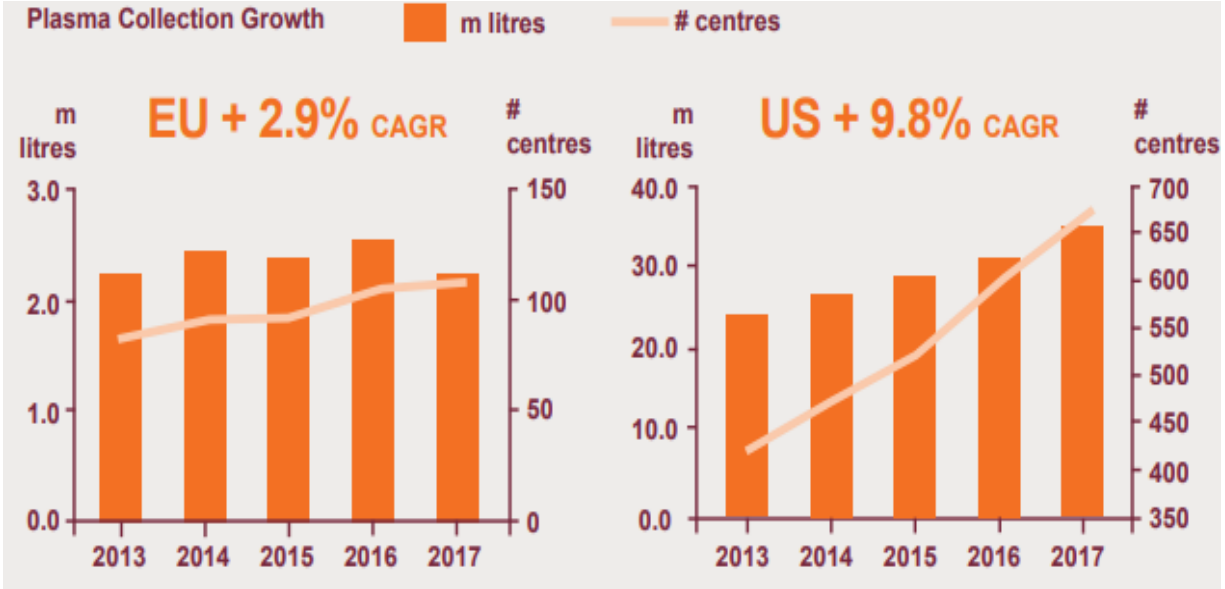
Collection of source plasma (obtained through dedicated plasmapheresis) in the U.S. has expanded rapidly over the past few years to meet increasing demand

Plasma Collection

- Plasma can be obtained in two primary forms: **recovered plasma** (obtained from the “by-product” of whole blood collection) and **source plasma** (obtained through dedicated plasmapheresis, a process where plasma is separated from red blood cells and other cellular components of blood which are then returned to the donor)
- In a **regulated environment**, **plasma is collected by licensed blood establishments** (blood centers and apheresis collection centers) that are inspected by the relevant National Regulatory Authorities (NRAs)
- **Collection of source plasma in the U.S. has expanded rapidly** over the past few years to meet increasing demand, especially for immunoglobulins
- Source plasma is also collected in significant quantities in China, Germany, Austria, Czech Republic and Hungary
- By 2019, China had 263 plasma collection centers drawing some 2.9 million qualified plasma donors across 650 counties



- **Both the collection centers and plasma collected in U.S. have increased vastly with 9.8% CAGR in the period of 2013-2017 whereas EU had registered only 2.9% CAGR for the same period**
- Australia: In 2018/19, for the first time, the AUSTRALIAN RED CROSS collected more units of plasma than whole blood, approximately 61,000 vs. 60,000 units, respectively. This contrasts with over 100,000 whole blood donations and ca. 25,000 plasma donations 10 years previously
- **Regarding Asia and Pacific countries,**
  - Some countries have achieved good manufacturing practices (GMP) compliance and are involved in (contract) manufacturing (like Japan, Australia, New Zealand, Singapore, Malaysia, Hong Kong, Taiwan, South Korea)
  - While some countries are improving their blood transfusion organizations with the aim of conforming with GMP standards and optimizing the quality of plasma (e.g. Indonesia, Thailand, Vietnam, Sri Lanka), other countries (in particular India) have a long way to go

Source : 2017 reports - PPTA, Annals of Blood, edqm

Plasma Industry Process: Plasma that comply with quality and testing requirements are only used for fractionation and this production cycle takes a few weeks to several months

Reception of plasma shipped by blood establishments
Control of shipping parameters and reconciliation

Quarantine of plasma in cold room (<=20˚c or colder)
Additional testing and quality control

Preparation of plasma batch

Conditioning of plasma packs

Pooling and large-scale processing

- Cryoprecipitation
- Bulk fractionation (e.g. ethanol fractionation)
- Preparation and storage of immediate fractions
- Protein downstream processing and anti-viral treatment of individual proteins
- Finishing and terminal sterile filtration (0.2µm)

Aseptic dispensing
Filling in vials/ bottles and Freeze drying

Quarantine – quality control

Check of production batch records and documentation

Labelling – Packaging

Boxing – Shipment

- Only individual plasma donations that comply with quality and testing requirements are used for fractionation
- In a few countries, product batches may be released by regulatory authorities
- The production cycle of fractionated products takes a few weeks to several months
- Europe and North America are leading regions in geography size for plasma fractionation

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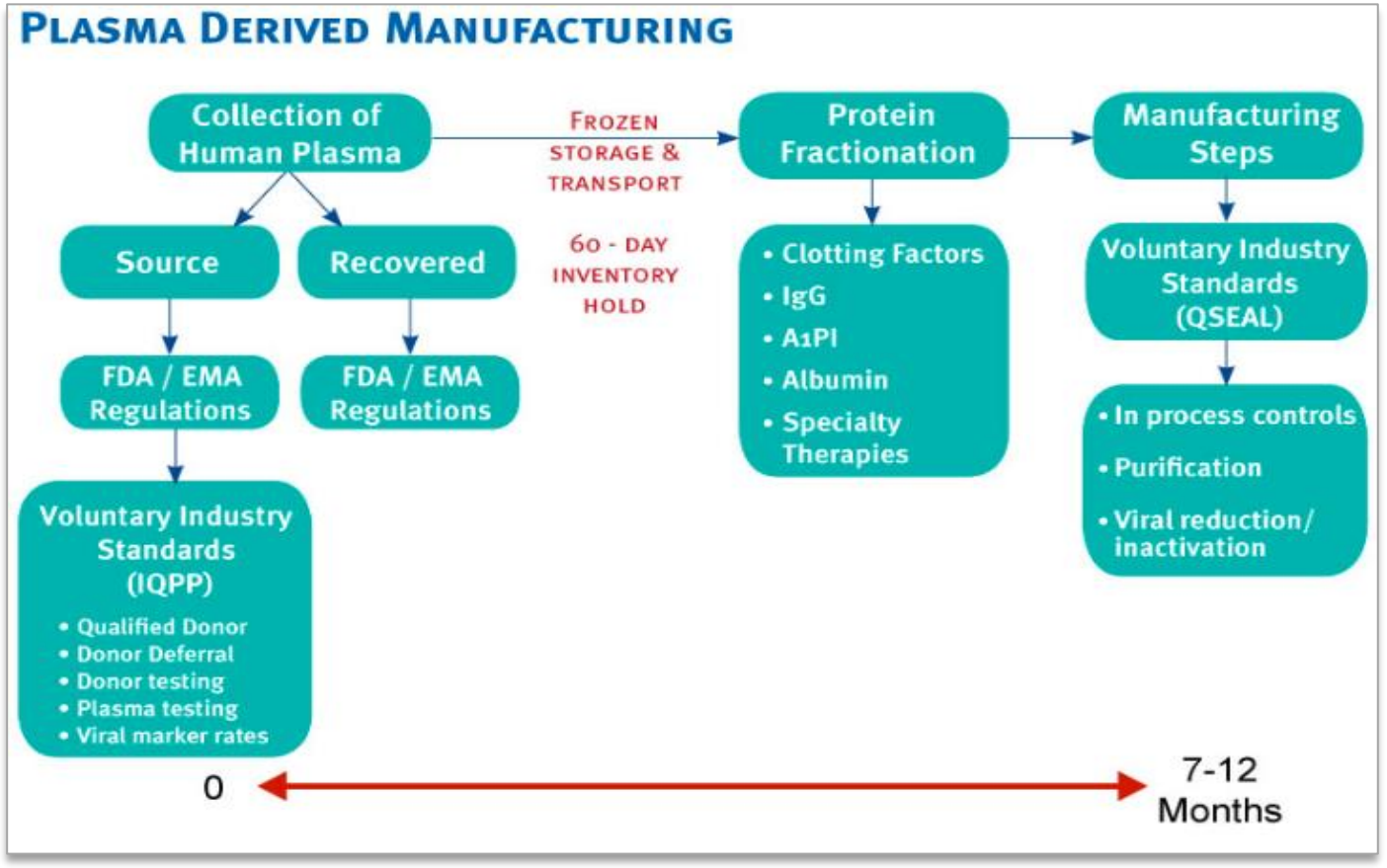
Source : PPTA, Modern Plasma Fractionation Report

Manufacturing a therapy often takes 7 to 12 months from donation to final product release and most of the larger manufacturers conduct fractionation and purification processes on fractions equivalent to pooled plasma volumes of 3,000 liters - 20,000 liters

Manufacturing

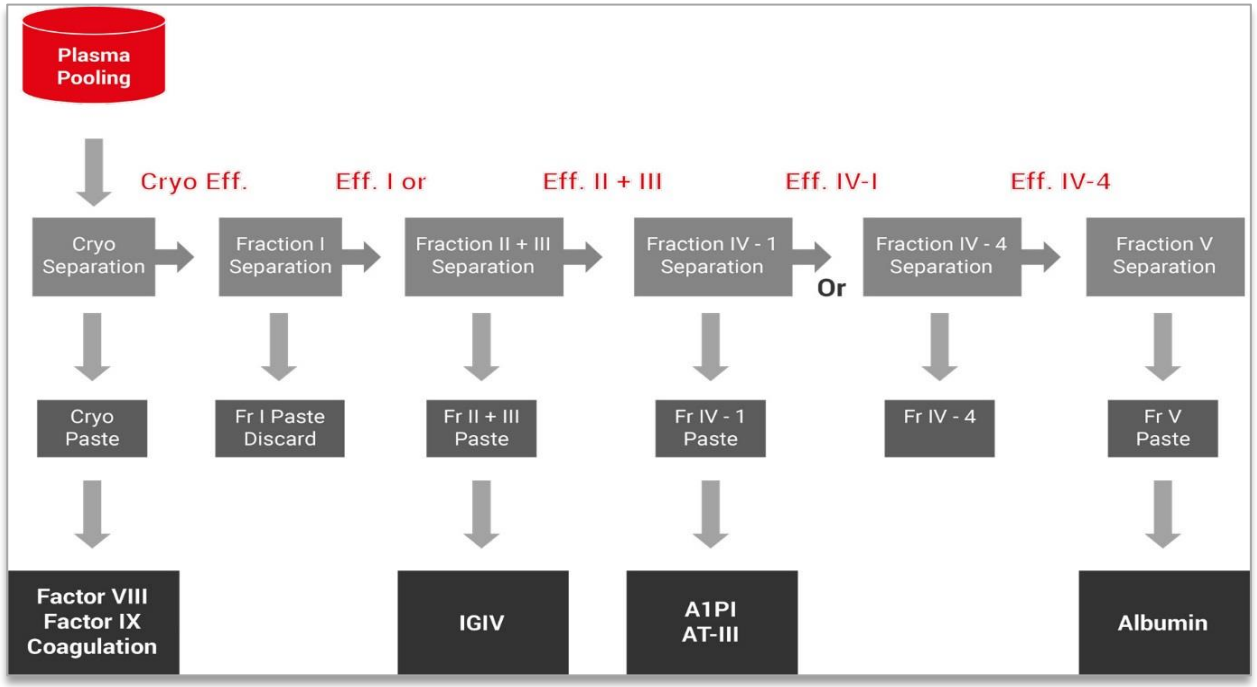
- The manufacture of plasma proteins is characterized by high capital costs, complex manufacturing processes, and a considerable regulatory burden
- **The economic and regulatory pressures require that high-quality manufacturing facilities be designed and maintained**
- Source and recovered plasma is the starting material used to manufacture lifesaving therapies
- **Cohn and co-workers developed plasma protein separation process which allowed the establishment of large-scale commercial fractionation enterprises** and this process remains the technological basis of the industry to this day
- In **fractionation, plasma is pooled and processed that employs time, temperature, pH, and alcohol concentrations to extract specific therapeutic proteins**
- These are then subjected to various purification methods and viral inactivation and removal processes to further ensure their safety and efficacy



- Preparing a therapy often takes **from seven to twelve months between donation and final product release**
- Continuous improvements to increase yield and throughput are important factors in the therapeutic plasma protein manufacturing environment, as is the adoption of new technologies
- Most of the larger manufacturers conduct fractionation and purification processes on fractions equivalent to pooled plasma volumes of 3,000 liters - 20,000 liters

Source : PPTA, Modern Plasma Fractionation Report, Annals of Blood

Over the years, the Cohn fractionation process was improved and complemented by new technologies in order to maximize production yields



No. of Fraction	% Protein	Components
I	5-10	Fibrinogen
		Clotting factor VIII
II+III	25	IgG
		IgA
		IgM
IV-1	5-10	α-and β-globulins
		α_1-antitrypsin
		Antithrombin III
IV-4	5-10	Complement components
		Ceruloplasmin
		Haptoglobin
		Transferin
V	50-60	Albumin

