



Plasma-Derived Therapies Basics



July 12, 2019

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Takeda Pharmaceutical Company Limited

Better Health, Brighter Future

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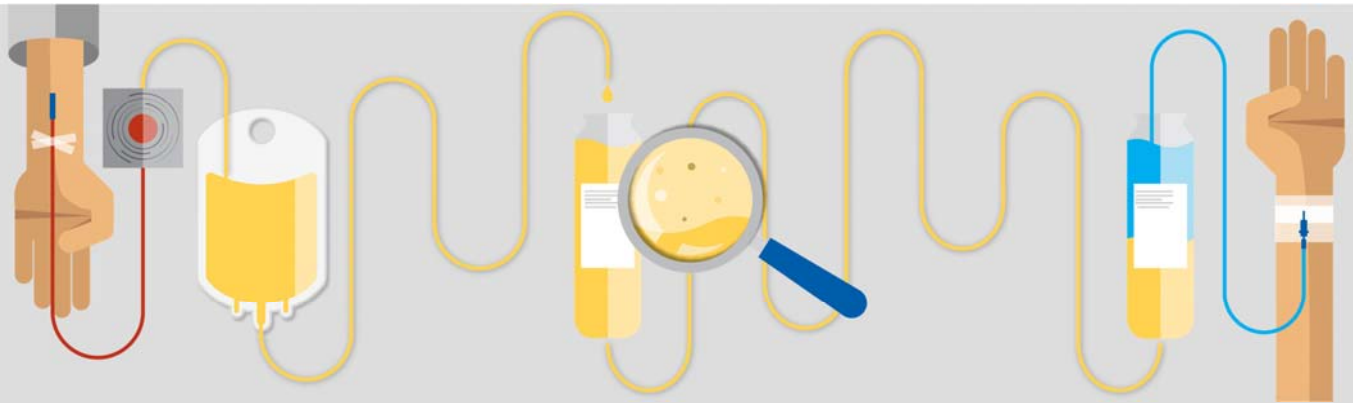
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Takeda's financial statements are prepared in accordance with International Financial Reporting Standards ("**IFRS**"). The financial statements of Shire plc ("**Shire**") are presented in accordance with accounting principles generally accepted in the United States ("**U.S. GAAP**"). Therefore, the respective financial information of Takeda and Shire are not directly comparable.

The Shire acquisition closed on January 8, 2019, and our consolidated results for the fiscal year ended March 31, 2019 include Shire's results from January 8, 2019 to March 31, 2019. References to "Legacy Takeda" businesses are to our businesses held prior to our acquisition of Shire. References to "Legacy Shire" businesses are to those businesses acquired through the Shire acquisition.

AGENDA:



1

What are plasma-derived therapies (PDT)?

2

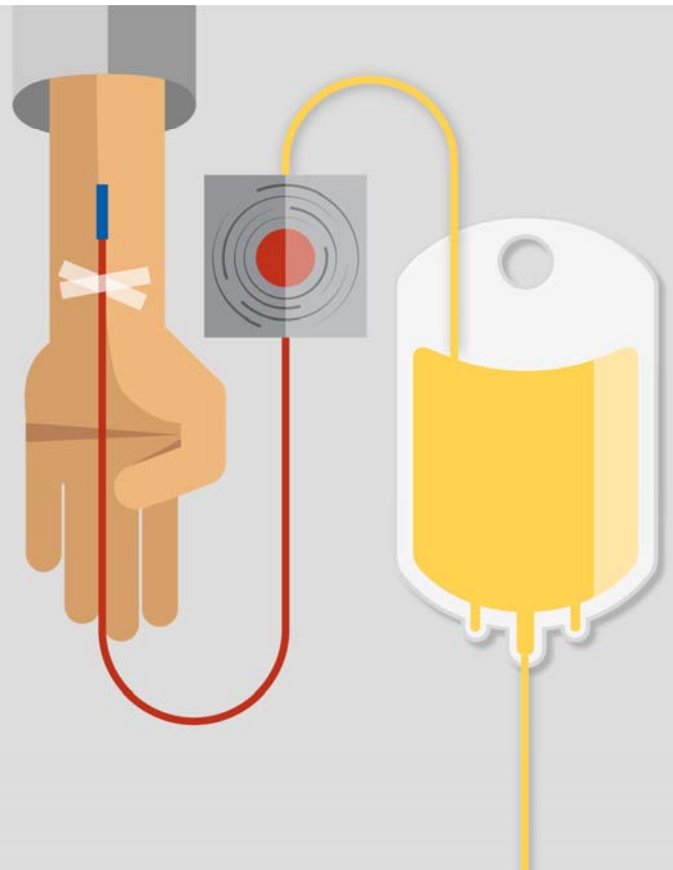
What is the PDT market?

3

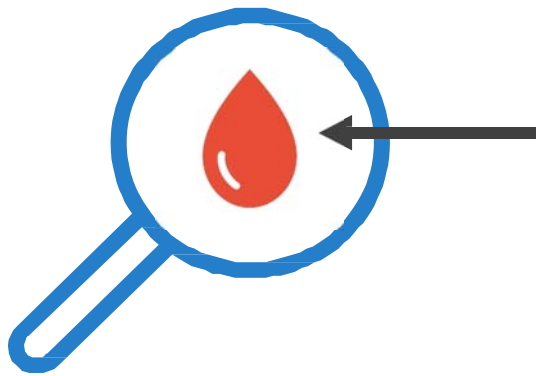
What is Takeda's PDT business?

1

What are plasma-derived therapies (PDT)?



What is Plasma?



Blood contains...

55%

Plasma

44%

Red blood cells

1%

White blood cells & platelets

Definition of Plasma :

Plasma is the clear, straw-colored liquid portion of blood that remains after red blood cells, white blood cells, and platelets are removed. Plasma has multiple components with different clinical uses and it cannot be manufactured in a laboratory.

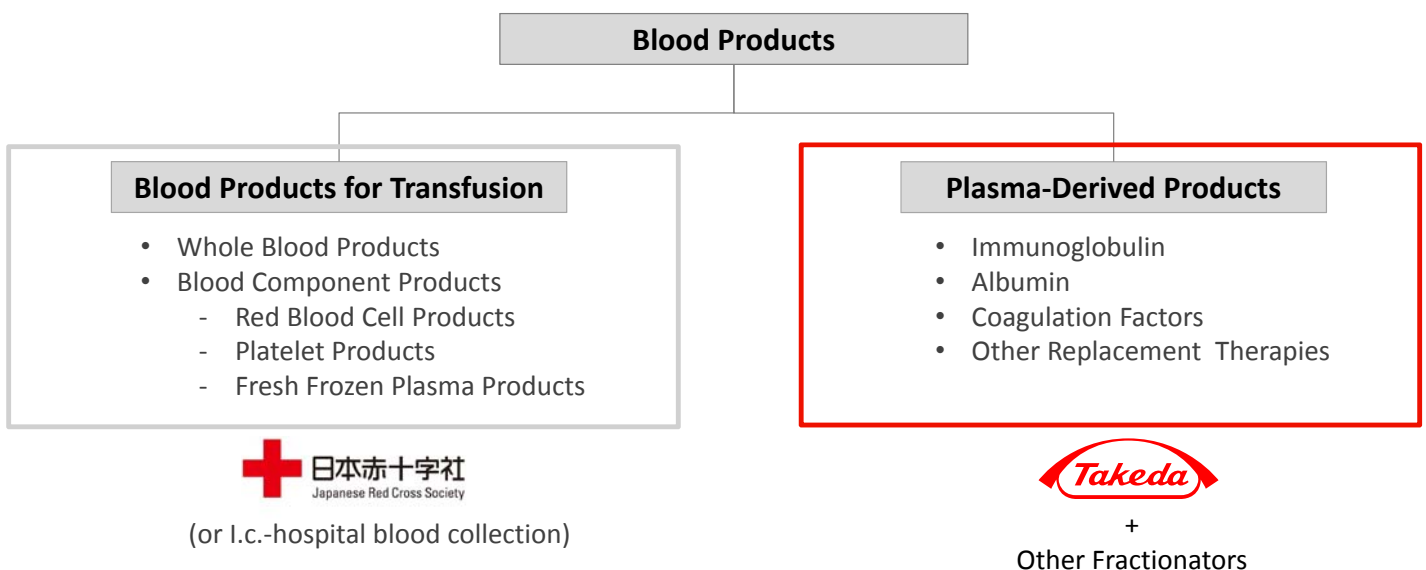
Source: B Positive Plasma website https://www.bpositivetoday.com/#iLightbox/gallery_image_1/0

