

Setting the Scene for the Future of Blood and Plasma Donations

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The Marketing Research Bureau, Inc.

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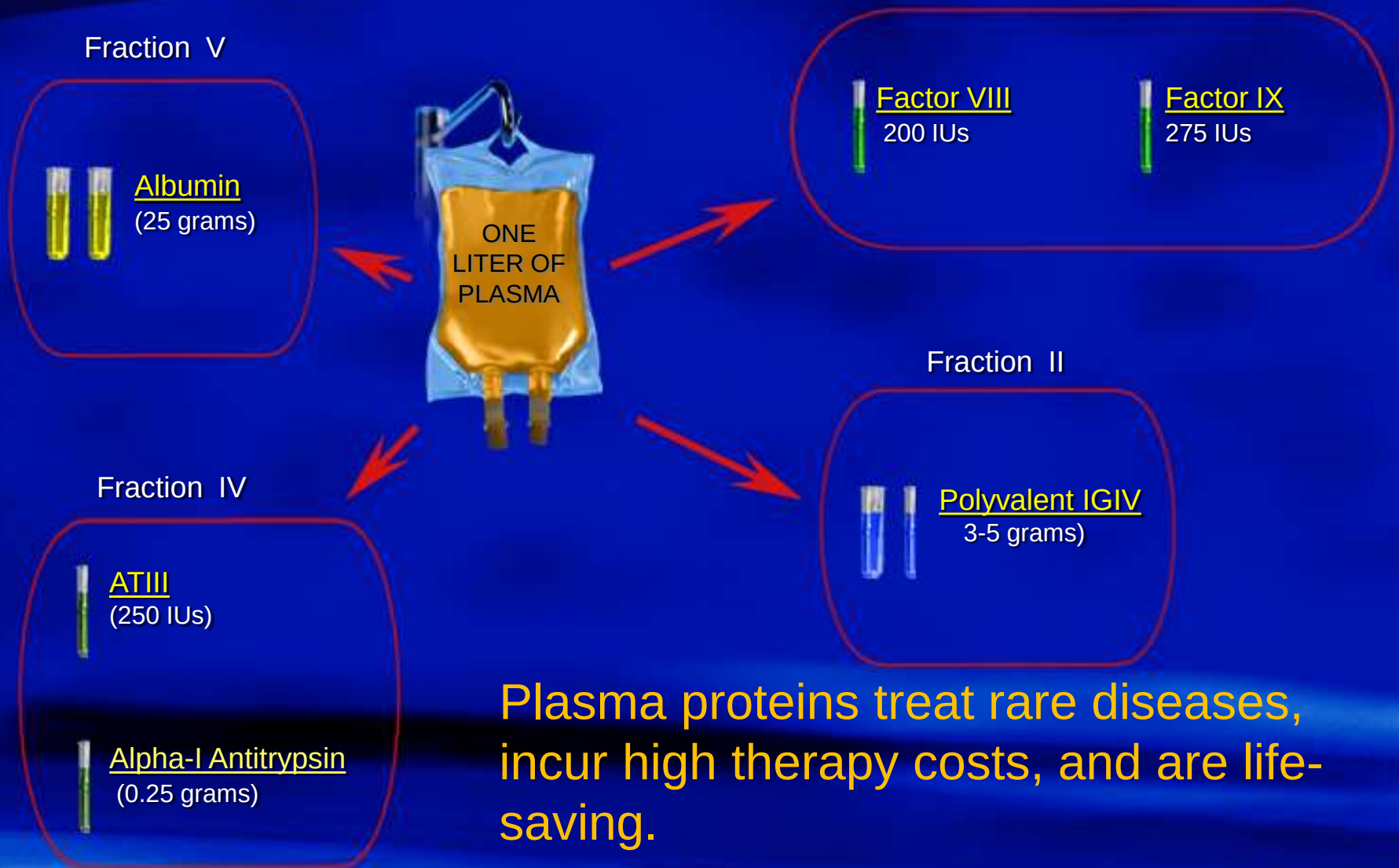
METHODOLOGY

The data used to develop the charts and tables shown in this presentation have been compiled from surveys conducted by the Marketing Research Bureau in some fifty countries, and published in various syndicated reports.

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PLASMA FRACTIONATION



Plasma proteins treat rare diseases, incur high therapy costs, and are life-saving.