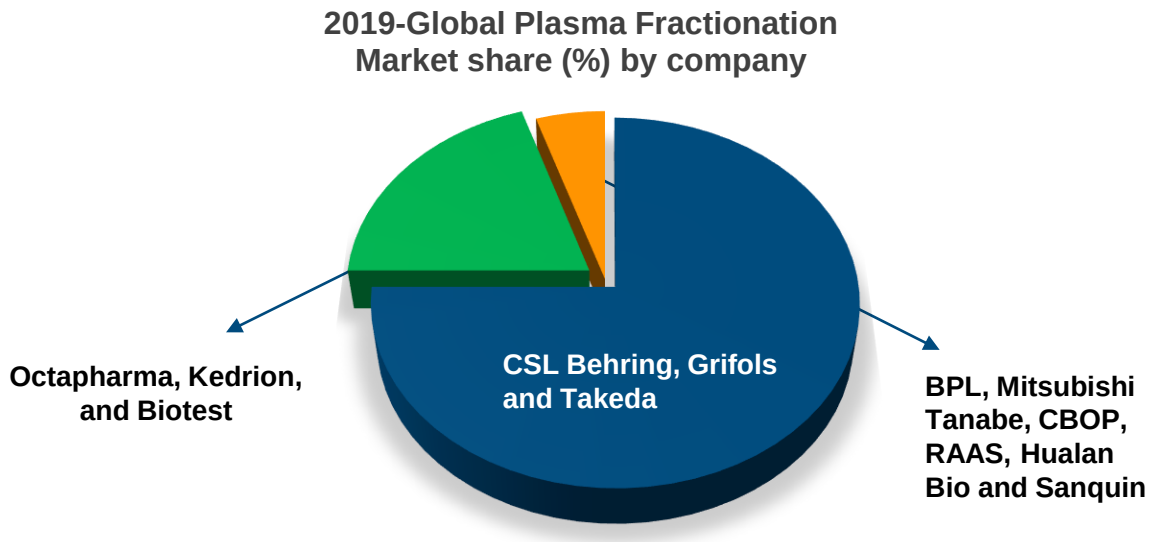
Percentage of the main proteins in different fractions

Fractionation

- Validated dedicated steps **inactivate and/or remove infectious agents** potentially present in the starting plasma pool
- In Cohn's method of fractionation, five fractions could be obtained by the adjustment of pH, the concentration of ethanol, ionic strength, temperature, and concentration of protein
- Over the years, the Cohn fractionation process was improved and complemented by new technologies. Using chromatography processes to purify specific proteins, the industry has significantly increased production yields, in particular Intravenous Immunoglobin
- More recently, some companies, such as Prometic and Evolve Biologics are using ligands to extract and purify plasma proteins achieving higher yields, but they have not yet introduced any product on the market. Companies continuously endeavor to maximize their production yields so as to get the most from human plasma and generate more revenues from a liter of plasma
- This sophisticated industrial process is performed under highly hygienic conditions in licensed facilities (plasma fractionation plants) that are operated in compliance with good manufacturing practices and following quality assurance principles

Source : PPTA, Modern Plasma Fractionation Report

Around 85% of plasma fractionated worldwide is obtained by source plasma. CSL Behring, Takeda and Grifols dominate world's plasma fractionation market with 75% share



- **85% of the plasma fractionated worldwide is obtained by source plasma** and **the rest is the recovered one**
- **U.S. commercial blood establishments supply the largest proportion of the source plasma used for fractionation**
- For the year 2018, total source plasma (SP) collections for fractionation in **U.S. - 48,721,545 L and in EU – 2,888,390** L
- For the year 2017**,** Europe has the highest portion of recovered plasma (RP) been fractionated. Despite of huge collection of RP, Europe is dependent on U.S. source plasma
- In Thailand, 28,334 liters of recovered plasma is collected for fractionation in 2015 and 108,193 liters in 2018
- **The three dominating plasma fractionation companies in the world are CSL Behring, Grifols Therapeutics and Takeda with a 75% of the market - roughly 25% or 10 million liters of yearly fractionation capacity for each one;** A second tier of companies, including Octapharma, Kedrion, and Biotest account for a further **8 million liters of plasma fractionation capacity**
- Nowadays millions of liters of plasma are fractionated in one year **with an estimated global business worth $30.9 billion by 2024 including a CAGR of 6.9% in the forecast period 2019 to 2024**

Source : 2017 reports - PPTA, Annals of Blood, 2019 reports - Edqm, Altran

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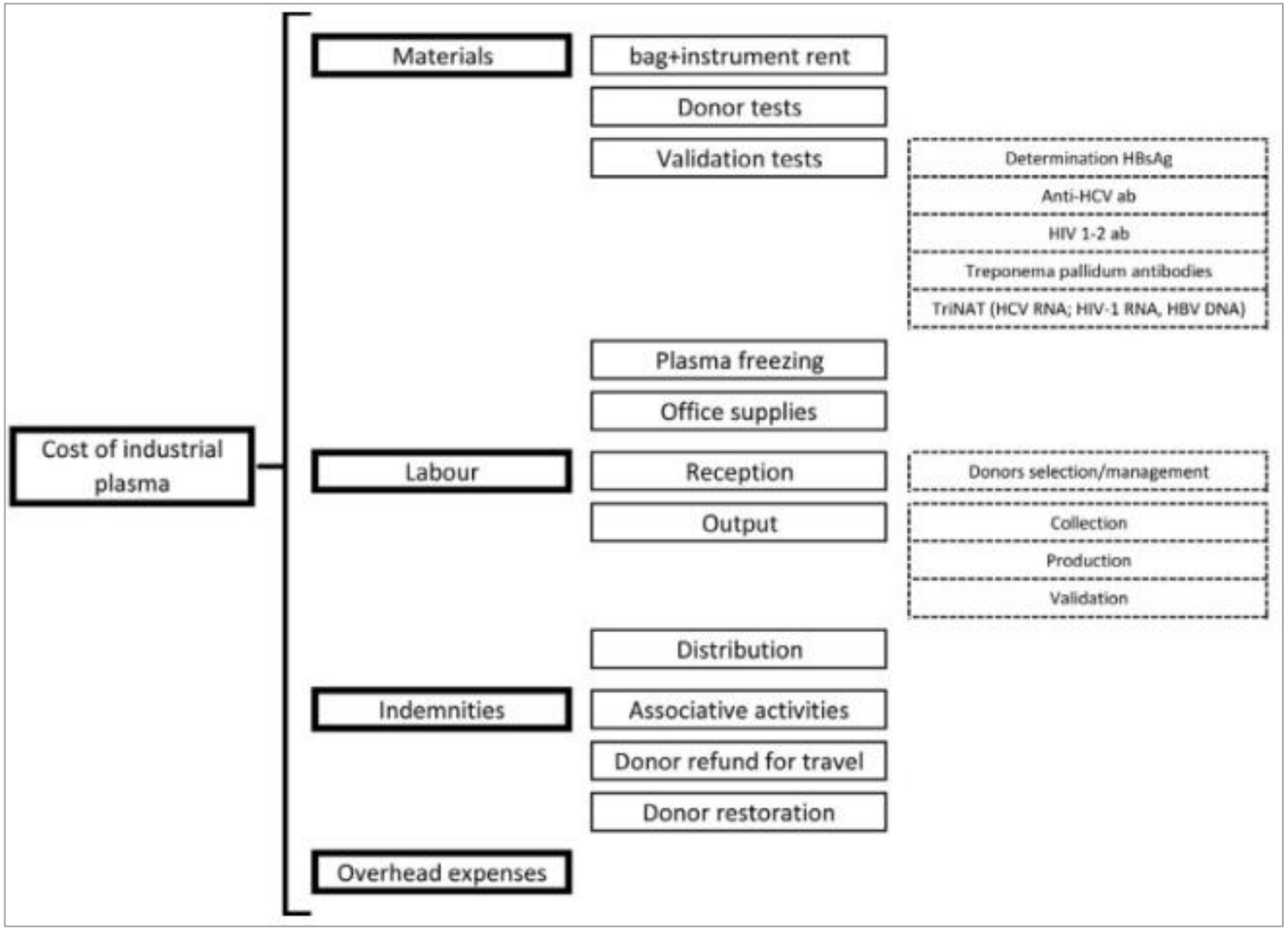
Higher production costs of plasma industry is majorly due to the involvement of large work force, complex logistics, strict regulations and donor compensation



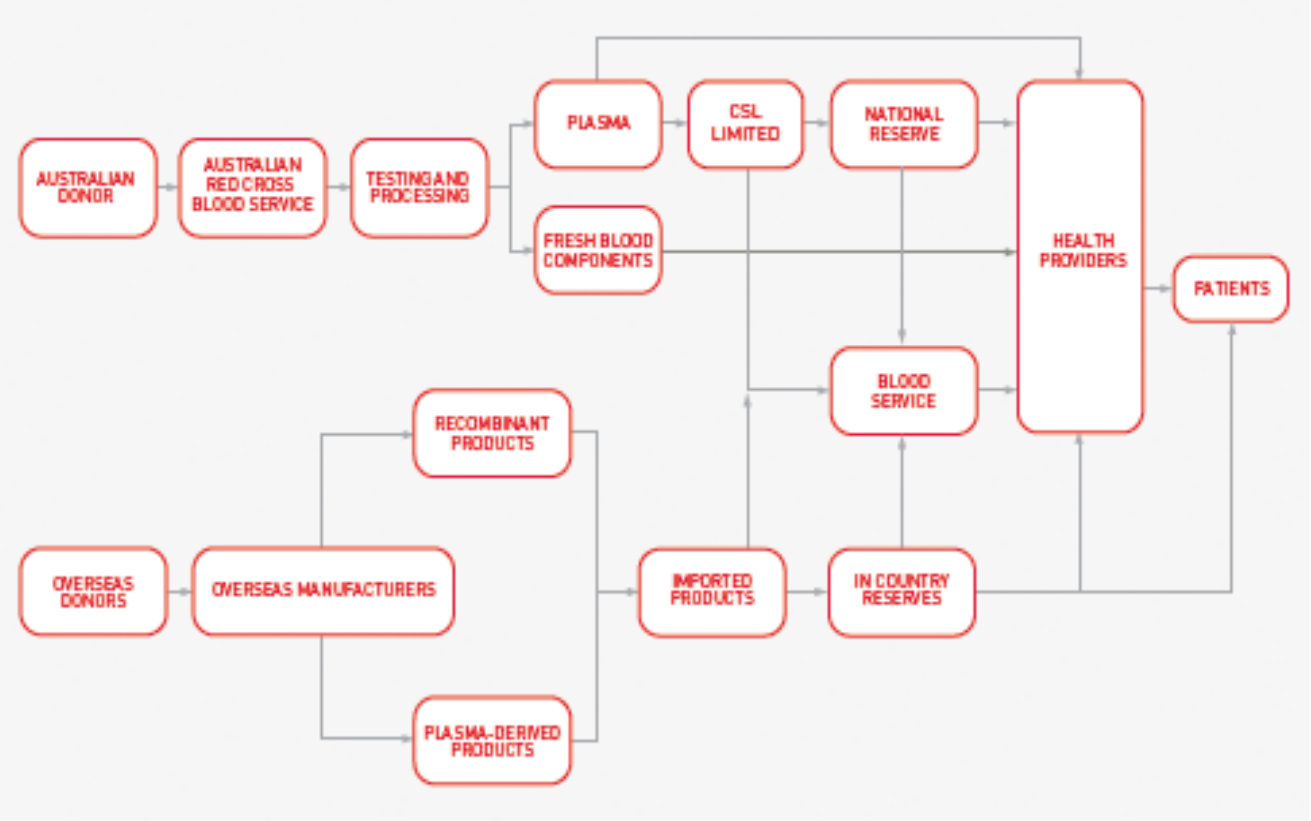
Plasma Industry Economics

- It is generally estimated that plasma, **the raw material, represents roughly 50% of the total cost** to produce plasma-based therapeutic proteins
- Plasma is **expensive because collecting plasma is a complicated and delicate operation**, involving a large work force due to the need to collect plasma from thousands of people
- **Components of this cost include plasmapheresis equipment and highly qualified staff**, donors must donate plasma frequently and many donors are needed by the companies, complex logistics, strict regulations, and donor compensation
- **The commercial sale of all the major products obtained from 1 liter of plasma generates around US$ 696 in 2019**
    - **T**herefore a fully operational mid-size plasma fractionation plant processing **35 tons of plasma per week on a 46 weeks production schedule would generate US$ 1,120 million every year**
- The Blood Plasma Market which includes product, application and region is **expected to exceed more than US$44.0 billion by 2024 at a CAGR of 9.3%** in the given period

Source : PPTA, EuropePMC, Market Watch

Different blood plasma supply chains: In countries like U.S., the plasma supply is collected, processed and distributed by private industry whereas in most of Europe, Pacific countries, plasma supply is controlled by government owned blood establishments

Australia Blood Plasma Supply Chain



- In Australia, the National Blood Authority (NBA) manages the national planning and purchasing of blood and blood products
- Australian Red Cross Blood service collects plasma and delivers it to CSL Limited for manufacture of PDPs
- **For the year 2018, Australian Red Cross blood service has delivered 675.3 tonnes of plasma to CSL for fractionation for use in plasma products**

Grifols Blood Plasma Supply Chain

SUPPLY

Grifols owned plasma collection network of 295 centers in U.S. and Europe

MANUFACTURING

US (Clayton, North Carolina and Los Angeles, California) and Spain (Barcelona)

DISTRIBUTION

Direct presence in Europe, U.S, Canada, Latin America and Asia

Source : Grifols, NBA, PPTA reports

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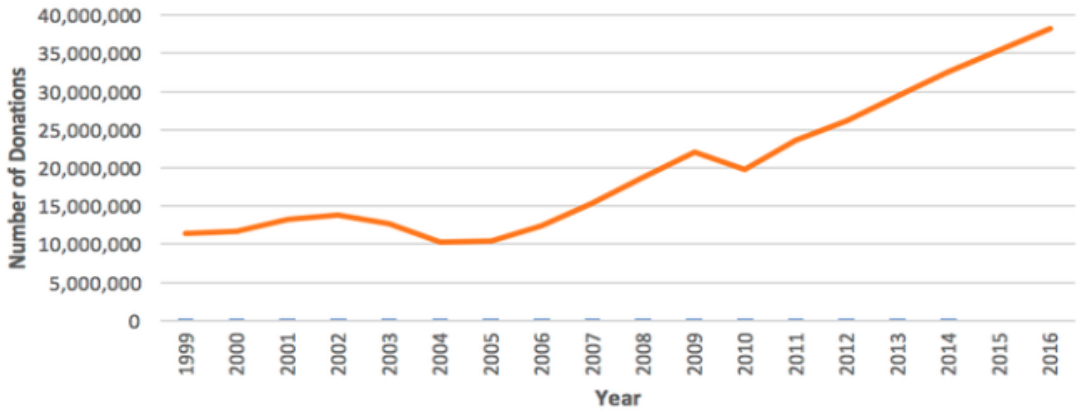
U.S. regulations permit more frequent donations and greater total volume withdrawn per year than other countries within a favorable regulatory climate