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What are blood products? What are plasma-derived products?

Blood Products Market in Japan







Source: MHLW. Blood Business Report (2018)

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Clinical uses of plasma products span four primary categories

	Description	Uses
 Immuno-globulin (IG)	<ul style="list-style-type: none"> Assists in the destruction of foreign molecules Main function of the humoral immune system 	<ul style="list-style-type: none"> IVIG/SCIG – congenital antibody deficiencies, neurologic, hematology – 200+ diseases Hyperimmune – target antigens of specific conditions
 Albumin	<ul style="list-style-type: none"> Maintains intravascular colloid osmotic pressure Can compete with non-protein based volume replacement solutions such as starches, Ringer's Lactate, or saline 	<ul style="list-style-type: none"> Albumin – Fluid loss, sepsis/septic shock, plasma exchange, burn therapy, renal dialysis
 Coagulation Factors	<ul style="list-style-type: none"> Replaces missing factors in the clotting cascade due to deficiencies or dysfunctions 	<ul style="list-style-type: none"> Factor VIII/IX – Hemophilia A/B vWF – Von Willebrand Disease Factor II, V, VII, X, XI, XIII & fibrogen – deficiencies for blood loss or congenital
 Other Replacement Therapies	<ul style="list-style-type: none"> Plasma proteins used to treat extremely rare diseases 	<ul style="list-style-type: none"> AT-III – excessive clotting AAT/A1PI – COPD, cirrhosis, jaundice C1-INH – Hereditary Angioedema

IVIG: Intravenous Immunoglobulin, SCIG: Subcutaneous Immunoglobulin, vWF: Von Willebrand Factor, AT-III: Antithrombin III, AAT/A1PI: Alpha-1 Antitrypsin/Apha-1 Proteinase Inhibitor, COPD: Chronic Obstructive Pulmonary Disease, C1-INH: C-1 Inhibitor
 Source: PPTA (Plasma Protein Therapeutics Association)

It can take 1000+ donations to derive a 1-year-therapy for 1 patient and, for some patients, plasma products are the only treatment they can rely on

Estimated donations needed for one patient for one year

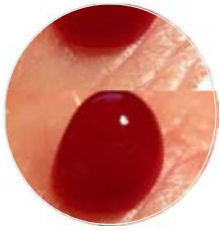
- 130:**  Primary immunodeficiency disease
- 900:**  Alpha 1 antitrypsin deficiency
- 1200:**  Hemophilia

Availability of non-Plasma Products

Immunoglobulin	None globally
Albumin	Recombinant albumin*
FVIII/FIX/FXIII	Recombinant FVIII, Recombinant FIX, Bi-specific Antibody
Inhibitor Products	Recombinant FVII, Bi-specific Antibody
Anti Thrombin III	Recombinant Anti Thrombin III
Prothrombin	None globally
C1 inactivator	Icatibant acetate
Protein C	None globally
Fibrin Sealant	None globally

*: Recombinant albumin product was approved but not available
 Source: PPTA (Plasma Protein Therapeutics Association), MHLW

Plasma can be collected either as recovered plasma or as source plasma via a process called apheresis



Recovered plasma is obtained from whole blood donations

- Plasma is separated after the blood has been removed from the body
- Whole blood donations are governed by different regulations than plasma donation:
 - **Generally non-remunerated**
 - **Less frequent** because the body takes more time to replenish blood cells than plasma
- **~16%** of total global plasma supply; **~75%** of total Japanese plasma supply



Source plasma is obtained by apheresis while blood cells are returned to the donor

- Plasmapheresis **collects plasma but returns blood cells** to the donor simultaneously, using sterile single-use equipment
- **Few countries allow donor remuneration**, e.g., US, Germany, Austria, Hungary, Czech Republic
- Commercial plasma centers are either owned and operated by **fractionators** or by **third party collectors** who resell the plasma to fractionators
- **~84%** of total global plasma supply; **~25%** of total Japanese plasma supply

Source: MRB, Japan Red Cross Website, MHLW, Blood Business Report (2018)

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Plasma Collection Requirements vary by country