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- **Plasma Proteins Market Overview**
- **Plasma Fractionation and Supply**
- **Current Issues faced by the Plasma Industry.**

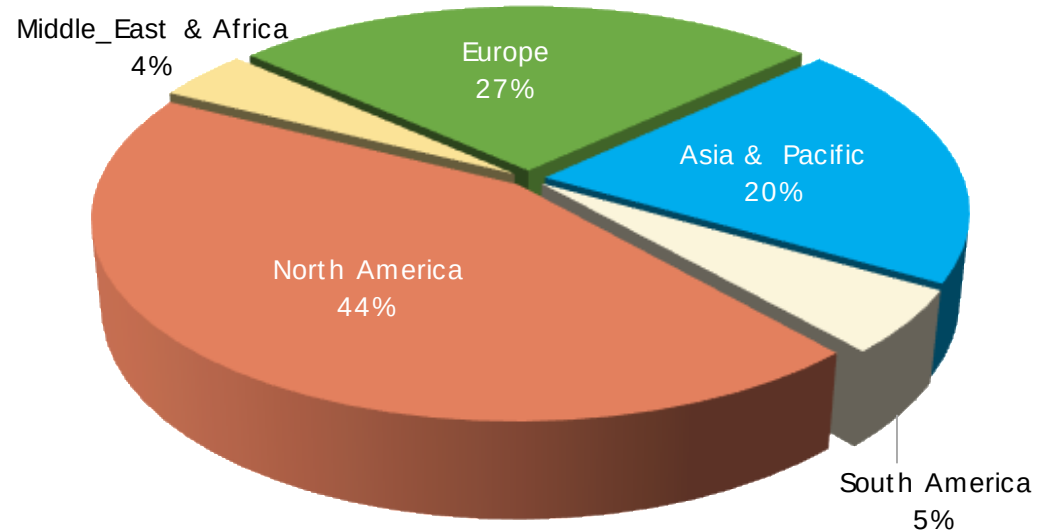
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Regional Breakdown:

North America has 5% of the world population and 44% of the global plasma products market, Europe 10% of the population and 27% of the market

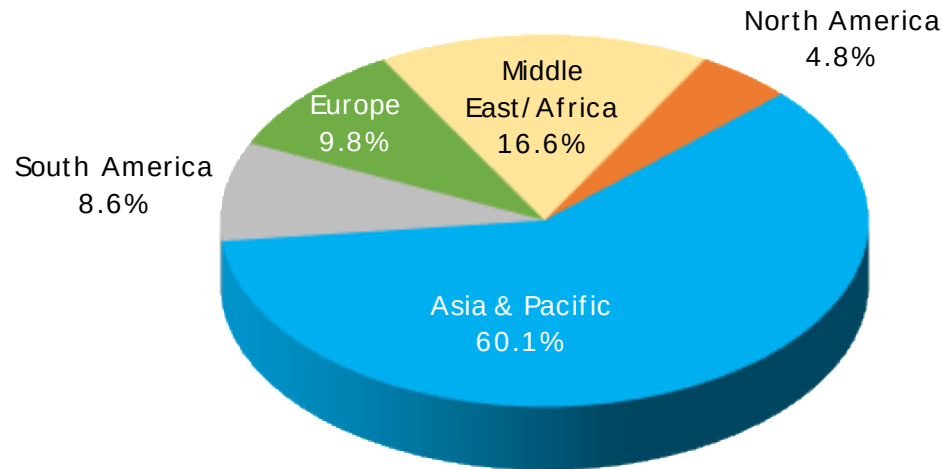
THE WORLDWIDE PLASMA PRODUCTS MARKET - 2016
BY REGION