Donation Guidelines

Collection parameters	United States*	Council of Europe*	Germany*	U.K.*
Maximum Donation Frequency	104/yr	33/yr	45/yr	24/yr
Maximum times/week	Twice/week	Once/week	Once/week	Twice/week
Maximum volume/donation (weight dependent)	800 mL	750 mL	850 mL	1,050 mL
Volume/year	83 L	25 L	38 L	15 L

Over a decade (2006-2016), the number of donations in U.S. tripled

The Number of Annual Plasma Donations in the U.S., from 1999 to 2016



- U.S. blood and plasma are collected, processed and distributed by private industry that is regulated by the FDA under two national laws: the Public Health Service (PHS) Act, and the Federal Food, Drug and Cosmetic (FD & C) Act and European Medicines Agency (EMA) regulates in Europe
- Donors eligible to donate plasma for fractionation are individuals who meet donation criteria (such as age and donation frequency), do not present risk factors of blood-born infectious agents, and comply with requirements defined by the plasma fractionator and the NRAs of the country of plasma collection and of use of the products
- Special criteria may exist for the collection of hyperimmune plasma (used to make hyperimmune IgG preparations), such as procedures for donors' immunization and minimal antibody titer
- **U.S. regulations permit more frequent donations and greater total volume withdrawn per year than other countries**
  - The leading nations allowing remunerations are USA ($30-50), Germany ($30), China (ranging from several dollars, along with paid leaves for employees and credits for college students), Austria ($28), certain provinces of Canada ($30-50) and Russia ($5.5/plasma donation if donated 60 times annually)
- Several countries, including Austria and Germany have adopted more flexible rules that enable them to collect more plasma than other European countries
- Additionally, in contrast to most European countries, the U.S. does not regulate marketing activities and incentives to recruit and retain plasma donors

Source : PPTA, Annals of Blood reports

The European standards for temperature of freezing have become industry standards for both source plasma and recovered plasma as stringent European parameters are science-based

U.S. standards for components of plasma for fractionation

Processing elements	Source plasma	Recovered plasma
Collection method	Plasmapheresis	Whole blood or apheresis
Time from collection to freezing	immediately	Undefined
Freezing conditions, temperature	≤–20 °C	Undefined
Storage expiration	≤–20 °C, 10 yr	Undefined
Shipping temperature	≤–5 °C	Undefined
Allowable deviation	Can exceed <–20 °C for <72 hr total; never >–5 °C, always frozen	Undefined

EU standards for components of plasma for fractionation, and for transfusion

Processing elements	European Pharmacopoeia			Council of Europe	
Purpose	Labile proteins for fractionation	Non labile protein for fractionation		For transfusion	
Collection method	Plasmapheresis or plasma from whole blood	Plasmapheresis	Plasma from whole blood	Whole blood plasma	Apheresis
Time from collection to freezing	≤24 hrs	≤24 hrs	≤72 hrs	≤18 hrs (≤6 hrs optimal); if 20–24 °C, then ≤24 hrs	≤6 hrs; if 20–24 °C, then ≤24 hrs
Freezing conditions, temperature	Frozen to a core temp of ≤–25 °C in ≤12 hr	Chamber at ≤–20 °C		To <30 °C within 1 hr	
Storage	≤–20 °C			If –18 to –25 °C, 3 months; if <–25 °C, 36 months	
Shipping temperature	≤–20 °C			–18 to –25 °C for 3 months storage; <–25 °C, for 36 months storage	
Allowable deviation	Exceeds –20 °C not more than 72 h total; one time >–15 °C; never >–5 °C			None	

Source : PPTA, Annals of Blood reports

- Source plasma and recovered plasma must meet standards of collection, freezing, storage, and shipping
- **The European standards for temperature of freezing have become industry standards** for both source plasma and recovered plasma, which is one factor that makes Plasma for fractionation derived from these plasmas suitable for marketing in Europe as well as the U.S.
  - Placing Source Plasma in the freezer “immediately after filling” is a more problematic requirement
  - Separating plasma from cells by plasmapheresis and freezing it rapidly is the optimal way to preserve protein activity and recovery
  - This requirement, however, **limits the ability of non-commercial blood establishments** to collect apheresis plasma for manufacturing on mobile units because **mobile units often cannot return to a central facility in time to freeze plasma**
- Although **recovered plasma does not have any required standards in practice, most blood facilities in the U.S. follow the European Pharmacopoeia** standards for recovered plasma

Countries that are in the process of developing a national blood program could benefit from taking some aspects of the U.S. regulatory approach to expand their donor base of source plasma for manufacturing, beyond aiming to accept plasma only from voluntary unpaid donors (VUDs)

- Source plasma from paid U.S. donors will continue to be the major source of Plasma for Fractionation (PF) for many years to come
- The voluntary standards of the fractionation industry significantly enhance the minimal requirements of the FDA
  - These voluntary standards are measures to recruit and keep healthy donors, and to exclude those who are intent on gaming the system. Although paid Qualified Donors of Source Plasma still have a modestly higher prevalence of transmitted infections than VUDs, their donations will not compromise the safety of PDPs because of the overwhelming effectiveness of viral clearance in the manufacturing of PDPs
- In addition to the stringent regulations and good manufacturing procedures imposed by healthcare regulatory agencies, Plasma Protein Therapeutics Association (PPTA) sets and monitors certain additional voluntary standards which further document the safety and quality of plasma collection for both the plasma donor and the receiving patient

Challenges faced in plasma industry due to stringent regulations on donations

- In most countries, the collection of blood is reliant on voluntary blood donors, and it is not remunerated for. Many of these countries are importers of plasma from those few countries that allow remunerating plasma donors
- Canada bans source plasma collections from compensated donors in all but two provinces based on a decades-old perception that plasma from such donors is not without certain risks
- In Europe, some countries believe that plasma from compensated donors is not safe and plasma for therapies should only come from recovered plasma from uncompensated donors. Yet these same countries import therapies made from U.S. source plasma
- Current European regulations require at least one physician on site to provide medical expertise as well as donor oversight, evaluation, and management. These positions are generally difficult to fill, mainly due to the numerous competing career paths for new physicians
- The consequences of a lower number of physicians means limitations on plasma center operations and may reduce opportunities for people to donate in European countries
- Many variables could be impacting patient access to therapies, including growing clinical need, global regulatory policies, issues with distributors and/or manufacturers, as well as physician, hospital, or pharmacy protocols
- Overreliance on one source like the United States for plasma exposes the supply chain to significant risks. Europe is a significant importer of plasma, and it has been suggested that plasma collection within the region must be increased to mitigate the supply chain risks

Source : PPTA, Annals of Blood reports

PESTEL Analysis of Plasma Industry

Political

- Governments all over the world are encouraging submissions from the industry in technological as well as operational aspects
- Government and private organizations support blood donation camps and programs to meet the rising demand of plasma

Economical

- The Blood Plasma Market is expected to exceed more than **US$44.0 billion** by 2024 at a CAGR of 9.3% in the given forecast period
- Sales of blood therapeutics were **$30.9 billion** in 2017. By 2024, these products will reach **$57.5 billion**, reflecting a five-year CAGR of 8.2%
- High complexity and cost associated with the collection of blood plasma
- Preparing a therapy often takes seven to twelve months, between donation and final product release

Social

- An increase of **11.6 million** blood donations from voluntary unpaid donors from 2008 to 2015 has been reported by 139 countries. The highest increase of donations is in the South-East Asian Region **(83%)** and the Americas **(70%)**
- About **78** countries collect more than **90%** of their blood supply from voluntary unpaid blood donations
- Initiatives to raise awareness of the unique nature of plasma protein therapies and the value they provide to patients

Technological

- A new red blood cell testing technology aimed at patients with illnesses that require frequent transfusions
- FDA laboratory is evaluating this new technology which identifies the genetic characteristics of a patient's red blood cells so they can be more precisely matched to a donor
- Companies are working to develop oxygen carriers that could substitute for red blood cells

Environment

- Holding plasma, freshly harvested from Citrate phosphate dextrose (CPD)-whole blood, at ~ 4°C for up to 24hrs before freezing at -20°C for 4 months was shown to induce close to **25%** loss of FVIII activity compared to plasma frozen immediately
- Can be environmentally very toxic if spilled or not managed properly
- Donated blood or plasma can have infectious pathogens. So, having proper discarding process is of utmost importance

Legal

- It's one of the heavily regulated industry both at national and international level
- Stringent regulatory standards on the import and export of plasma product

Source : WHO, Market watch reports

Porter's five forces

Threat of new entrants

Low, as it's a very cost intensive industry so a new entrepreneurial venture is less likely but existing pharmaceutical giants can easily venture with their monetary reserve and experience in product development

Threat of substitute

Medium, as with the advent of new molecule research by companies and a huge pipeline products can affect the market. Points can also be given to a disruptive product any day, as the amount of capital being spent on research and development is huge.

Rivalry among competitors

For now it is low as the focus of firms right now is to expand capacities and increase market share by diversifying product portfolio

Bargaining power of supplier

High, as most of the firms are dependent on national institutions for their plasma supply, though they have their own collection centers but in case of sustaining on their own supply alone it would not be an easy job.

Bargaining power of consumer

The bargaining power of the end consumer is low. As in some part of the world, company to customer marketing is allowed but the major portion still depends on influencers whose bargaining power can be characterized as high.

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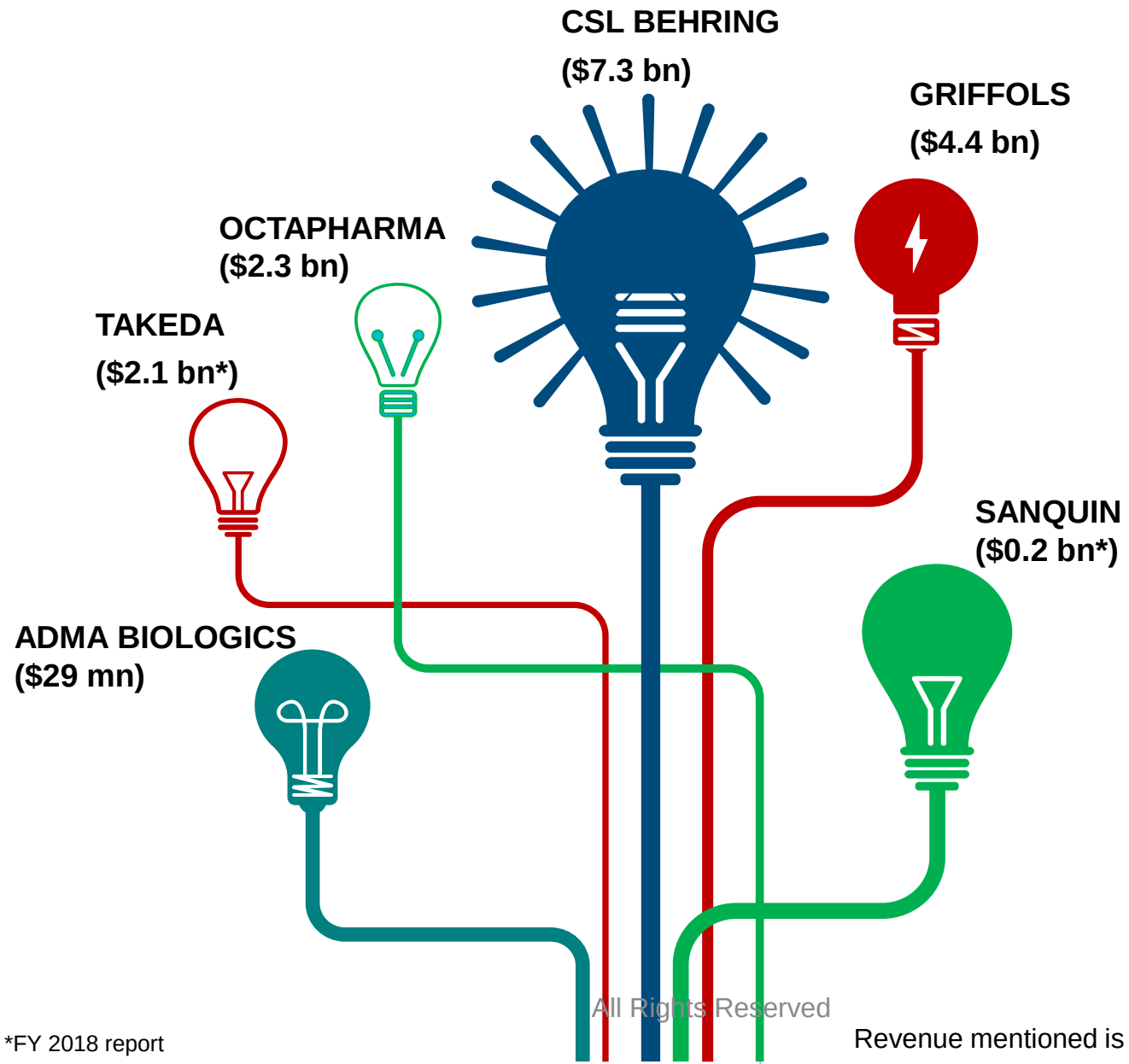
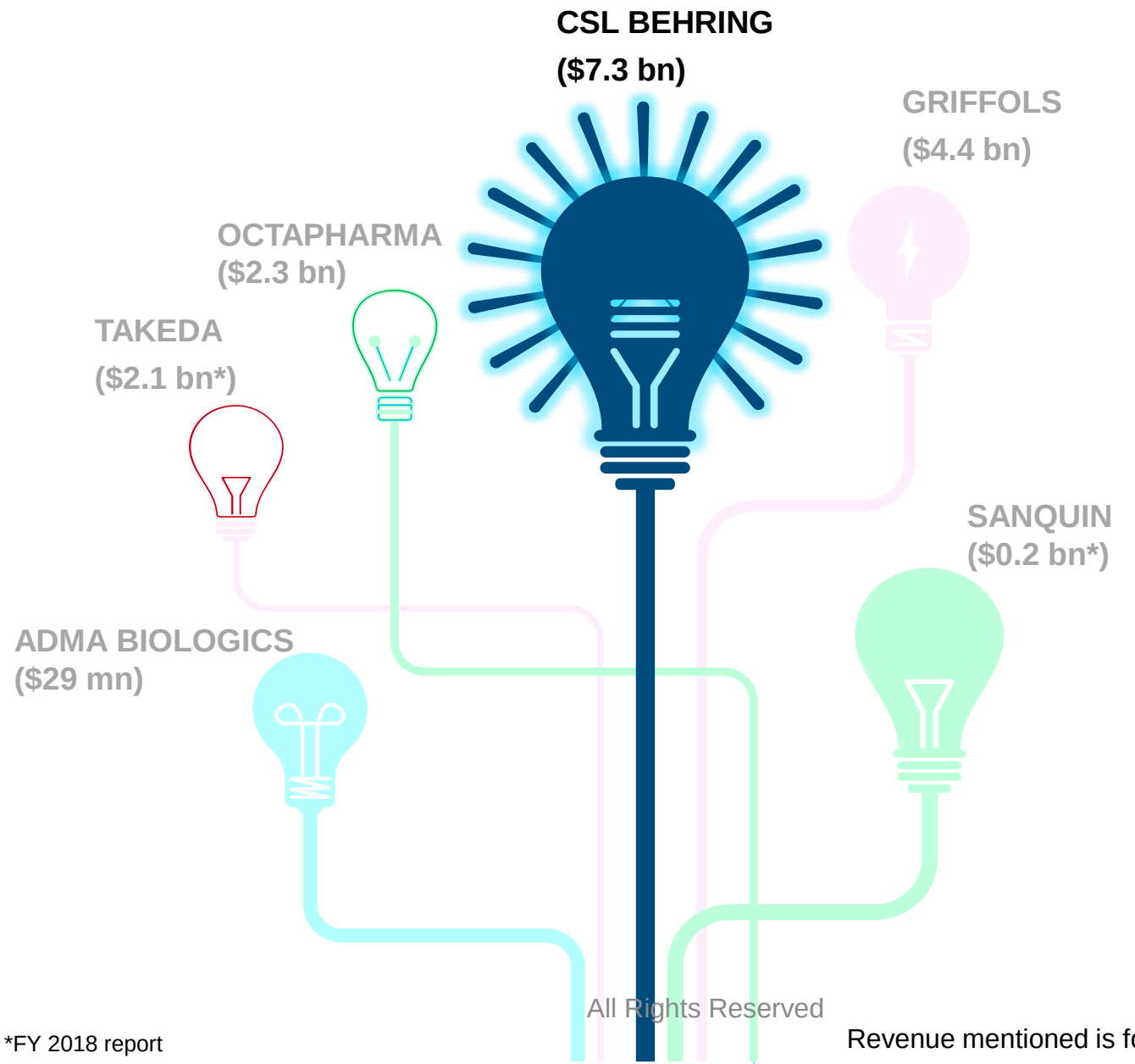
CSL together with Grifols currently hold more than 50% share in the global plasma market. Other key players are Takeda, Octapharma, etc..