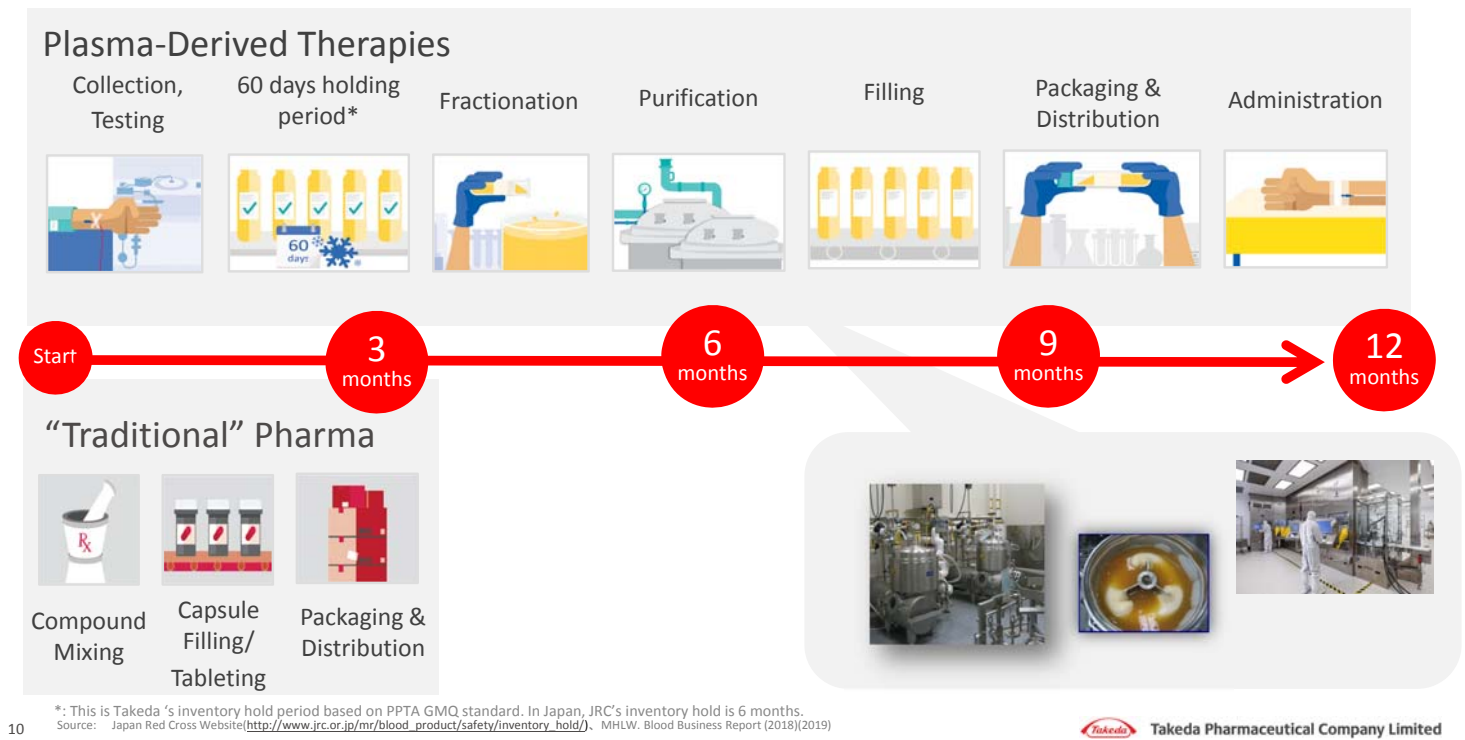
	U.S.	Austria	Japan
Primary Regulator/Regulations	FDA Blood Safety Law	EMA Blood Donor Decree	MHLW Blood Law
Plasma Collection	Private and Public	Private and Public	Red Cross only (no private centers allowed)
Plasma Donation Volume	690 - 880 ml per donation depending on body weight	600-850 ml per donation depending on body weight	- 600 mL (no more than 12% of circulating blood)
Age	18 and older	18 and older	18 – 69 years old
Weight	110 lbs (≒ 50 kg) or greater	50kg or greater	Male: 45kg or greater Female: 40kg or greater
Plasma Donation Intervals	48 hours between donations No more than 2 donations in 7 days	72 hours between donations No more than 2 donations in 7 days No more than 3 donations in 14 days No more than 50 times per year	Every 2 weeks or less No more than 24 donations per year

Compensation for source plasma is only allowed in US, Germany, Austria, Hungary and Czech Republic
Variations in donation frequency, number and volume exist amongst all 5 countries

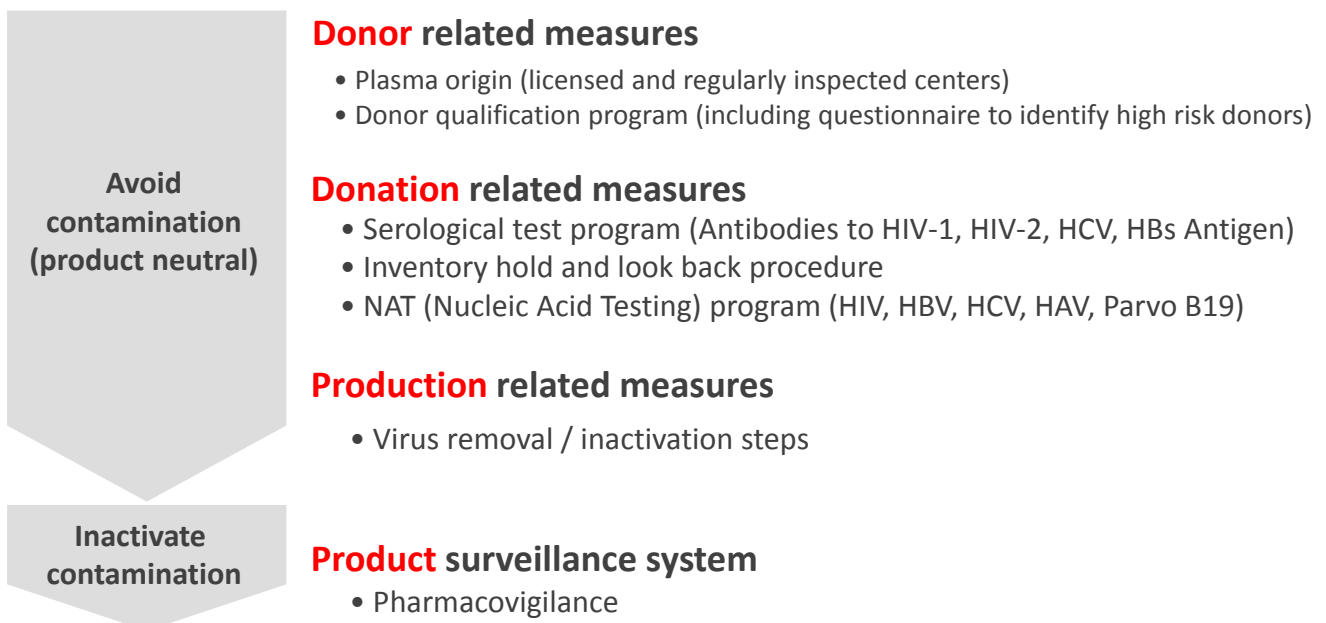
Source: Japan Red Cross Website, MHLW, Blood Business Report (2018)

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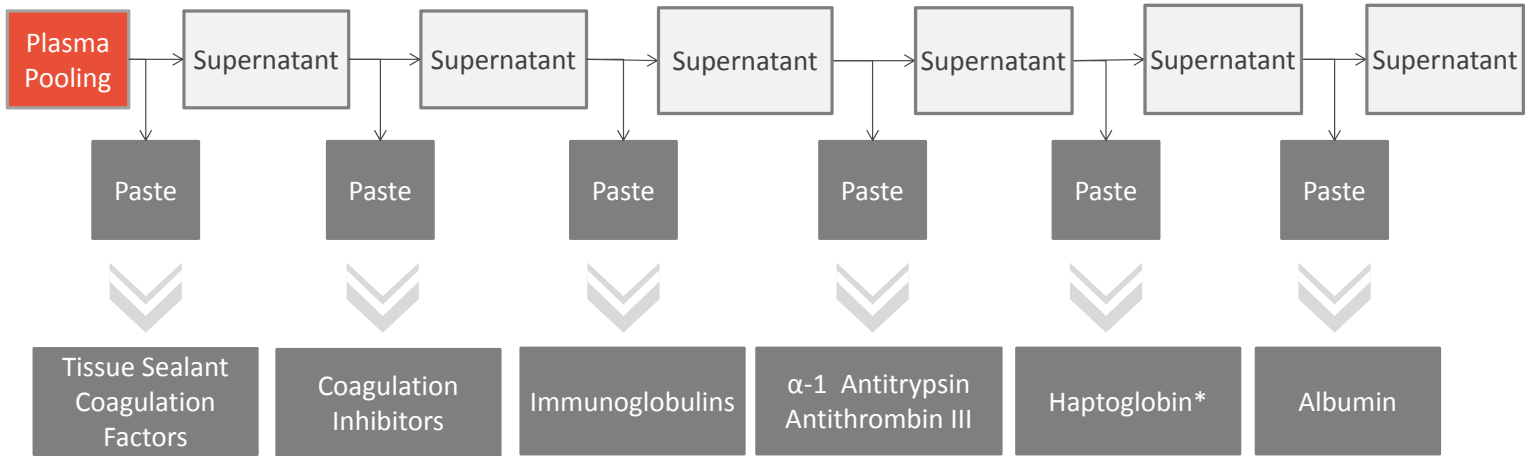
From donor to patient, typical PDT production journeys can take ~12 months to complete