Total Market: \$20,274 Million *

* Provisional Data

World Population by Region - 2016



Source: Population Reference Bureau

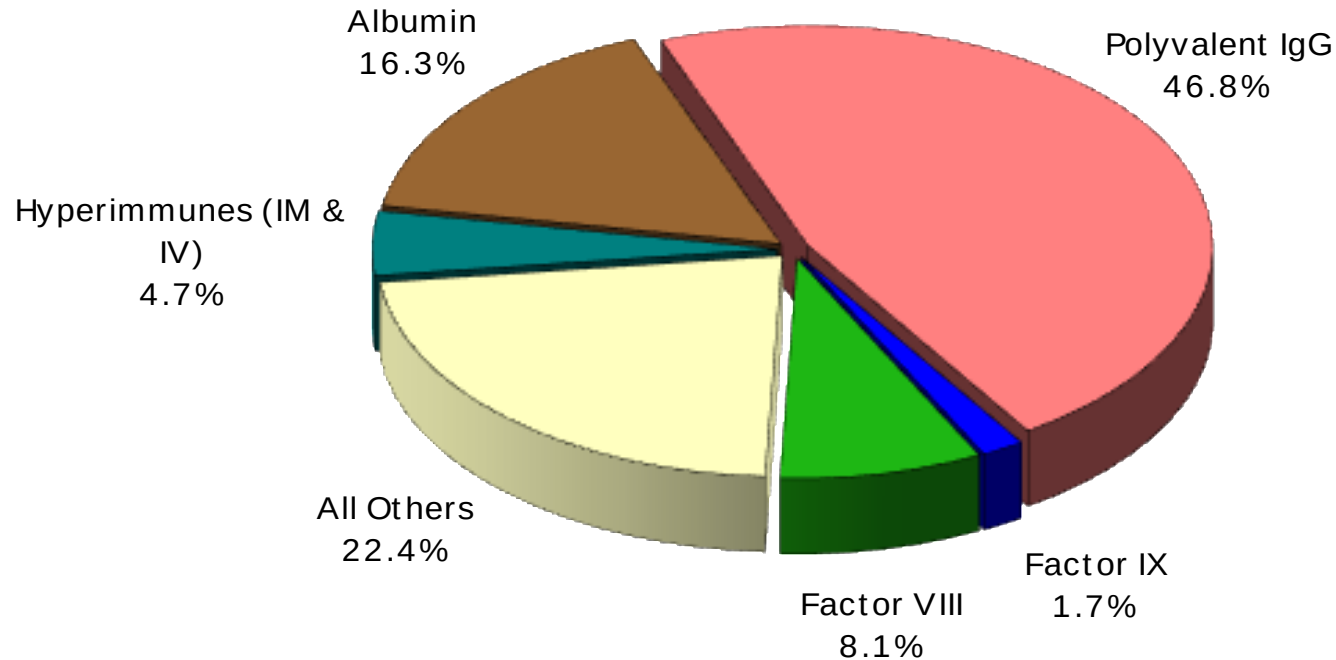
The discrepancies stem from history, health priorities and policies, diagnosis of rare diseases, high cost of therapy, and availability of funds.

THE WORLDWIDE PLASMA PROTEINS MARKET BY PRODUCT - 2016

Product Breakdown

WITHOUT RECOMBINANT FACTORS

Total Market \$20,710 Million *



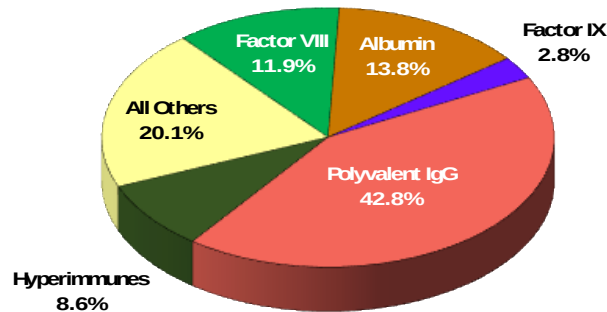
* Provisional Data

IgG (IVIg+ SCIG) represent 47% of the total market, albumin 16%, and factor VIII, 8%

Global Pharmaceutical Market in 2015: \$1,052.3 Billion (IMS), generics included
Global plasma Products Market 2014: \$20.2 Billion (MRB)

THE WORLDWIDE PLASMA FRACTIONS MARKET BY PRODUCT - 2008

Total Market \$10,528 Million



Market Mix Change over forty Years

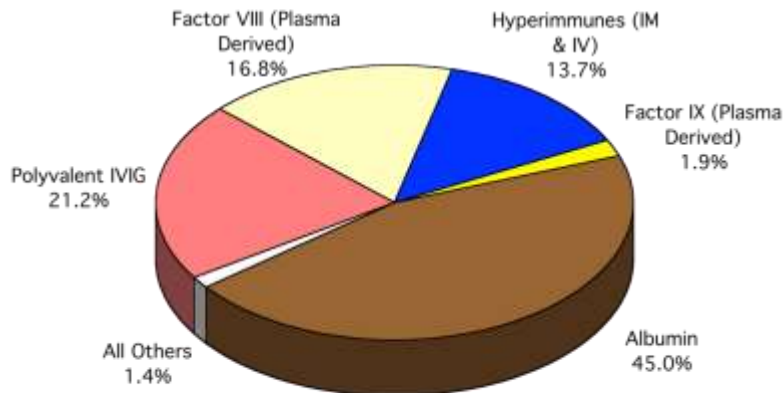
In 1977, IVIG sales represented 0% of the US market, albumin, 67%.

In 1986, albumin's share dropped to 45% and IVIG's represented 21% of the global market.