Source : Annual reports 2019; *FY 2018 report

Revenue mentioned is for plasma business only

CSL holds 1st position with ~44% share in the global plasma market



Source : Annual reports 2019; *FY 2018 report

Revenue mentioned is for plasma business only

PharmaACE

CSL Behring is a biopharmaceutical company, manufacturing plasma-derived and recombinant therapeutic products and related services

Company Overview

- CSL Limited was incorporated in 1991 and listed on the Australian Securities Exchange (ASX) in 1994 with **specialization in the treatment of rare and serious diseases such as Immunology and Neurology, Hematology and Thrombosis, Cardiovascular and metabolic, Transplant, Respiratory and Vaccines**
- CSL Plasma a subsidiary of CSL Behring, is the largest collector of human blood plasma in the world, sourcing plasma from hundreds of thousands of donors globally to produce a range of life-saving medicines for critically ill patients

Pipeline Product Portfolio

- **Research/Pre-clinical:** Improved Fibrinogen, CSL787 Nebulised Ig, P. gingivalis POD* OH-CRC, Discovery Projects
- **Clinical Development:** Hizentra®, Privigen®, HAEGARDA®, CSL730, CSL312 anti-FXIIa, CSL334 IL-13r, **CSL324 anti-G-CSFr,** Mavrilimumab anti-GM-CSFr, CSL889 hemopexin, CSL200, CSL630, CSL312, CSL311 anti-beta common, CSL346 anti-VEGF-b, CSL112 Apo-A1, CSL964, CSL842 C1-INH AMR, Clazakizumab Anti IL-6 Vitaeris
- **Registration/Post-Launch:** Hizentra® CIDP, Privigen® PID, Privigen® CIDP, CSL830 C1-INH Subcut, Haegarda®, Kcentra®, Idelvion®, Afstyla®, Zemaira®

Leadership Team

Paul Perreault
CEO and Managing Director

David Lamont
Chief Financial Officer

Andrew Cuthbertson
Chief Scientific Officer and R&D Director

Headquarters: King of Prussia, Pennsylvania, United States

5th largest biotechnology company with 25,000+ Employees around the world plus 1,700+ R&D employees

US$8.5 Billion in annual revenue with US$4.5 billion of sales revenue and US$1,919 million in reported net profit after tax.

35+ Countries of operations around the world with 8 subsidiaries

US$3.3 Billion in R&D investments in the last 5 years advances product pipeline

230+ Plasma collection centres across Europe and North America

CSL Behring
Biotherapies for Life™

Source : CSL Behring reports

Inline Products Portfolio

HEMATOLOGY AND THROMBOSIS

- AFSTYLA, Beriate, Beriplast
- Beriplast P Combi-Set, Beriplex P/N, Biostate, Cluviat, Cluvot, confidex, Corifact
- Factor X P Behring, Fibrogammin P, Haemate P, Haemocomplettan P, Humate-P, IDELVION, Kcentra, Kybernin, Kybernin P, Mononine, MonoFIX-VF, Prothrombinex-VF RiaSTAP, Stimate, TachoSil, Thrombotrol VF, Voncento

RESPIRATORY

- Respreeza
- Zemaira

IMMUNOLOGY AND NEUROLOGY

- Beriglobin P, Berinert, Berinert 2000/3000, Berirab P, Carimune NF, Evogam (16g/100mL),
- HAEGARDA, Hepatitis B Immunoglobulin P, Hizentra, Intragam P, Intragam 10, Privigen, Rhophylac, Tetagam P
- Tetanus Immunoglobulin-VF, IM Zoster Immunoglobulin-VF

ALBUMIN

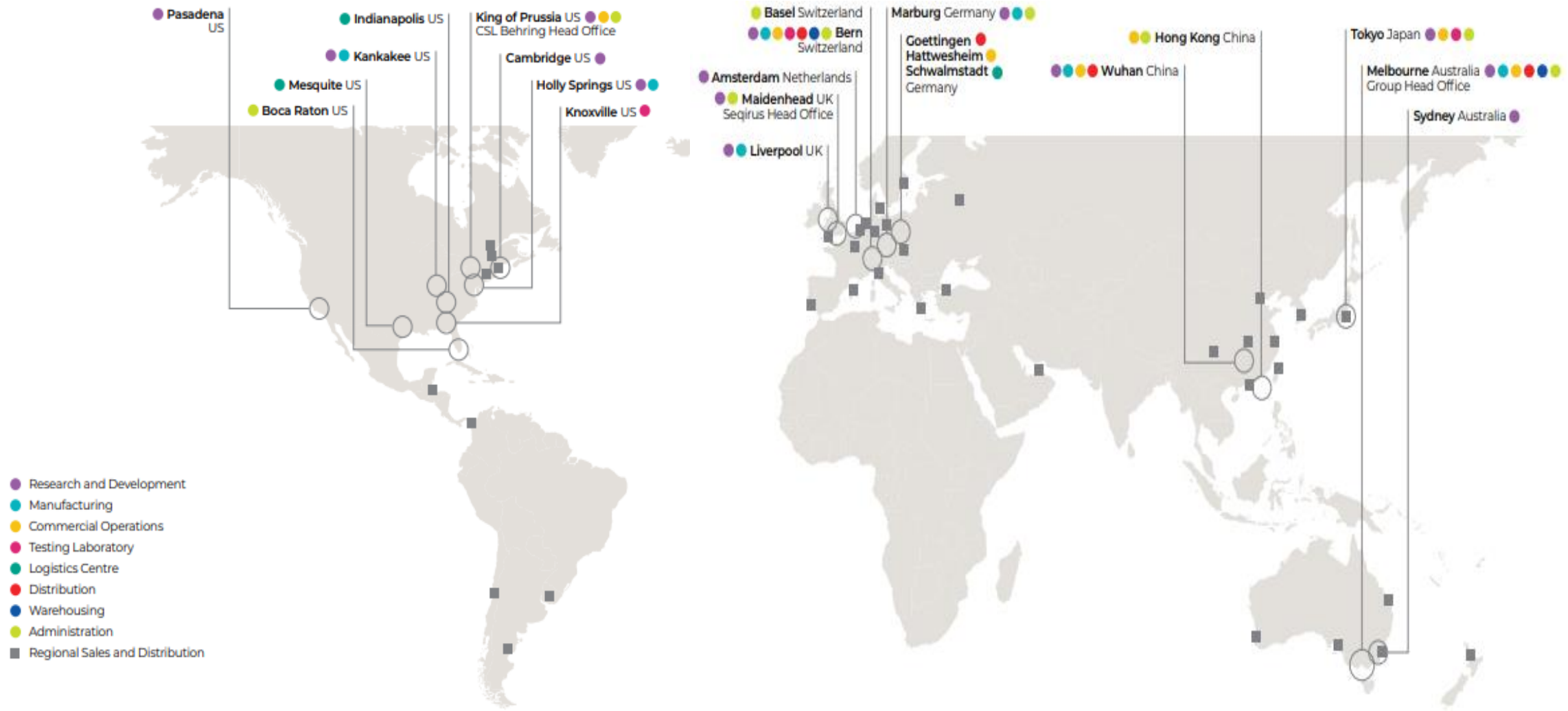
- Albapure
- Albumeon, Albumex
- Albuminar, Albunate, Alburex, AlbuRx
- Human Albumin, Humanalbin

CSL Behring
Biotherapies for Life™

PharmaACE

Source : CSL Behring reports

CSL Behring Worldwide Locations



CSL Behring
Biotherapies for Life™

Source : CSL Behring reports

PharmaACE

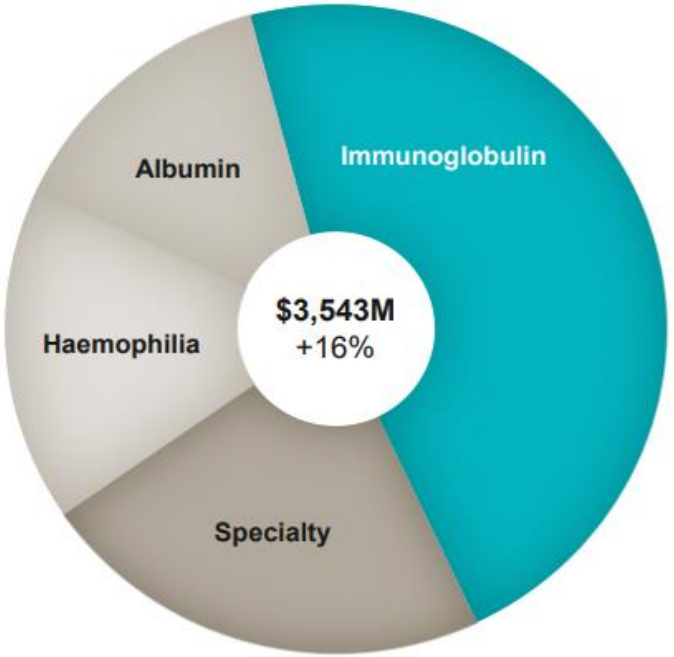
CSL Behring is planning to open ~40 new plasma collection centers in FY-2020

Significant target launch dates

2019	2020	2021-2025	
HIZENTRA® CIDP Japan	PRIVIGEN® PID Japan	Garadacimab (Anti-FXIIa) HAE	Clazakizumab AMR
PRIVIGEN® CIDP Japan	IDELVION® 21 Day Dosing	HIZENTRA® DM	IVIG Kidney AMR
AFLURIA® QIV 6m+ (AUS)	FLUAD® QIV 65yrs+ US, EU	HAEGARDA® Japan	CSL842 C1-INH rAMR
FLUCELVAX® QIV 9yrs+ EU		Improved Fibrinogen	CSL964 GvHD
		FLUCELVAX® 6m+ US, EU, AUS	CSL112 ApoA-I
		aQIVc 50yrs+	

Partnered Projects

Immunology and Neurology | Haematology and Thrombosis | Respiratory | Cardiovascular & Metabolic | Transplant | Influenza Vaccines