Throughout the value chain, Takeda products are based on pathogen safety principles



Plasma fractionation is the core of our production process leading to more than 20 different plasma products that meet the patients needs

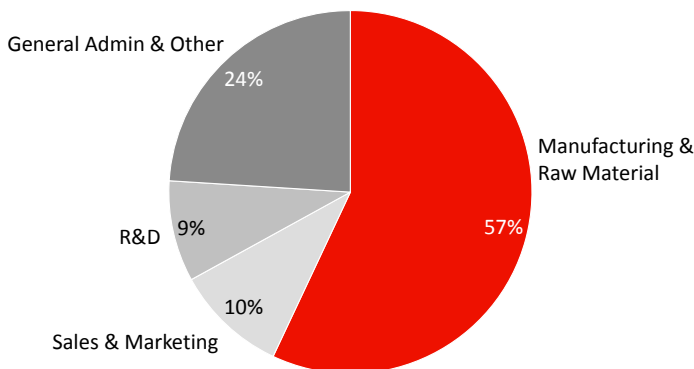


*: Not manufactured by Takeda

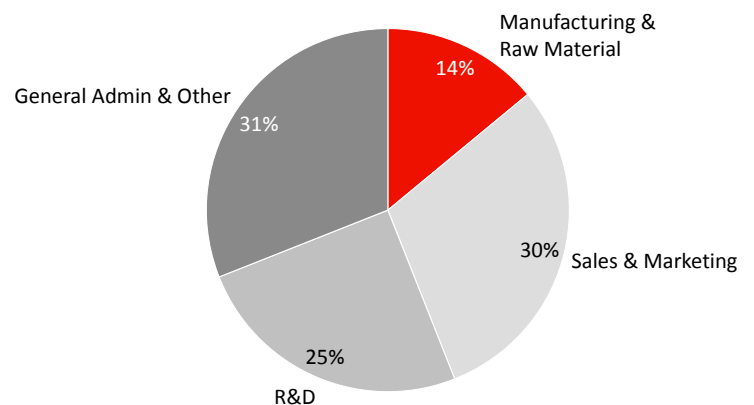
COGS are the major cost driver in the plasma industry, typically attributed to high raw-material and fractionation process cost

INDUSTRY VIEW, NOT SPECIFIC TO TAKEDA

Plasma industry cost structure (Average)

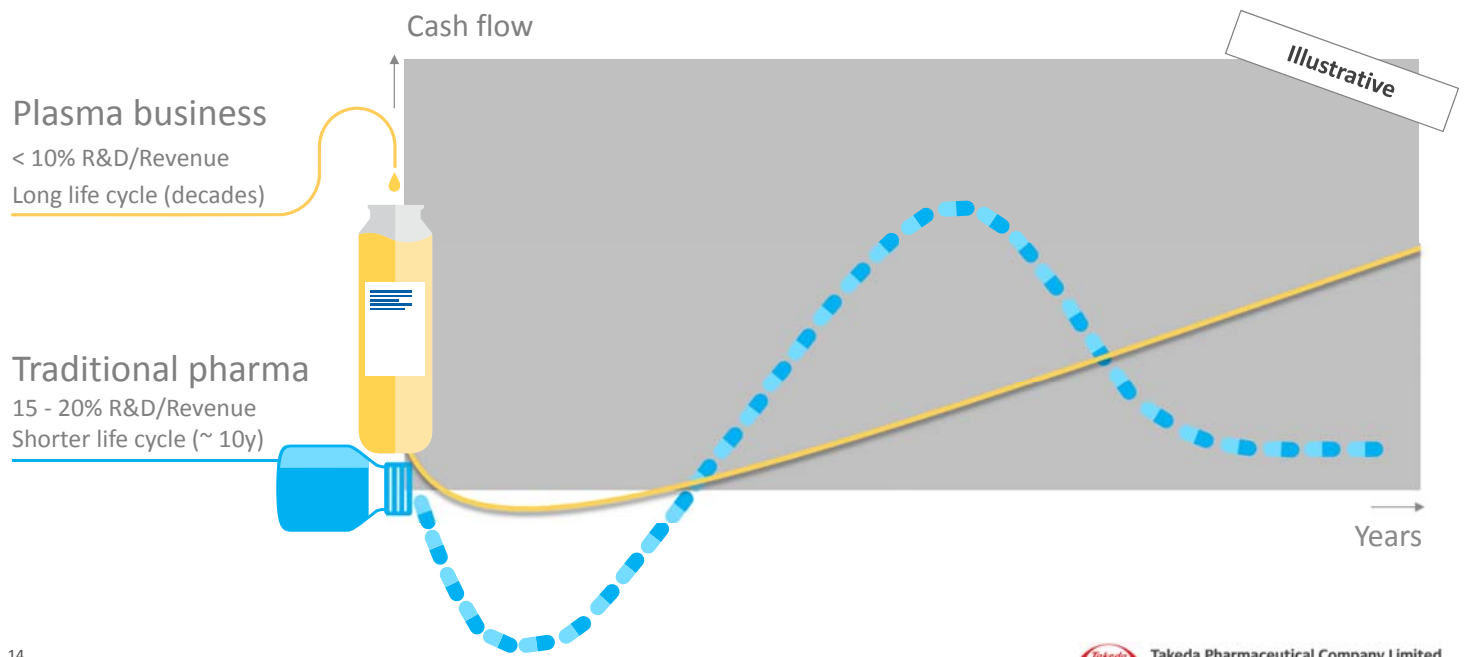


Non-plasma pharmaceutical industry cost structure (Average)

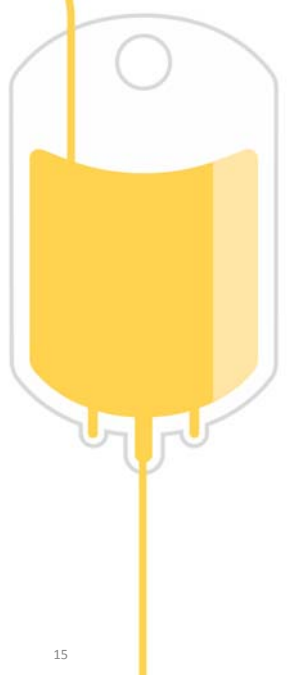


Source: Industry Reports & Estimation 2011, S&P Capital IQ

Plasma has a unique financial profile with relatively lower R&D costs as a proportion of revenue and is generally not subject to patent cliffs



The Plasma business is different from traditional pharma

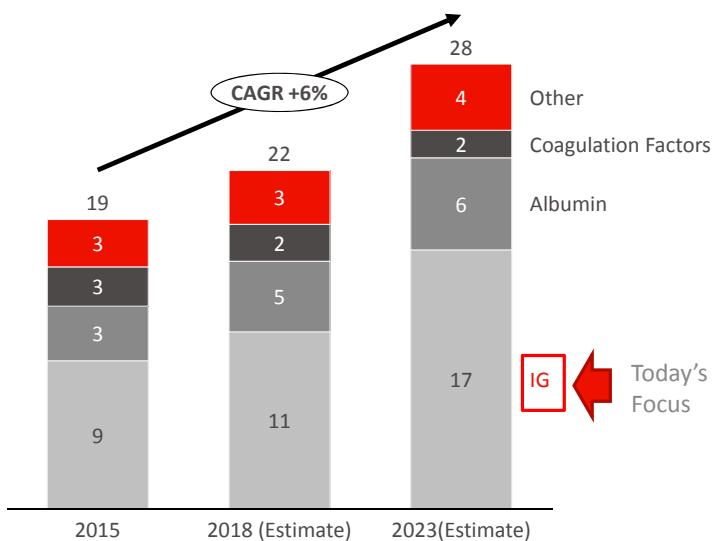
- 
- Plasma is collected from **human donations** – precious supply
 - It can take **1,000+ donors** to derive a 1-year-therapy for **1 patient**
 - Plasma collection is **heavily regulated**
 - Plasma donation is a **sensitive topic**
 - It's a capital intensive business
 - **Production** timeline is longer, **COGS** are higher
 - **Plasma economics** add further complexity
 - Plasma products are **not subject to patent cliffs**
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What is the PDT market?