In 2008, IVIG had 43% and albumin's share was down to 13%.

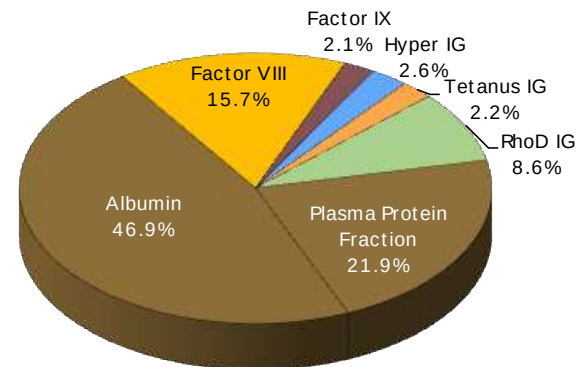
THE PLASMA FRACTIONS MARKET BY PRODUCT 1986

Total Market \$1,853.7 (MM)



THE PLASMA PROTEINS MARKET IN THE UNITED STATES IN 1977

Total Market: \$158.8 Million

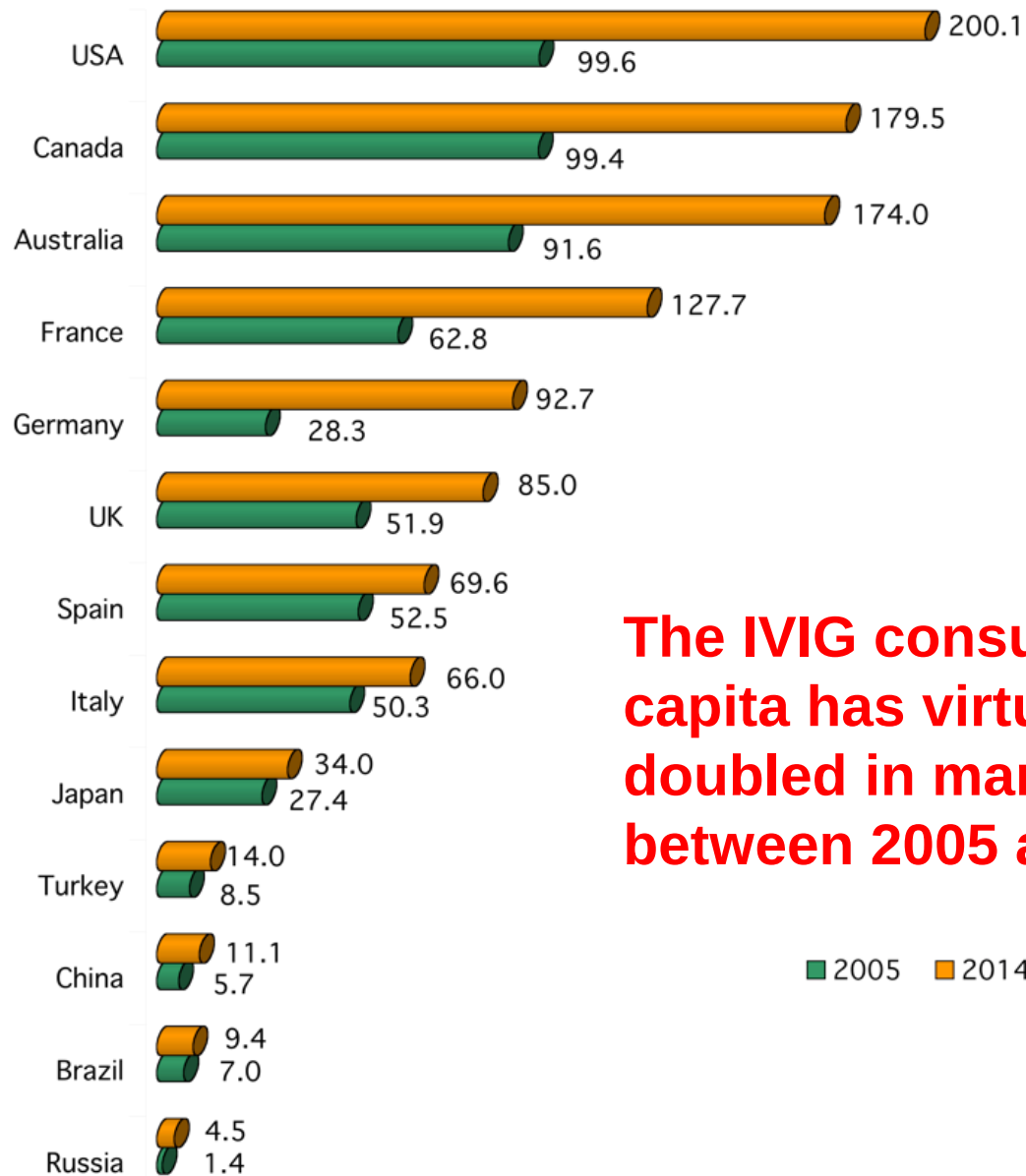


Albumin + PPF = 68.8%

- Human albumin was the main plasma product sold in the early times of fractionation besides immune globulins.
- In the late 1960's, factor VIII was introduced. Its production required more plasma than albumin, making it soon the market driver: The fractionators based their production on the demand for factor VIII.
- Recombinant factor VIII was introduced in North America, Europe and Japan in the early 1990's, and gradually replaced plasma-derived factor VIII in the high income countries.

- In the early 1980's, polyvalent IVIG was introduced in Europe, North America and Japan, and gained rapid acceptance.
- As IVIG was very successful, it displaced factor VIII as the market driver in the 1990's.