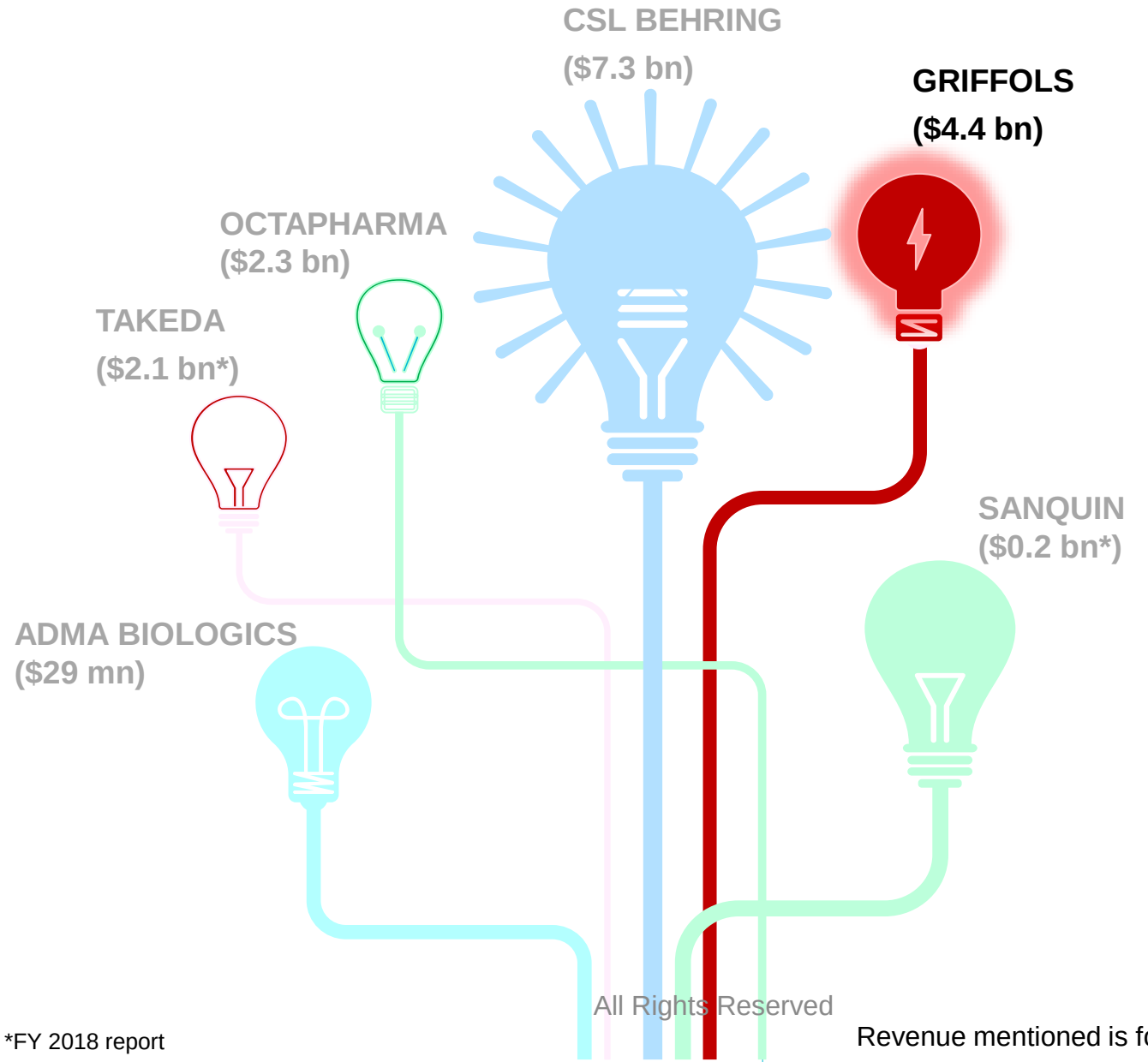


Plasma Sourcing

- CSL Behring opened 30 new plasma collection centers in US
- Total plasma collection centers – 221 in the US, 8 in Germany, 3 in Hungary and 5 in China
- Planning to open ~40 new centers in FY20
- Liquid saline & sodium citrate facility purchased in South Carolina US to support plasma collection
- A substantial 5,000m2 expansion of the Bio21 Institute in Parkville, Australia, incorporating CSL's Global Hub for Research and Translational Medicine was officially opened in December 2018
- CSL continues the base fractionation capacity expansion projects across their facilities in Broadmeadows, Kankakee and Marburg to meet the future global demand for their products by expanding production capacity and supporting end to-end manufacturing of plasma-derived therapies
- In order to meet the high demand for immunoglobulin products, CSL Behring is expanding its production capacity in Bern by investing CHF 300 million in the project which has created around 50 new jobs in the city of Bern

Source : CSL Behring reports

Grifols holds 2nd position in plasma market with ~27% market share



Source : Annual reports 2019; *FY 2018 report

Revenue mentioned is for plasma business only

Grifols Biosciences division (plasma-derived medicine production) leads 78% of their total revenue

Company Overview

- Since 1909, pioneer in the field of the plasma science and is one of the largest plasma companies with a growing network of donation centers worldwide
- Grifols main research areas are Transfusion Medicine, Immunology, Pulmonology, Hepatology, Hematology, Neuroscience, Critical Care
- The Bioscience Division is a leading producer of plasma-derived medicines for the treatment of rare, chronic and sometimes life-threatening conditions
- Grifols enters a strategic alliance with Shanghai RAAS to boost growth of its plasma-derived products and diagnostic solutions in China. Under the agreement, Grifols controls a 26.2% stake in Shanghai RAAS (economic and voting rights) in exchange for a non-majority share (45% economic and 40% voting rights) in Grifols Diagnostic Solutions (GDS)

Pipeline Product Portfolio

- **Clinical Development:** Albutein - *Acute-on-chronic liver failure, Liver Cirrhosis*; Alphanate- *Hemophilia A*; Immunoglobin- *Myasthenia Gravis*; IV Fibrinogen; Thrombate- *Cardiopulmonary bypass*; VistaSeal for *Pediatrics*
- **Registration/Post-Launch:** Albumin in bags, Plastem, SC Immunoglobin

Leadership Team

Joel Abelson
President, Bio-Science division

Carsten Schroeder
President, Diagnostics Commercial Division

Rob Jagt
President, Hospital Commercial Division

Headquarters: Barcelona, Spain

24,000+ Employees around the world with 72% American 18% Spanish and 10% rest of the world employee share

Increases its revenues by 14.5% to EUR 3,738 million in Q3 2019

Subsidiaries in 30 countries or regions and 13 production sites worldwide.

The Bioscience Division leads revenue growth, increasing by 13.4% to EUR 2,945 million, driven by demand of main plasma proteins in Q3 2019

290+ plasma donation centers and every day, an average of more than 30,000 donations are made at their centers.

GRIFOLS

Source : Grifols reports

PharmaACE

Inline Products Portfolio

COAGULATION

- Thrombate III, Antithrombin III (Human);
- ALPHANATE (antihemophilic factor/von Willebrand factor complex [human]); PROFILNINE (factor IX complex);
- AlphaNine SD(coagulation factor IX [human])

PULMONOLOGY

- PROLASTIN-C (Alpha1-proteinase inhibitor (human))

IMMUNOLOGY AND NEUROLOGY

- HyperTET S/D Tetanus Immune Globulin (Human), HyperHEP B S/D Hepatitis B Immune Globulin (Human); HyperRHO S/D Rho(D) Immune Globulin (Human); Flebogamma 10% DIF Immune Globulin Intravenous (Human), 10%; Flebogamma 5% DIF;
- GamaSTAN; GAMUNEX-C; HyperRAB

CRITICAL CARE

- Albutein 5%
- Albutein 25%
- Plasmanate
- Plasbumin-5

GRIFOLS

PharmaACE

Source : Grifols reports

Grifols, Bio sciences– Production Units World-wide


Dublin


Los Angeles

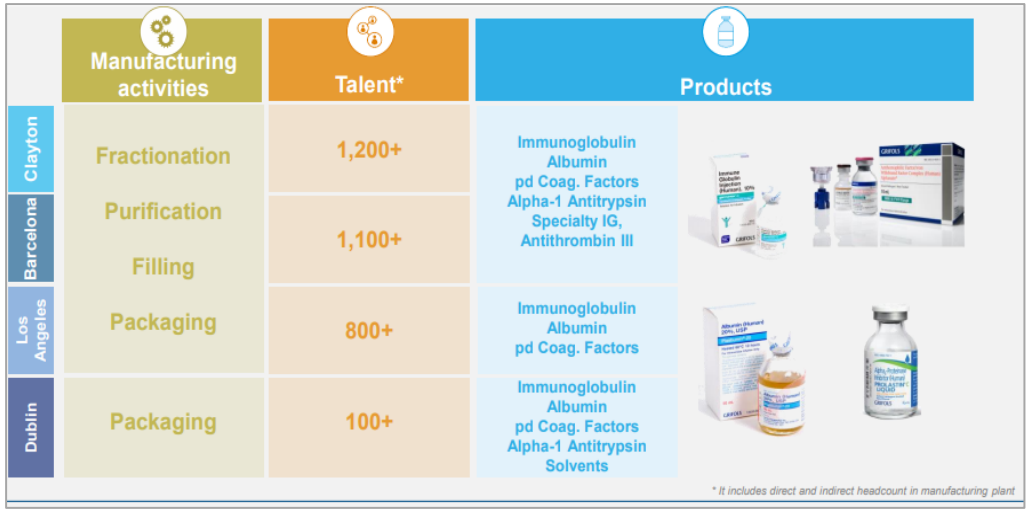

Barcelona

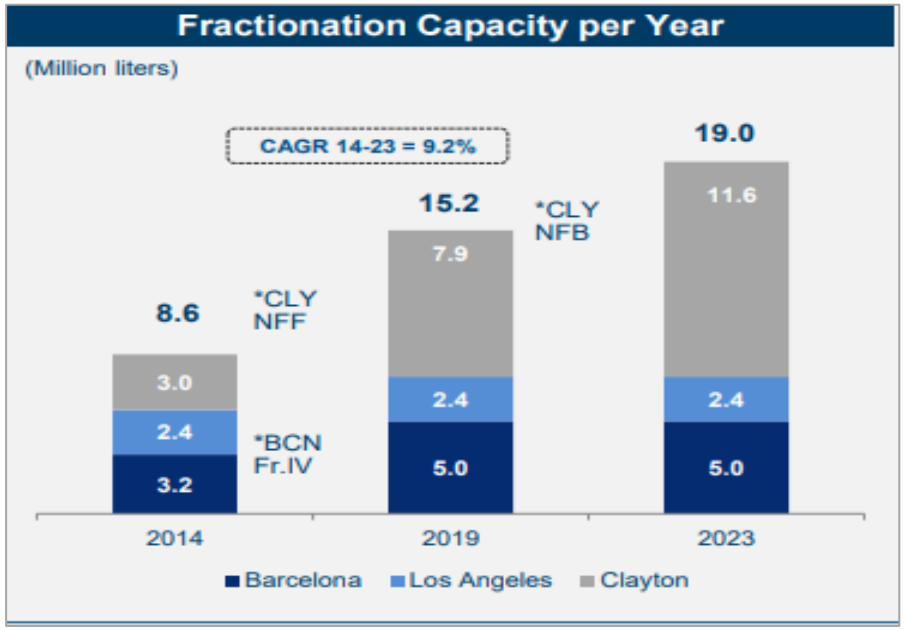

Clayton

GRIFOLS

PharmaACE

Grifols operates the largest network of plasma centers in the world, with 295 centers





- There are five Grifols-owned state-of-the-art facilities, three in the US (Austin and San Marcos, Texas, and Memphis, Tennessee) , one in Germany (Berlin) and another one in Spain (Barcelona)
- Four manufacturing plants:
  - A plasma fractionation plant in the US (North Carolina), expected to be operational by 2021
  - A purification plant for intravenous immunoglobulin in the US
  - Another plant for alpha 1-antitrypsin in Spain
  - Purification plant for albumin at the Grifols facilities in Dublin (Ireland) with capacity to produce between 130 and 150 million grams/year of albumin
- Grifols expands in Latin America with start of production at new plant in Brazil with a capacity of more than 10 million blood collection bags annually, the more than 5,500-square-meter facility in Campo Largo, Brazil, will serve the Latin American region
- Currently, global plasma collection network of 295 centers on two continents, 252 in U.S. and 43 in Europe; **Will expand to approximately 370 by 2024**

GRIFOLS

Source : Grifols reports

PharmaACE

At present, Grifols has a fractionation capacity of 15.2 million liters of plasma per year

Warehouses and QC Labs

Enhancing Manufacturing Chain

Capacities

Warehouses

North Carolina Final product Warehouse

- CAPEX ~ USD 12M
- +6,000 pallet positions → 31,250 ft²
- More efficient storage
- Improve physical & IT control over final product
- Risk reduction and no 3rd party

Los Angeles Packaging Operations

- CAPEX ~ USD 17M
- +17,000 pallet positions → +105,000 ft²
- Two new packaging lines
- Future Albumin in Bags packaging line
- +6% of final product storage capacity

QC Labs

QC Laboratories in Barcelona

- CAPEX ~ EUR 2.2M
- 6 Kardex carousel → +1.3 M samples
- Clinical archive of samples Library → up to 0.7 M in 2021
- R+D Lab enlargement (+450 m²)

QC Laboratories North Carolina & LA

- CAPEX ~ EUR 5M
- Micro / Sterility Lab
- +107% of area expansion
- Improve performance of assays
- Sterility testing area based on isolators

Alignment across the supply chain drives cost reductions

Infrastructure

Highly automated plasma logistics centers (7.7m liters global storage) capacity)

Clayton/Benson	Los Angeles	Barcelona	Dublin
4.4m liter capacity	1.5m liter capacity	1.0m liter capacity	0.8m liter capacity

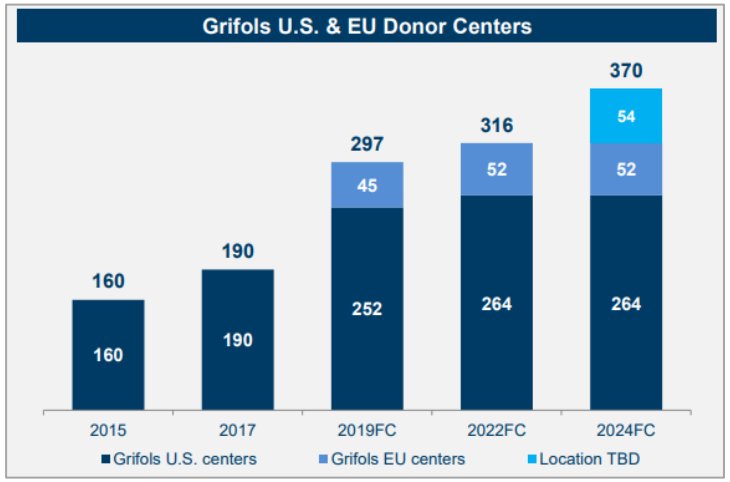
Dedicated trucking companies · Specialized ocean freight carriers

Processes

- Geographic alignment of centers to plasma logistic warehouse → 50+% U.S. freight cost/l reduction since 2011
- Ocean container shipments to Europe → 40% transit time reduction since 2016
- Ocean container load maximization → 20% ocean freight cost reduction since Q1 2017

Integrated global plasma supply chain → Coordinated movements of material between U.S., Ireland, and Spain

On-Test plasma shipments to plasma logistics centers → 65% center inventory reduction since 2011