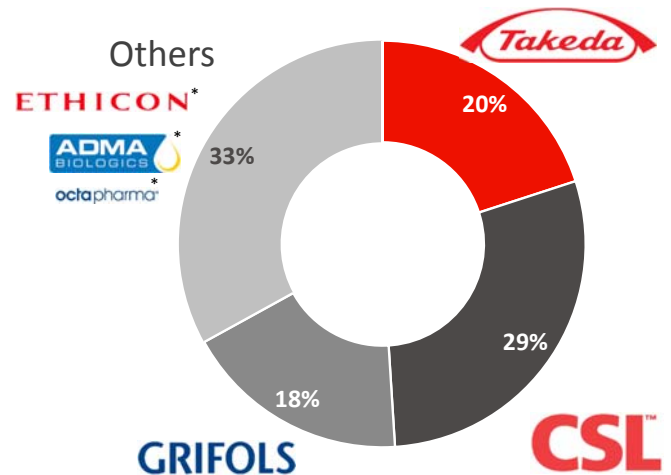


There is a growing need for PDT products led by Immunoglobulin (IG) and Takeda is one of the top 3 global companies

Global Plasma Market (\$B), 2015-23



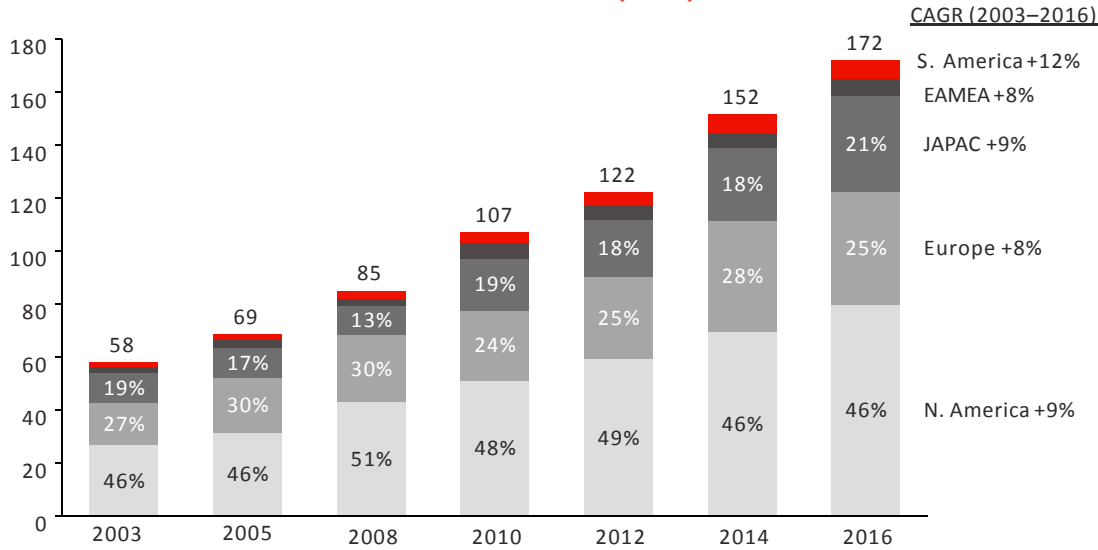
Global PDT Revenue Market Share (2018)



*: These are examples and not an exhaustive list

Immunoglobulin (IG) demand is growing globally

Global IG Market (Tons)



Reasons for Growth

- Improved standard of care
- Improved diagnosis rate and disease awareness
- Expanded indications

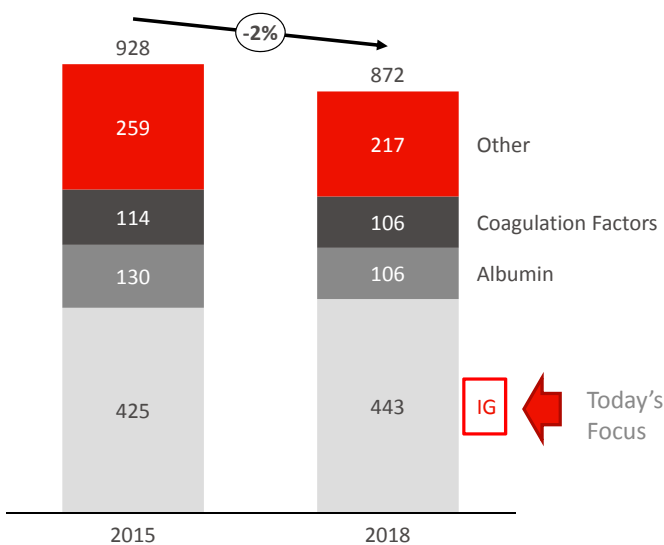
Supplying plasma to meet the increasing demands is challenging

SOURCE: MRB_WW_History 2016, Internal estimates; EAMEA = Eurasia, MEA

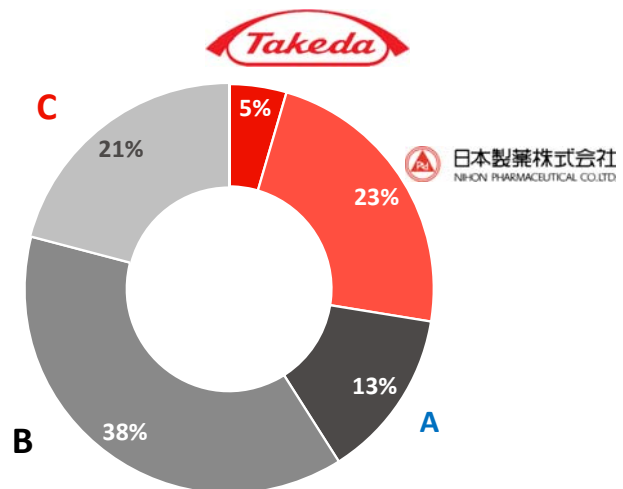
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In Japan, although overall PDT market is decreasing, IG growth is still strong

Japan Plasma Market (\$M), 2015-18



Japan PDT Revenue Market Share



Pd: plasma derived, IG: Immunoglobulin

NOTE: The category of product type is based on Takeda internal standards. Converted at April 2018-March 2019 average exchange rate of 111 JPY/USD