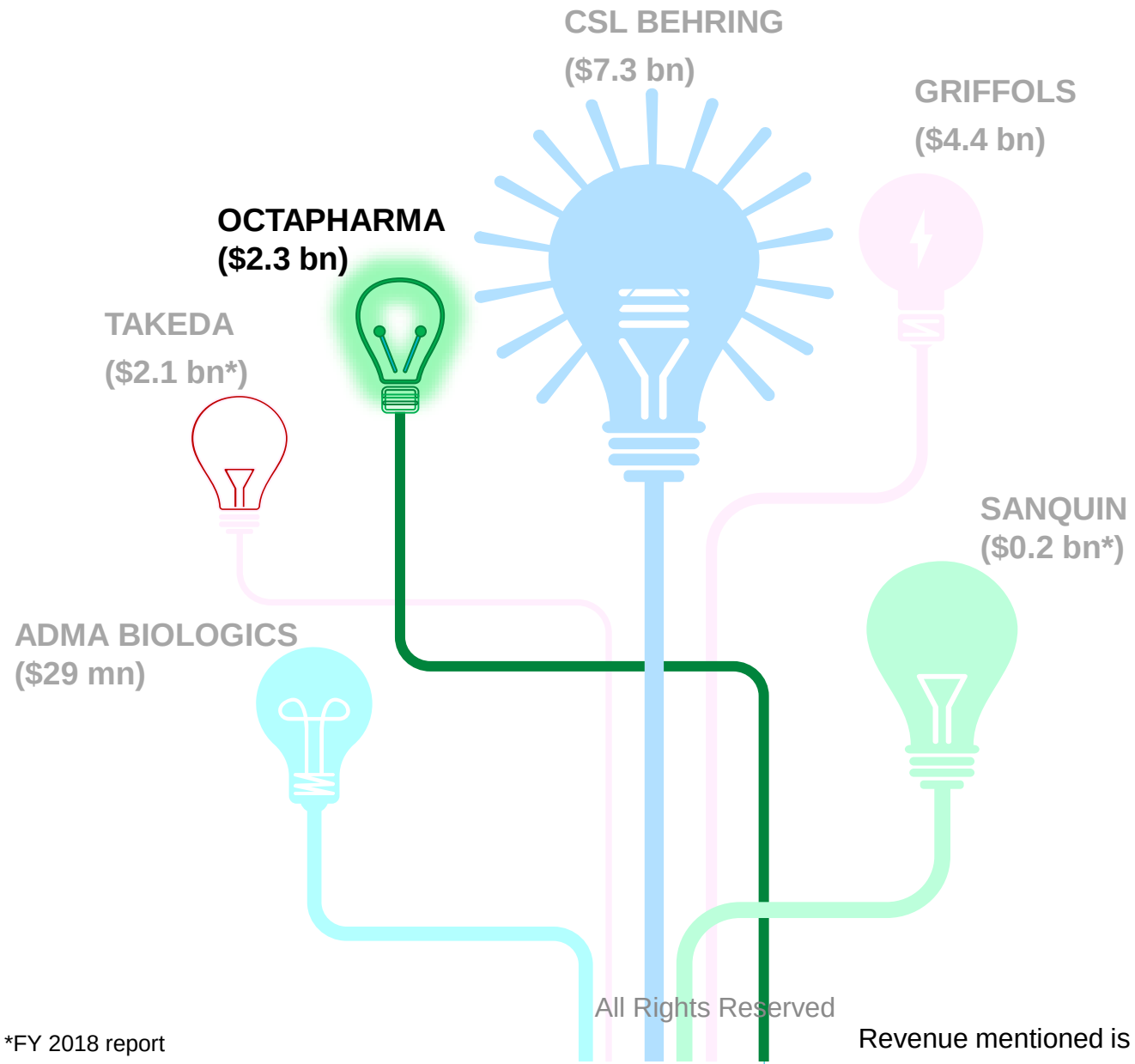
- Grifols U.S. centers and warehouses currently operate with centralized release, enabling efficiencies in inventory management
- Construction of the world's first purification, dosing and sterile filling plant of immunoglobulins in flexible bags. The plant will have an annual production capacity of 6 million equivalent liters of plasma and is expected to be operational in 2022
- Plasma obtained have increased significantly, Grifols Plasma Volume Performance in Liters driven by improved processes, extension of hours, facility expansions, and acquisitions
- Process efficiencies allow continuous incremental capacities: 3% fractionation capacity increase over 2018
- Grifols increased its capacity to 45,000 average daily donations and total volume of plasma obtained for fractionation to nearly 15.2 million liters

GRIFOLS

PharmaACE

Source : Grifols reports

Octapharma holds 3rd position with market share of ~14% in plasma industry



Source : Annual reports 2019; *FY 2018 report

Revenue mentioned is for plasma business only

PharmaACE

OCTAPHARMA, the largest privately owned and independent plasma fractionator in the world

Company Overview

- They develop and manufacture medicines for patients in three therapeutic areas: hematology, immunotherapy and critical care
- Octapharma is a family owned global healthcare company since being established in 1983
- Octapharma Plasma GmbH has 13 donation centres in Germany and helps to ensure an independent supply of plasma in Germany and the rest of Europe
- Octapharma's clinical R&D sites are in Vienna, Austria; Lachen, Switzerland; and Hoboken, New Jersey, USA who are responsible for all their product trials and for the life-cycle management support of all their marketed medicines

Product Portfolio

Clinical Development:

- Currently, they run over 15 ongoing interventional clinical studies
- Presented an update on the clinical development plan and pre-clinical data with SubQ-8, a novel subcutaneous recombinant factor VIII (FVIII) in development, at the 27th International Society on Thrombosis and Hemostasis (ISTH) Congress in Melbourne, Australia, ISTH 2019

Leadership Team

Wolfgang Marguerre
Chairman and CEO, Octapharma Group

Frederic Marguerre
President Octapharma Plasma Inc. USA

Flemming Nielsen
President Octapharma USA Inc.

Headquarters: Lachen, Switzerland

9,300+ Employees around the world. 5,509 female 3,798 male across 71 nationalities

Sales increase of €417 million (23.2%) compared to 2018. Operating income increased by €78.6 million (22.7%) compared with 2018, to €424 million

Serving patients in 118 countries with **6 manufacturing sites and 7 preclinical and clinical R&D sites**

For the year 2019, €75 million were invested in Research and development

More than 120+ plasma centers across Europe and the US.

octapharma

Source : Octapharma reports

PharmaACE

Inline Products Portfolio of Octapharma

IMMUNOTHERAPY

- Albunorm, Human Albumin solution
- Atenativ, Human Anti-thrombin III concentrate
- OctaplasLG/Octaplas, Pharmaceutically licensed plasma
- Octaplex, Human prothrombin complex concentrate
- Fibryga, Human fibrinogen concentrate

HAEMATOLOGY

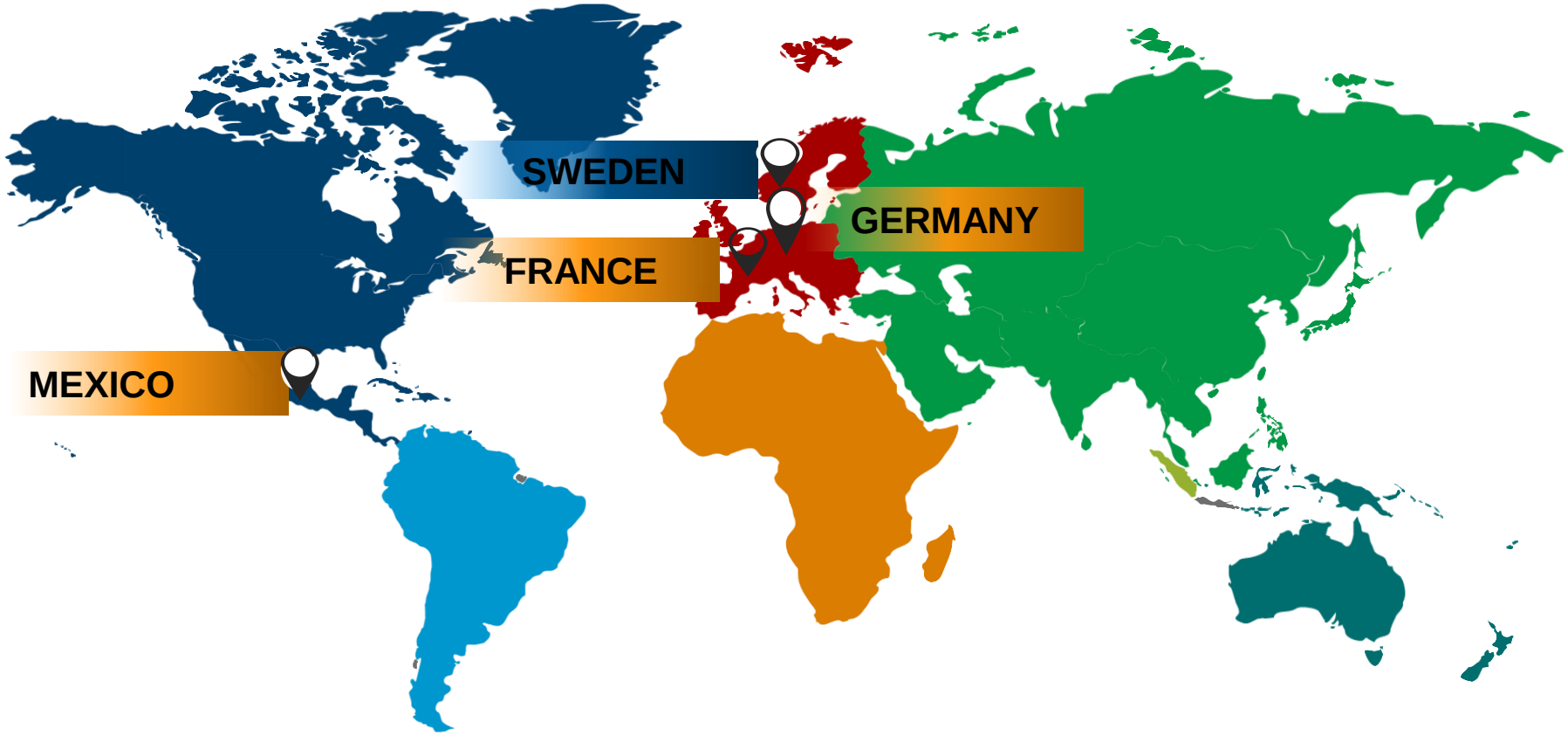
- Cutaquiq, SC human normal immunoglobin
- Gammanorm, Subcutaneous Human Normal Immunoglobulin
- Rhesonativ, Anti-D Immunoglobulin
- Octagam, Intravenous Human Normal Immunoglobulin
- Panzyga, Intravenous Human Normal Immunoglobulin

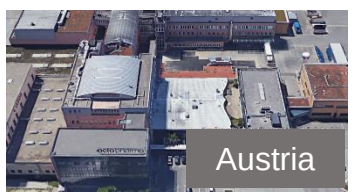
CRITICAL CARE

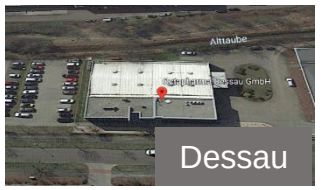
- Nuwiq, Human Coagulation Factor VIII (rDNA) (simoctocog alfa)
- Octanate, Human plasma-derived coagulation factor VIII concentrate, naturally stabilised with von Willebrand factor (VWF)
- Octanine F, High-purity plasma-derived human factor IX concentrate
- Wilate, High-purity, human von Willebrand factor/coagulation factor VIII complex concentrate

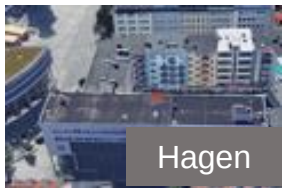
Source : Octapharma reports

Octapharma – Manufacturing Sites









octapharma

Frankfurt, Dessau, Hagen are cities in Germany

PharmaACE

Source : Octapharma reports

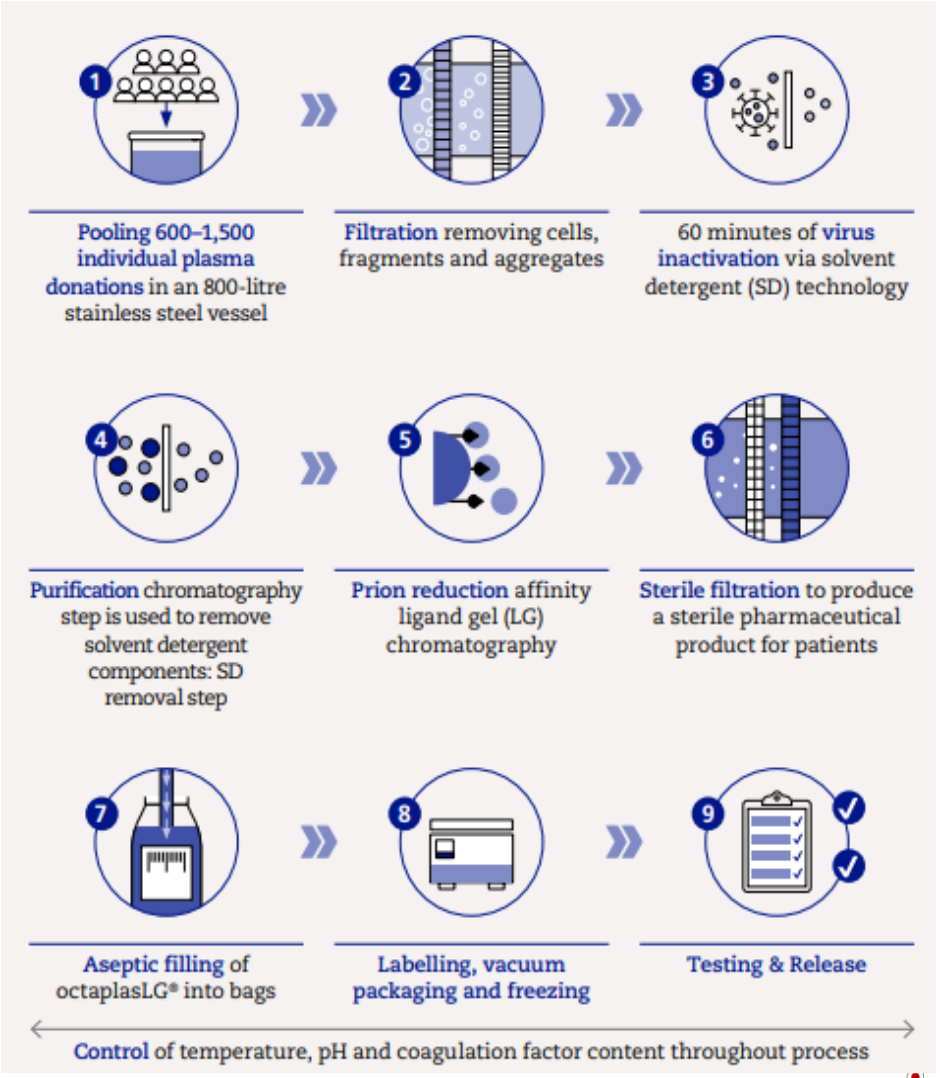
Plasma is central to Octapharma's business, with 80% of their supplies coming from company-owned donation centers

Plasma fractionation process

- A donation session takes 45-90 mins and 300-880 ml of plasma is taken for each donation with 61% of source plasma donors are male
- Thawing is the first step to separate plasma in which the plasma is deep-frozen at -25° to -30°C. The cool rooms are warmed slowly up to -5°C to thaw the plasma. The plasma remains in the cool room for about 16 hours, then it is driven to pooling
- The most important steps in the production of octaplasLG are the pooling and the virus inactivation
- There are three poolings done per day i.e. approximately 5,250kg of plasma are processed, which equates to 6,000–18,000 single donations
- After pooling, mass capture, cryoprecipitation, chromatography, centrifugation and precipitation takes place to get the desired product

Octapharma Capacity Analysis

- Annually, Octapharma **processes greater than 6 m liters** of plasma
- Plasma is central to Octapharma's business, with **80% of their supplies coming from company-owned donation centers**
- 18 pallets correspond to around 13,000 litres of plasma is transported by sea from USA to Germany
- In Stockholm, they pool 600–1,500 individual plasma donations in an 800-litre stainless steel vessel and produce an average of 3,600 bags of octaplasLG, which is 780kg of plasma and takes 24hrs for the whole process
- **Vienna is the central plasma warehouse in Europe and receives 70% of the total plasma used by Octapharma**
- The plasma pool size in Vienna IS 3190kg. Nine plasma pools are produced every week

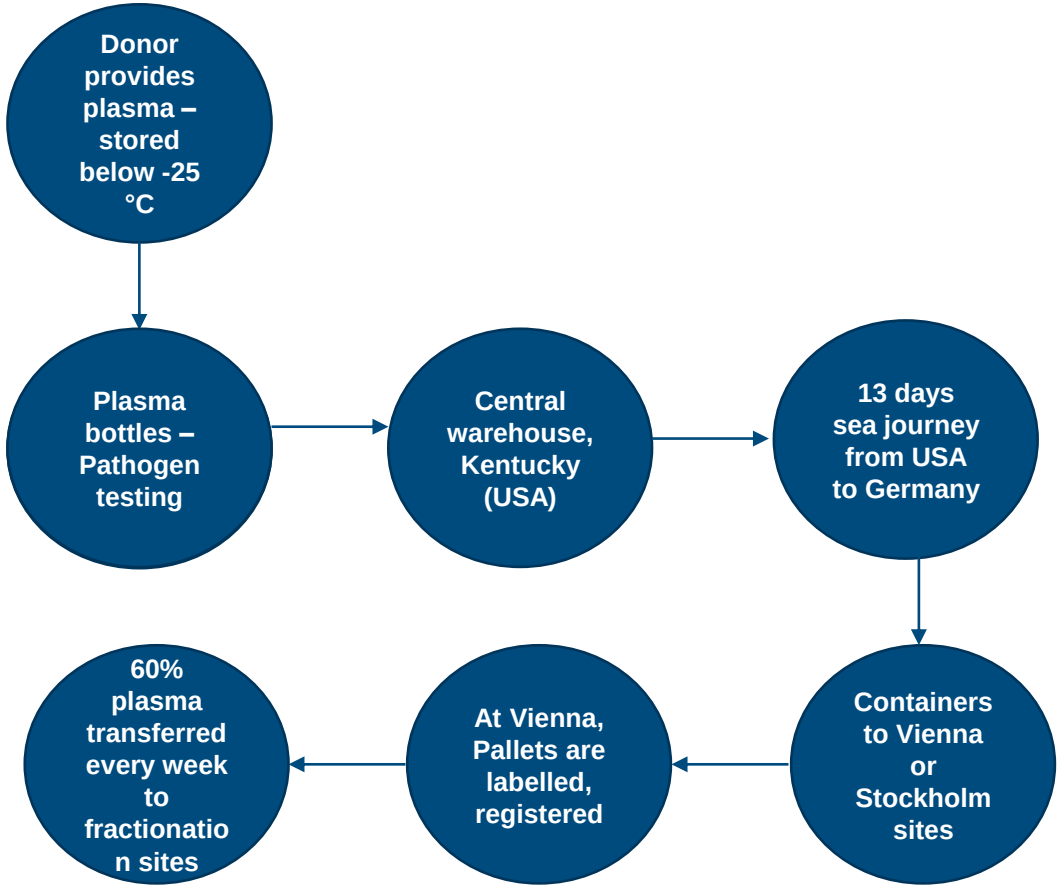


Source : Octapharma reports

Around 4,200 Octapharma Plasma, Inc.(OPI) employees navigate more than 20,000 donors across the USA every day

Plasma Transportation process

- The donor provides plasma via an apheresis machine and is frozen and stored below -25 °C in a plastic bottle. It is recorded in a Donation Management System
- Collected samples are sent for pathogen testing in different labs, including Octapharma Plasma Inc.'s Charlotte, N.C. (USA) laboratory
- Plasma bottles of suitable donations are packed in cartons and stacked on pallets and transported by truck to a central warehouse in Kentucky (USA)
- After a documentation check, the plasma pallets are loaded into a container and sent by truck to a port on the East coast, Norfolk, Virginia, USA
- Approximately 6-9 Containers are transported every week from USA to Bremerhaven port in Germany by sea (journey time - 13 days)
- The containers are transferred to a truck bound for the Vienna or Stockholm Octapharma sites
- After customs clearance at Vienna (Austria), the truck arrives at the Octapharma Vienna plant or the external warehouse where the pallets of plasma are labelled, registered and moved to the main freezer warehouse in 25 mins by 4 or 5 staff
- Around 60% of received plasma is transferred every week in temperature monitored trucks to other fractionation sites, such as Lingolsheim (France) and Springe (Germany)
- In production, the plasma bottles are cut open and put into the thawing tank

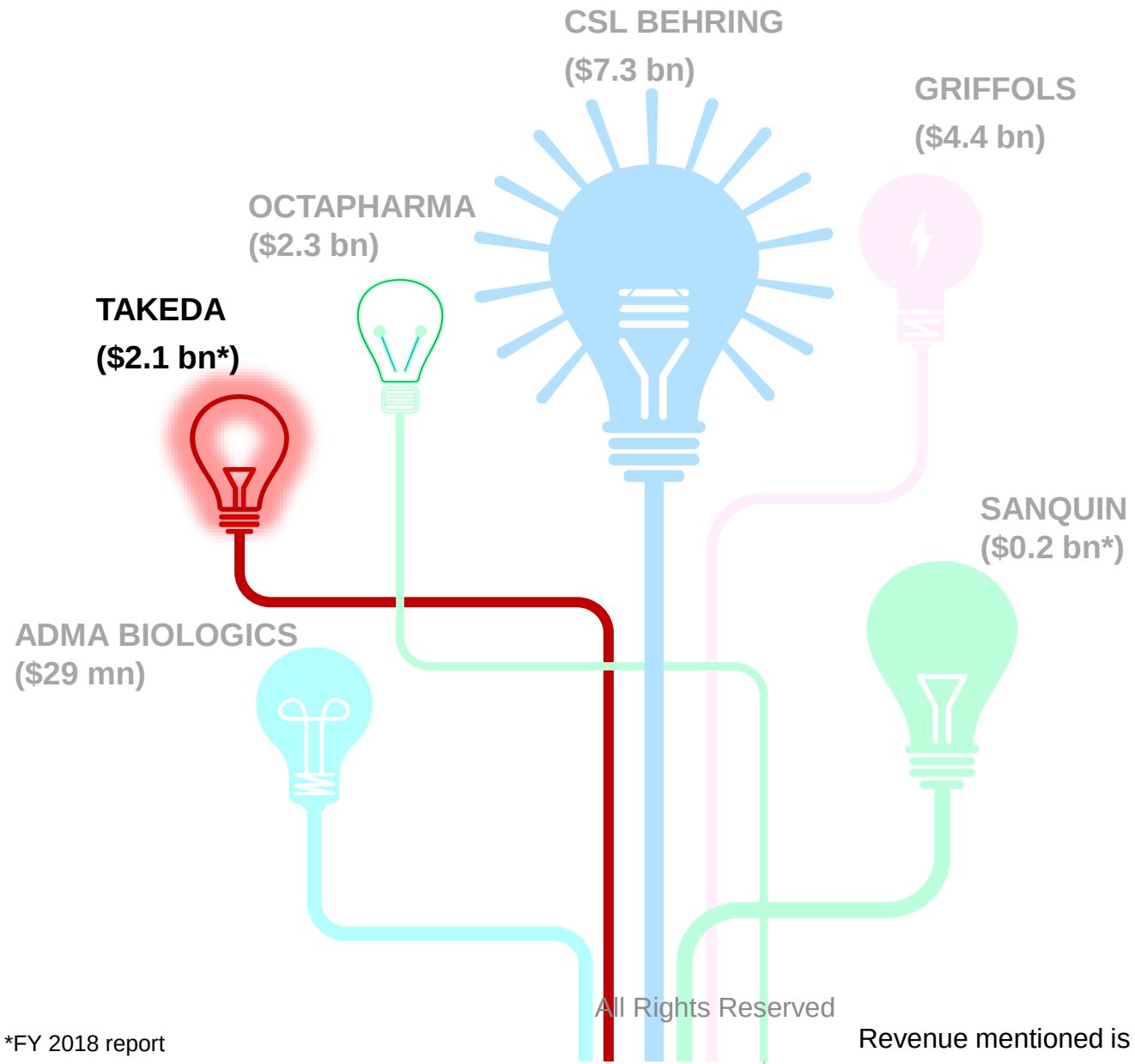


Key Points from Leadership and Team

- **Jonathan** and his team in North Carolina, USA, are responsible for the site selection process for new centers and **Bill Griner**, who runs the Operations and Marketing team plays a vital role
- Around 4,200 Octapharma Plasma, Inc.(OPI) employees navigate more than 20,000 donors across the USA every day whereas 540 employees navigate more than 1,800 donors a day in Germany

Source : Octapharma reports

Takeda, with ~13% market share holds 4th position in plasma industry



Source : Annual reports 2019; *FY 2018 report

Revenue mentioned is for plasma business only

PharmaACE

TAKEDA is a global, R&D driven biopharmaceutical leader with a presence in 80 countries and regions

Company Overview

- Takeda has a 75+ year pioneering legacy in producing plasma-derived therapies
- Takeda focusses on five key business areas of GI, rare diseases, plasma-derived therapies, oncology and neuroscience
- In the fiscal year ended Mar 31, 2019, revenue from plasma-derived therapy products was ¥111.7 billion
- Plans to increase plasma supply and manufacturing capacity by >65% over the next five years
- **BioLife, part of Takeda**, is their global plasma collection network and an industry leader in the collection of high-quality plasma

Product Portfolio

Clinical Development:

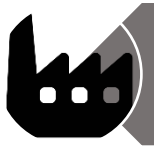
- They have a broad and differentiated portfolio of plasma-derived products, including more than 20 therapies with no patent expiry, including a diverse offering of subcutaneous IG (SCIG) products

Leadership Team

Christophe Weber
Representative director, President & CEO

Masato Iwasaki
Director
President, Japan Pharma Business Unit

Andrew S. Plump
Director
President, R&D



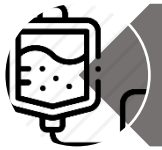
Headquartered in Japan

As of Mar 31, 2019, 49,578 employees around the world of which 6,941 were based in Japan and 42,637 employees were based outside Japan

Takeda's 14 global brands, with reported revenue of 836.4 billion yen in aggregate, posted a strong year-over-year underlying revenue growth of +20%

36 manufacturing sites spanning the globe, Takeda manufactures medicine for patients on 4 platforms: Small Molecules, Biologics, Plasma and Cell and Gene

As of Jan 14, 2020, Takeda has 3 research sites



As of Feb 4, 2020, 118 plasma collection centers in the U.S. and 31 ex-U.S

Source : Takeda reports

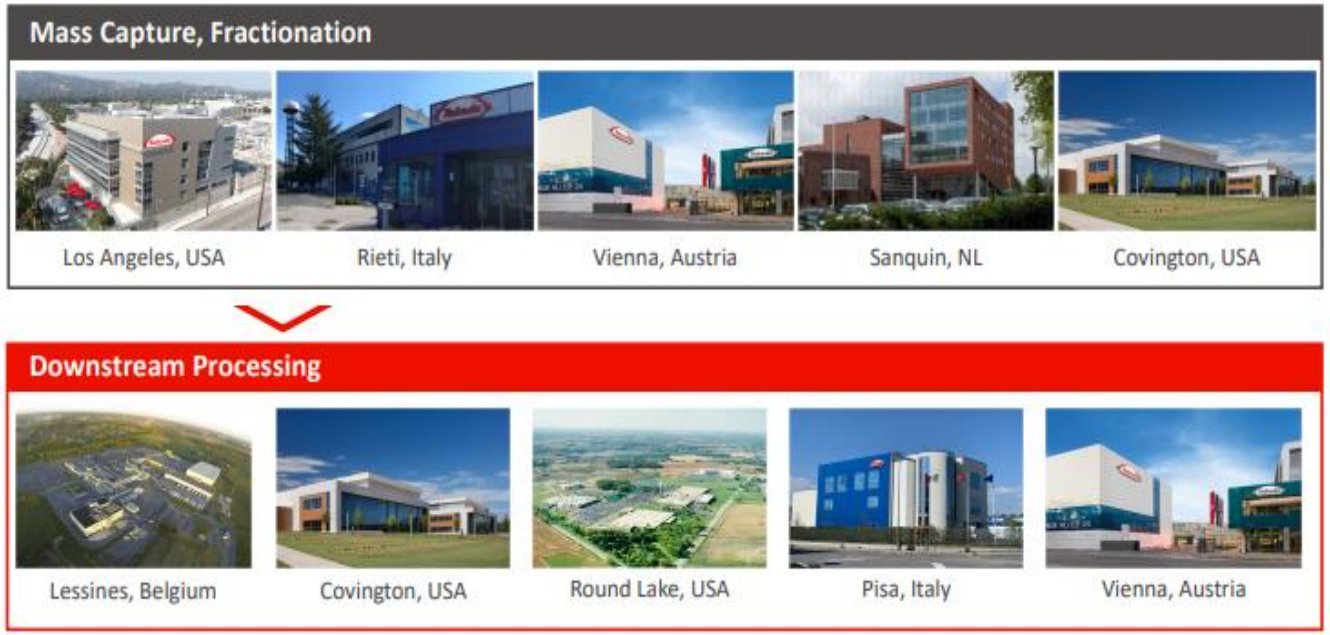
PharmaACE

Inline Products Portfolio of Takeda

HEMOPHILIA PRODUCTS	▪ Hemofil M, Feiba, Immunine, Immunate
IMMUNOGLOBULIN	▪ Gammagard Liquid, Kiovig, Cuvitru, Hyqvia, Kenketu Glovenin-I
ALBUMIN	▪ Flexbumin, HumanAlbumin, Kenketu Albumin, Kenketu Albuminate
OTHER PRODUCTS	▪ Aralast NP, Glassia, Cinryze, Ceprotin, Prothromplex NF 600, Kenketu Nonthron, Antithrombin III