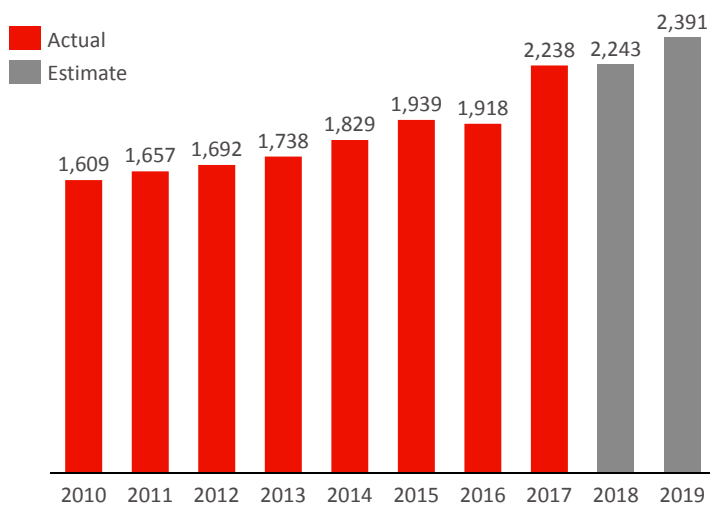
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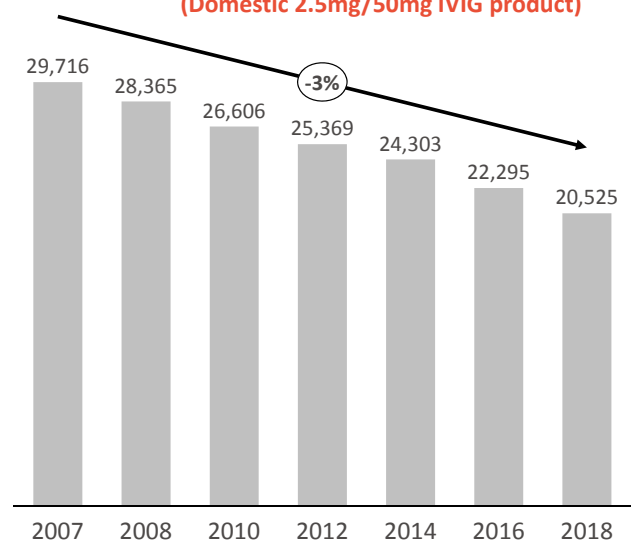
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In Japan, while Immunoglobulin (IG) demand is growing, IG product price is decreasing, resulting in ~30% lower compared to 2007

Japan IG Market (K bottles of 2.5mg)



Japan IG NHI Price in Yen (Domestic 2.5mg/50mg IVIG product)



Note: 2018 data is annualized with April-September actual data
 Source: MHLW "Building a Plan for Stable Supply of Blood Products in 2019" (<https://www.mhlw.go.jp/content/11121000/000452750.pdf>)、MHLW, Blood Business Report (2018)(2019)

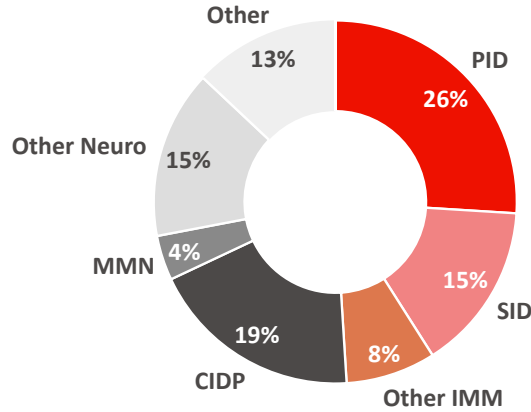
Immunoglobulin (IG) has multiple usages and available indications are increasing both in Japan and globally

Indication	Primary immunodeficiency (PID)	Chronic inflammatory demyelinating polyneuropathy (CIDP)	Multifocal motor neuropathy (MMN)	Others (Secondary immunodeficiency (SID), Kawasaki Disease, Infections, MG, GBS etc.)
Therapeutic area	Immunology	Neurology	Neurology	Multiple
Primary physician	Immunologist, Pediatrician	Neurologist	Neurologist	Multiple
Age groups	Various	Middle age to older adults	Middle age to older adults	Various
2017 Global Volume Growth	9%	9%	17%	6%

MG: Myasthenia Gravis, GBS: Guillain-Barre Syndrome
 Note: Indications of Immunoglobulins vary by country; For indications of each product of specific country, please refer to local product labeling

PID, SID, and CIDP composed of 60% of total usages of Immunoglobulin (IG)

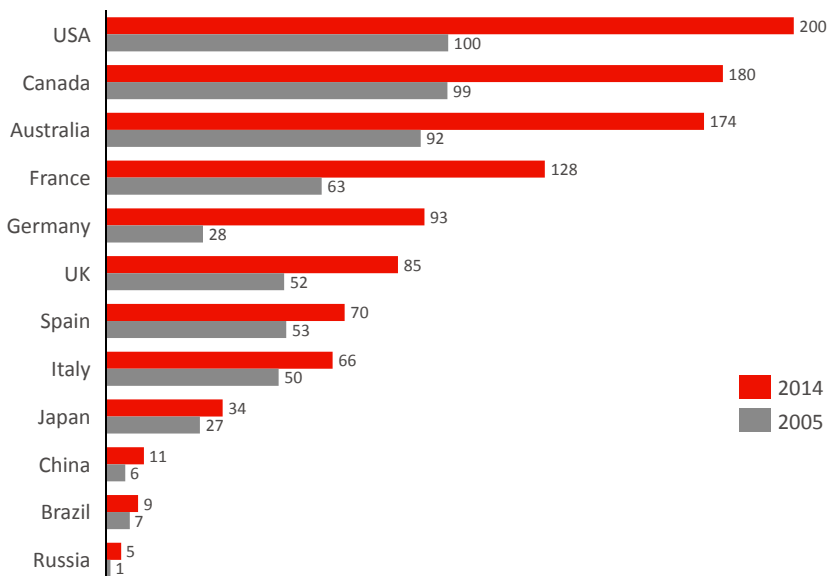
US & EU IG Market by TA, 2018e Forecast



PID: Primary Immunodeficiency; SID: secondary immunodeficiency; MMN: Multifocal motor neuropathy; CIDP: Chronic Inflammatory Demyelinating Polyradiculoneuropathy
 Source: 2016 WW MRB Report, 2017 US MRB Report, & Internal estimates

In Japan, immunoglobulin (IG) usage per population is still lower than other countries and its growth is also slower

IVIg/SCIG Consumption by Country (Kg per Million people)



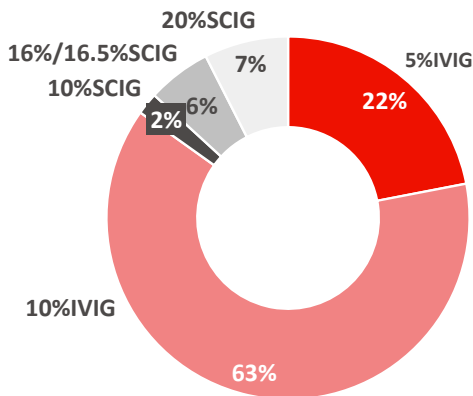
Reasons for differences among countries

- Product availability and history of commercial product introduction
- Diagnosis rate and disease awareness
- Price differences
- Influence of patient advocacy groups
- Market structure and purchasing process
- Medical education
- Available usage of IG (difference in indications/ off-label usage)