Source : Takeda reports

BioLife Plasma Services operates numerous state-of-the-art plasma collection facilities throughout U.S. and Austria where plasma is tested too



Plasma Sourcing

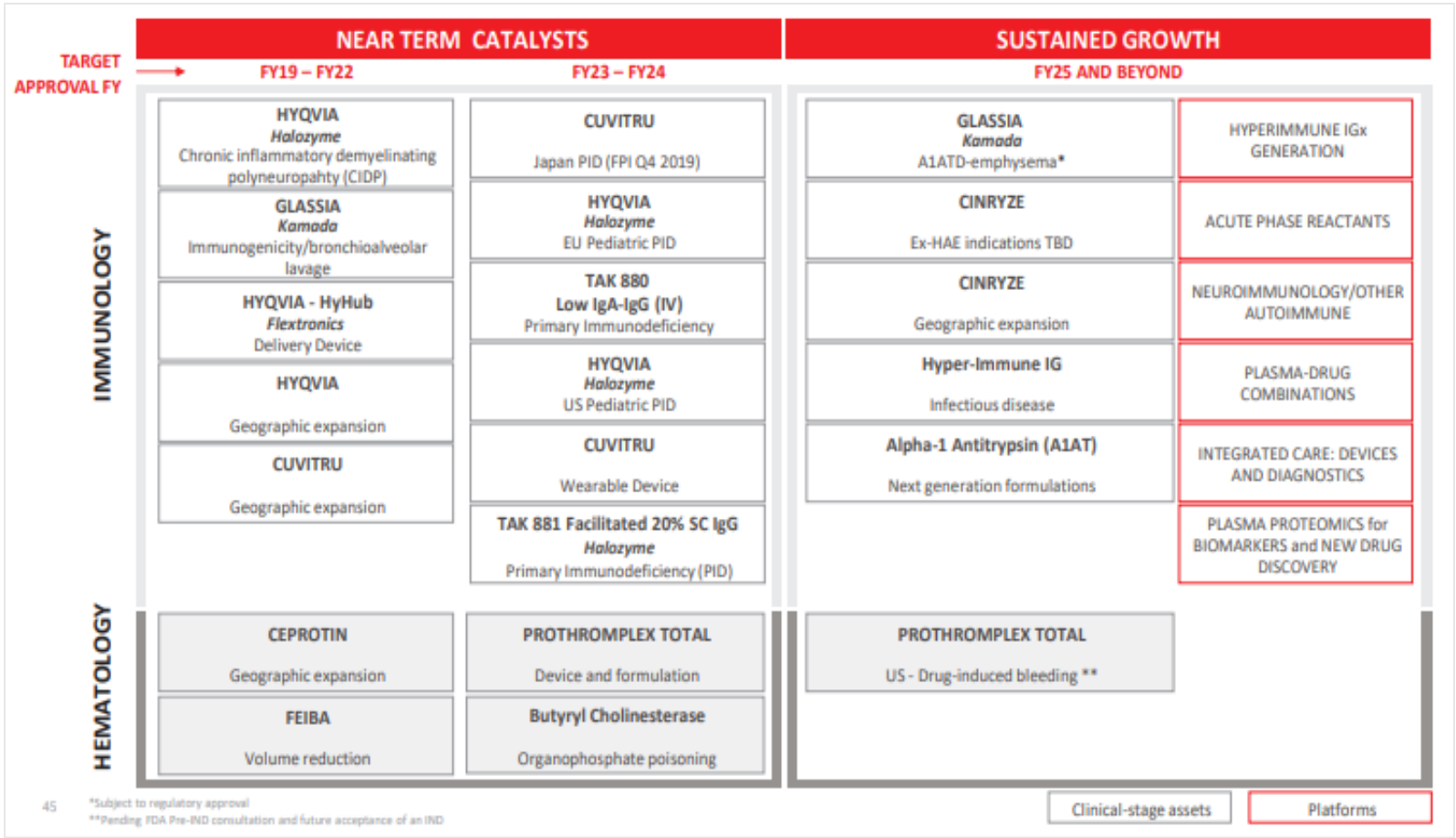
- Takeda has more than 140 plasma collection centers
- They increased plasma volumes by approx. 20% in 2018
- As of Feb 2020, they increased European plasma collection centers to 31
- They also leverage third party plasma supply through long-term contracts. Currently they have 5 US suppliers and 50 EU suppliers
- Takeda participates in contract agreements with government
- They acquired additional 10 plasma collection centers since Shire acquisition close- 1 in US, 2 in Austria and 7 in Hungary
- BioLife Plasma Services operates numerous state-of-the-art plasma collection facilities throughout the United States and Austria where plasma is tested too

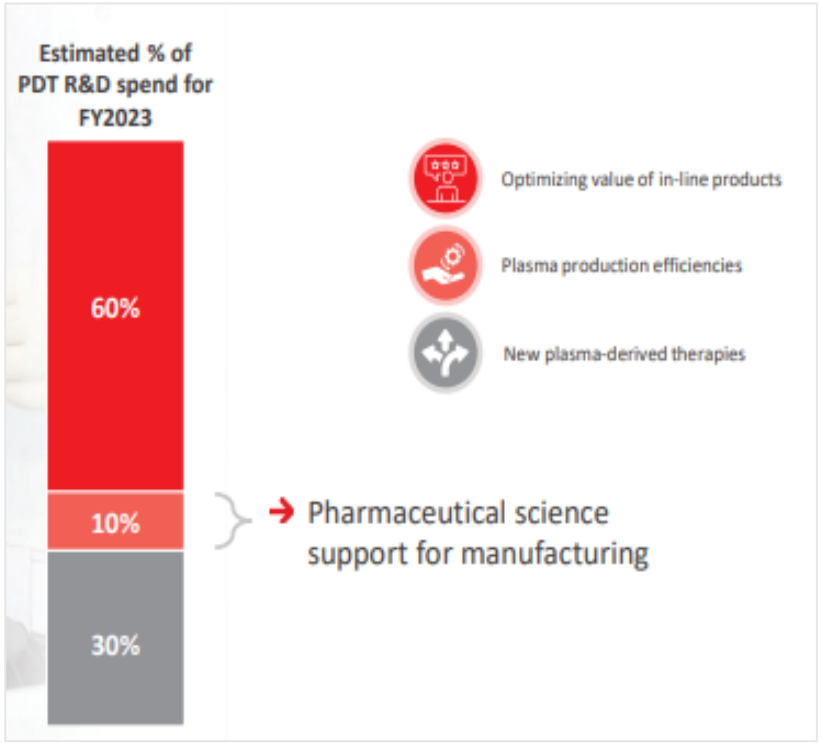
Plasma Manufacturing Capabilities

- In Japan, Takeda has domestic manufacturing capabilities through their subsidiary Nihon Pharma with a **fractionation capacity of 400 KL**
- They have 8 strategic manufacturing locations at Belgium, Italy, Austria, Japan, Georgia, Illinois, California and 4 external manufacturing partners at Netherlands, Israel, California, Indiana (Baxter)
- Over the next 5 years, Takeda plans to **increase their manufacturing capacity by 65% within its existing network**
- With respect to diagnosis, Takeda has partnered with large hospital systems in US to leverage electronic medical records
- Takeda co-chairs the Global Commission to end the diagnostic Odyssey for children with rare diseases
- They have more than 40 trained staff dedicated to virology department to maintain safety standards and has 3 screening labs
- Their Plasma Derived Therapies leadership team has 19 members

Source : Takeda reports

By 2023, Takeda plans to allocate 70% of resources to improve in-line products and product efficiencies





- By 2023, Takeda plans to allocate 70% of resources to improve in-line products and product efficiencies by
  - Device-driven solutions for management, diagnosis and long-term follow up
  - By expanding indications, global expansion of products and new formulations
- The rest 30% is planned to be allocated for new targeted therapies in diverse therapeutic areas

Source : Takeda reports

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Major Mergers & Acquisitions of Plasma Industry

Mar 2019, Grifols enters a strategic alliance with Shanghai RAAS to boost growth of its plasma-derived products and diagnostic solutions in China

- Under the agreement, Grifols will control a 26.2% stake in Shanghai RAAS (economic and voting rights) in exchange for a non-majority share (45% economic and 40% voting rights) in Grifols Diagnostic Solutions (GDS), a wholly-owned subsidiary

Jan 2019, Takeda completed $62 bn acquisition of shire, becoming a global, values-based, R&D-driven biopharmaceutical leader

Aug 2018, Grifols closed a transaction to acquire 24 plasma donation centers in the United States operated by Biotest Pharmaceuticals Corp for $286 Mn

Jun 2017, ADMA Biologics completed acquisition of Biotest's Therapy Business Unit (BTBU) assets

- As a result of this transaction, ADMA has acquired two U.S. Food and Drug Administration (FDA) licensed products, Nabi-HB™ (Hepatitis B Immune Globulin, Human) and BIVIGAM™ (Immune Globulin Intravenous, Human) and manufacturing and testing operations consisting of two facilities totaling approximately 126,000 square feet on approximately 15 acres of land located in Boca Raton, Florida
- ADMA has received $27.5 Mn in cash, with an additional $12.5 Mn commitment from Biotest Pharmaceuticals Corporation to invest in future ADMA equity financings

Jun 2016, Shire grew into a leader in Plasma derived therapies through its $32 bn takeover of Baxalta, the Baxter spinoff that had a portfolio of such products and the infrastructure to manufacture them

Source : Company reports

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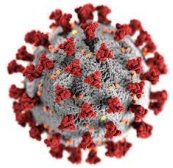
Effect of COVID-19 on Plasma Industry



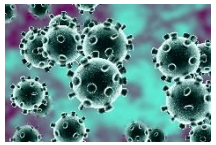
Blood draining spell by Corona

- **Blood collection centers around China have reported sharp drops in donations, with one even issuing a "red alert" as stocks dwindle**
- With quarantine measures to prevent the coronavirus spread limiting large gatherings, donation centers are struggling to match regular levels of giving by students, military members, employees at state-owned companies and walk-in contributions
- Some collection centers promoted donations as a way of supporting the fight against the pandemic
- **The same situation is in US. Dozens of blood drives have been canceled**, and regular donors are no-shows, industry officials said, especially in states like Washington and California where the virus is spreading more broadly within communities and health officials are urging residents to avoid public gatherings to reduce risk
- Worried citizens have two key concerns about the blood supply, officials said: whether potential donors are at greater risk of contracting COVID-19 infections by taking part in blood drives or at donation centers and whether donors infected with coronavirus risk contaminating the blood supply
- The American Red Cross said that **as of 19 March 2020, more than 5,000 of its blood drives were canceled across the US over coronavirus concerns – resulting in approximately 170,000 fewer donations**
- However, Red-cross officials are trying to emphasize that there is no data or evidence that COVID-19 can be transmitted by blood transfusion, and there have been no reported cases of transmissions for any respiratory virus, including this coronavirus, worldwide

Plasma to treat COVID-19 disease

- Doctors in Shanghai are using infusions of blood plasma from people who have recovered from the coronavirus to treat those still battling the infection, reporting some encouraging preliminary results, said Lu Hongzhou, professor and co-director of the Shanghai Public Health Clinical Centre
- **Mar 27, 2020,** Chinese researchers reported that **convalescent plasma appeared to help Covid-19 patients on ventilation**, but the study involved only five patient
- Mar 24, 2020, The FDA allowed **use of investigational convalescent plasma under single-patient emergency Investigational New Drug Applications (INDs), since no known cure exists, and a vaccine is more than 1 year away from becoming available**
    - This does not include the use of COVID-19 convalescent plasma for the prevention of infection, according to a statement issued by the FDA
    - FDA asked the Red Cross to help identify COVID-19 recovered donors and manage distribution of the plasma to hospitals treating patients in need

Source : FDA, Guardian and Medscape reports



Convalescent Plasma to treat COVID-19

octapharma

- **Apr 17, 2020,** Octapharma USA is supporting a new investigator initiated clinical trial led by George Sakoulas, M.D. of Sharp Memorial Hospital in San Diego, California focused on treating the most critical COVID-19 patients, those experiencing respiratory failure who become ventilator dependent

CSL Behring
Biotherapies for Life™

- **Apr 8, 2020,** CSL Behring and SAB Biotherapeutics (SAB) announced partnership for the rapid development of SAB-185, generated from SAB's proprietary DiversitAb™ platform producing large volumes of human polyclonal antibodies targeted specifically to SARS-CoV-2, the virus that causes COVID-19
- CSL Behring have donated their proprietary adjuvant technology, MF59®, to the **University of Queensland (AUS)** 's pre-clinical development program of COVID-19 vaccine

- **Apr 6, 2020, Biotest, BPL, LFB, and Octapharma have** joined the CoVIg-19 plasma alliance formed by **CSL Behring and Takeda** to develop anti-SARS-CoV-2 polyclonal hyperimmune globulin **(H-IG)** medicine with the potential to treat individuals with serious complications from COVID-19

emergent
biosolutions™

- **Apr 2, 2020,** Emergent BioSolutions partners with U.S. Government for the development of two Plasma-Derived Therapy, one based on horse-derived plasma and other human-derived plasma for COVID-19

GRIFOLS

- **Mar 25, 2020,** Grifols announced its formal collaboration with Biomedical Advanced Research Development Authority (BARDA), FDA and other Federal public health agencies **to collect plasma from convalescent COVID-19 patients, process this into a H-IG** in Clayton, North Carolina and support preclinical and clinical studies to determine if anti-SARS-CoV-2 **H-IG** therapy can successfully be used to treat COVID-19 disease
- **Grifols is providing viral inactivation technology to ensure inactivated plasma units for COVID-19 treatment** use for which it will be building a new facility in the Clayton site
- In Spain, the **Grifols is collaborating with certain hospitals in the design of diverse clinical studies on the use of intravenous immunoglobulin and alpha-1 antitrypsin**, with the goal of proving their efficacy in the treatment of COVID-19
- In addition, **Grifols has accelerated the development and validation of an automated TMA (transcription-mediated amplification) based diagnostic test to detect SARS-CoV-2** with each unit able to run more than 1,000 samples per day, and is expected to be ready by early May

Source : Company reports