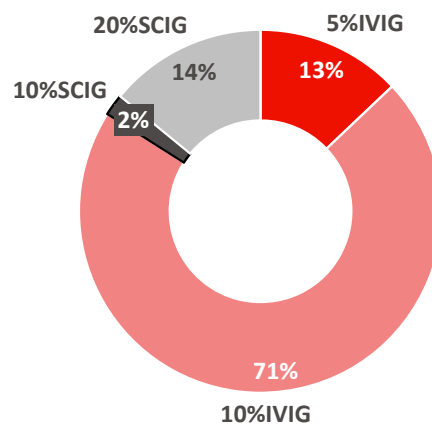
Source: Plasma Protein Therapeutics Association; https://www.cslproducts.com/safety/binary/pdf/professional_interview_no3.pdf

While in the U.S. and Europe, 10% IVIG is the majority, Japan still uses 5% IVIG

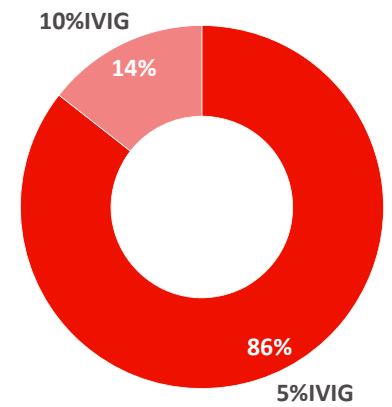
Europe IG Market, 2017



The U.S. IG Market, 2017



Japan IVIG Market*, 2018



*: SC usage in Japan is limited compared to Europe and the US

5% IVIG is mainly used in Japan partially because of late introduction and limited product options of 10% IVIG and SCIG

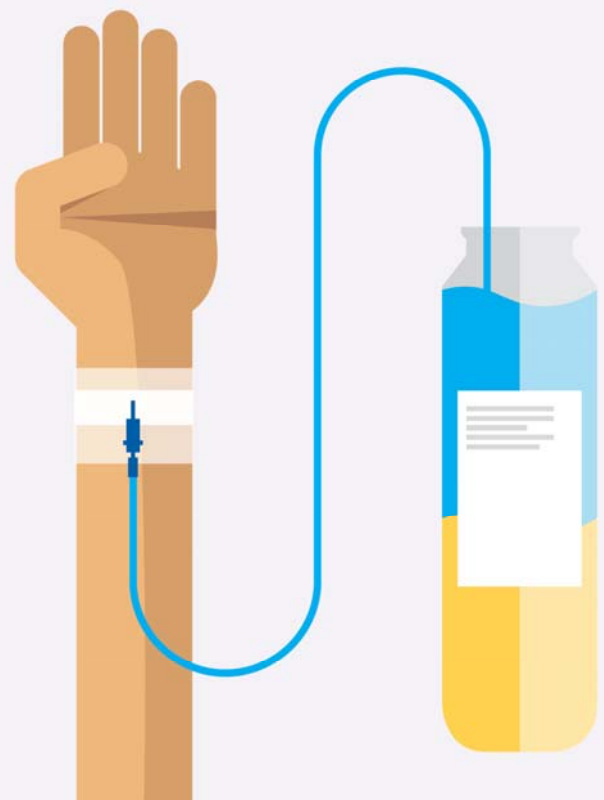
IVIG: Intravenous Immunoglobulin, SCIG: Subcutaneous Immunoglobulin

NOTE: The category of product type is based on Takeda internal standards.

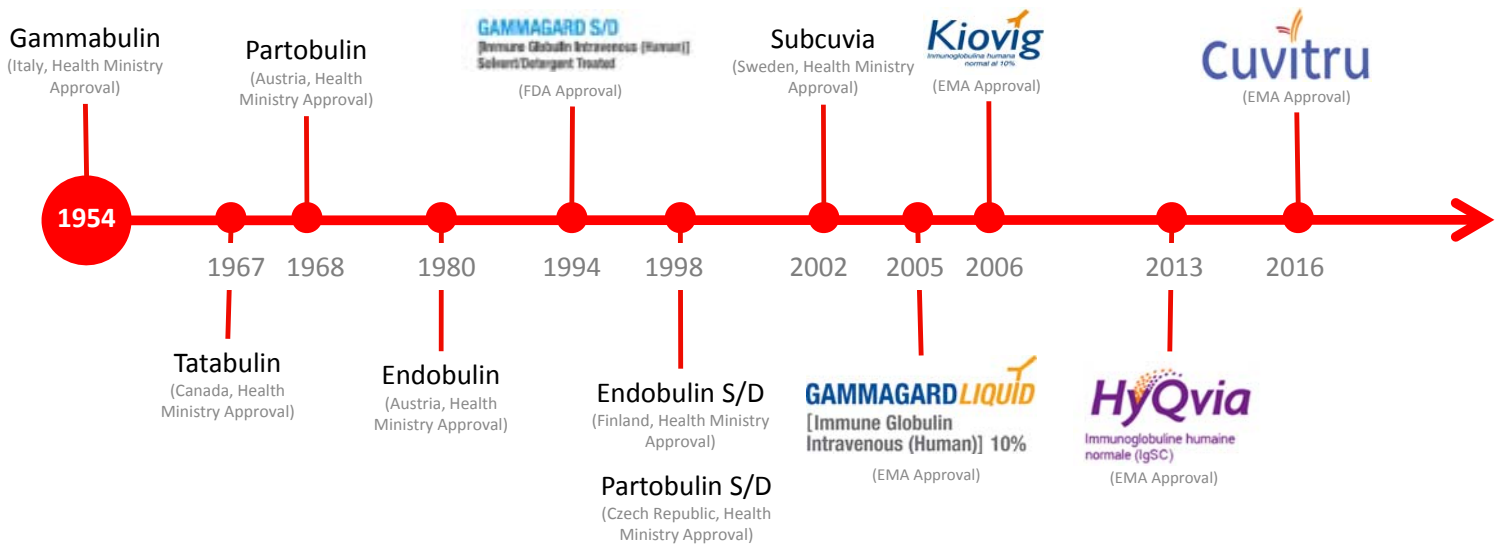
Source: Copyright © 2019 IQVIA. (Calculated based on JPM Jan-Dec 2018.) Reprinted with permission. The U.S. and EU data is based on Takeda internal analysis based on LoC's self report.

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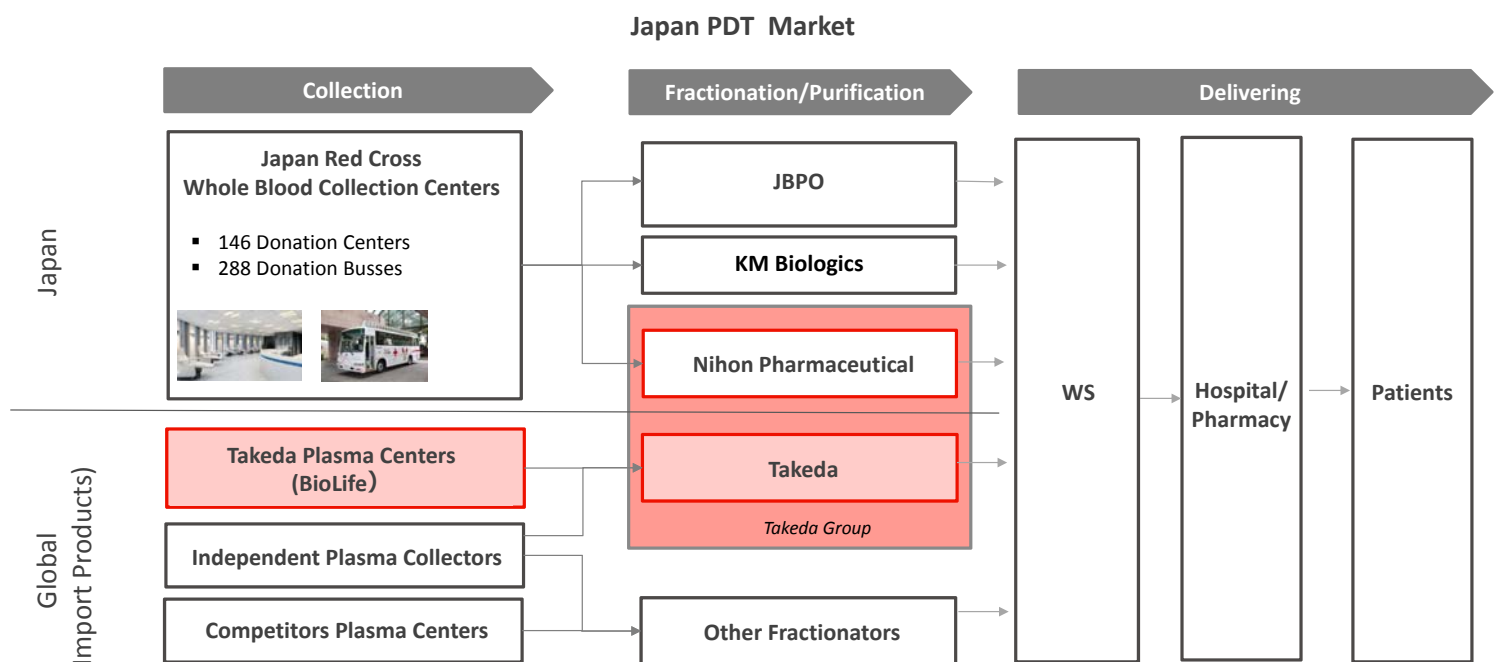
What is Takeda's PDT business?



Takeda has a long history in the PDT business



Takeda has access to global plasma as well as Japan plasma for Japanese market



Takeda is accelerating investments to grow plasma collections globally

Takeda Plasma Collection Operations



3rd Party Plasma Supplies



MANUFACTURING: RAMPING UP OPERATIONS AT COVINGTON

- Received US FDA approval to manufacture FLEXBUMIN in March 2019
- Ramp up to full production over next several years, with a focus on manufacturing the IG portfolio and Albumin, covering 1 million+ square feet with the opportunity to further expand with the aim of reducing the gap between demand and supply
- Additional internal capacity expansion under evaluation

SUPPLY: INVESTING IN PLASMA COLLECTION

Acquired 10 additional plasma collection centers since Shire acquisition close

- 1 center in Maryland, U.S.
- 2 centers in Austria
- 7 centers in Hungary

Current footprint of 105 centers in the US, and 30 ex-US
Intend to continue to invest in increasing plasma collection footprint aiming for double-digit increase in number of centers each year

Plasma manufacturing network is state-of-the-art with ongoing capacity investments

Cryo Precipitation, Absorption and Fractionation



Downstream Processing



Worldwide Distribution



*: Owned by Takeda's partner company

We have a broad PDT portfolio globally

	Key uses / clinical indications	Global TAKEDA Products	Japan TAKEDA Products
Immunoglobulin	<ul style="list-style-type: none"> Primary Immunodeficiency (PID), Idiopathic Thrombocytic Purpura (ITP), Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) etc. 		
Albumin	<ul style="list-style-type: none"> Fluid loss, sepsis/septic shock, plasma exchange, burn therapy, renal dialysis 		
Plasma derived coagulation factors	<ul style="list-style-type: none"> Factor VIII/IX – Hemophilia A/B vWF – Von Willebrand Disease 		(Non-PDT products)
Inhibitors	<ul style="list-style-type: none"> Hemophilia with inhibitors 		
Alpha-1 anti-trypsin	<ul style="list-style-type: none"> AAT – Chronic Obstructive Pulmonary Disease (COPD) 		None
C-1 esterase inhibitor	<ul style="list-style-type: none"> HAE – edema (swelling) in various parts of the body 		(Non-PDT products)
Prothrombin	<ul style="list-style-type: none"> Reversal of acquired coagulation factor deficiency induced by warfarin 		None
Others	<ul style="list-style-type: none"> Protein C deficiency Wound healing 		

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Takeda has extensive portfolio of IG

	Intravenous (IV) IG		Subcutaneous (SC) IG		
	~5%	10%	10% Weekly	20% Weekly	10% Monthly
CSL	✓	✓**		✓	
GRIFOLS	✓*	✓*	✓*	✓*	
 一般社団法人 日本血液製剤機構 Japan Blood Products Organization	✓***	✓***			
 KMJバイオロジクス株式会社	✓***				

*: Not available in Japan, **: Just approved in March 2019, ***: Only available in Japan

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IG and Albumin continue to be growth drivers

KEY GROWTH PRODUCTS



PID, MMN



Approved in 50+ countries (KIOVIG in EU)



Continue to build on GAMMAGARD LIQUID's position as a highly recognized IVIG brand that is standard of care treatment for PID and MMN



PID, SID, other neuro-immunological indications



Human Normal Immunoglobulin (20%)
Recombinant Human Hyaluronidase



HYQVIA approved in the U.S., EU, LATAM, and Middle East; CUVITRU approved in the U.S. and EU



Provides patients flexibility in their schedule of subcutaneous IG administration, whether monthly (HYQVIA) or more frequently (CUVITRU)



Intravenous Subcutaneous (Human) 20%

PID
SID (EU)



Phase 3 study ongoing for CIPD indication (HYQVIA)



(Human Albumin)



Hypovolemia,
Hypoalbuminemia



Approved in 40+ countries



Maximize opportunity top priority markets

FLEXBUMIN uses a closed system (collapsible bag) which is lightweight, aimed at reducing the risk of hospital infections, and allows minimal wastage

PID: Primary Immunodeficiency; SID: secondary immunodeficiency; MMN: Multifocal motor neuropathy; IVIG: Intravenous Immunoglobulin; CIPD: Chronic Inflammatory Demyelinating Polyradiculoneuropathy

PLASMA-DERIVED RARE IMMUNOLOGY PORTFOLIO REVENUE OUTLOOK OVER THE MID-TERM

~JPY 370B
~US\$3.4B



FY2018 Revenue
(pro forma)^{*1}

■ IG ■ ALBUMIN ■ OTHERS

INCREMENTAL
GROWTH

GROWTH DRIVERS

⊕ Key Growth Products

*1. Pro-forma April 2018-March 2019 combined revenue of Legacy Takeda and Legacy Shire products converted at April 2018-March 2019 average exchange rate of 111 JPY/USD



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We put the patients first to conduct our PDT business



1

Patient

Putting the patient at the center

2

Trust

Build trust with society

3

Reputation

Reinforcing our reputation

4

Business

Development our business



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Take Home Messages



- PDT products are **very different and unique business** from traditional pharmaceuticals
- Plasma market is **growing** led by IG
- **Takeda** is one of the **top three** global plasma fractionators
- To continue delivering our PDT products, Takeda is **enhancing plasma collection and manufacturing capabilities**
- **Immunoglobulin (IG) and Albumin** are growth drivers for Takeda PDT business



Better Health, Brighter Future