- Today, the volume of plasma fractionated depends on the needs for polyvalent IgG (intravenous and subcutaneous immune globulin).
- The needs for IgG have gone up in most countries, rich and poor, albeit at varying rates

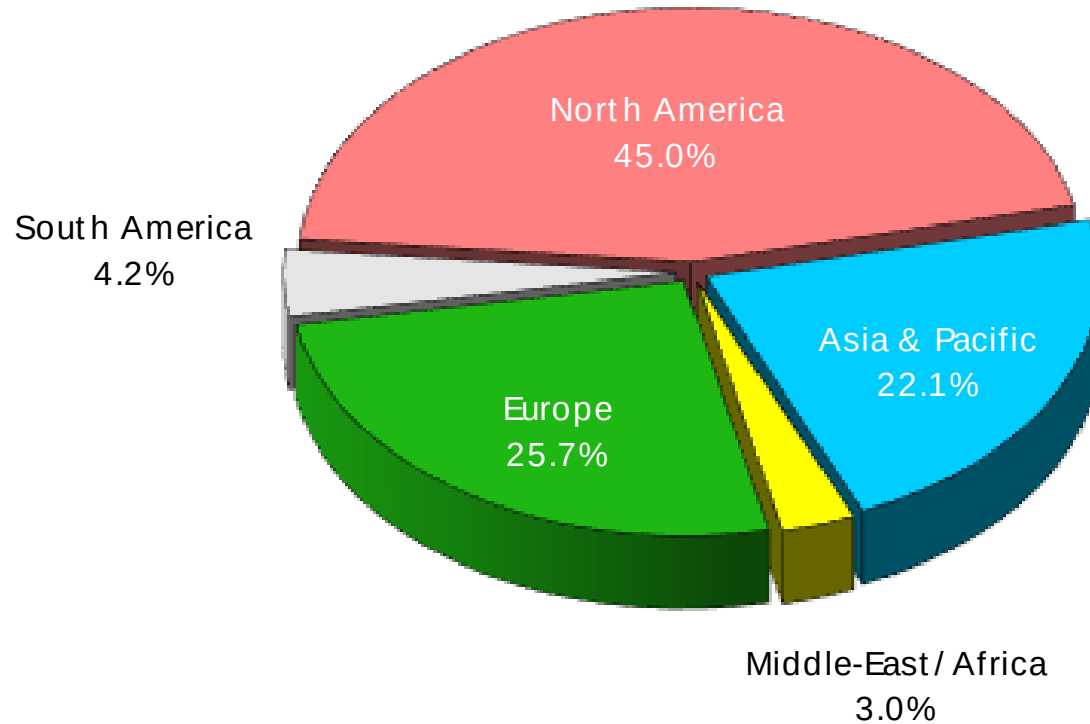
INTRAVENOUS/SUB-CUTANEOUS (IVIG/SCIG) CONSUMPTION BY COUNTRY (Kilograms per Million People)



The IVIG consumption per capita has virtually doubled in many countries between 2005 and 2014

THE IgG MARKET IN UNITS BY REGION - 2016

Total Market 164.9 Metric Tons



North America consumes 45% of the global polyvalent immune globulin

North America uses more IgG per capita than any other region because of:

- Earlier market introduction than in other countries, creating high awareness level,
- Funding available, including for off-label indications,
- Product safety, efficacy and supply,
- More patients on chronic therapy than elsewhere,
- Strong patients' advocacy groups,
- Companies educational & promotional activities,
- New, emerging off-label indications,
- Etc.

Medical Conditions for which IVIG has been prescribed

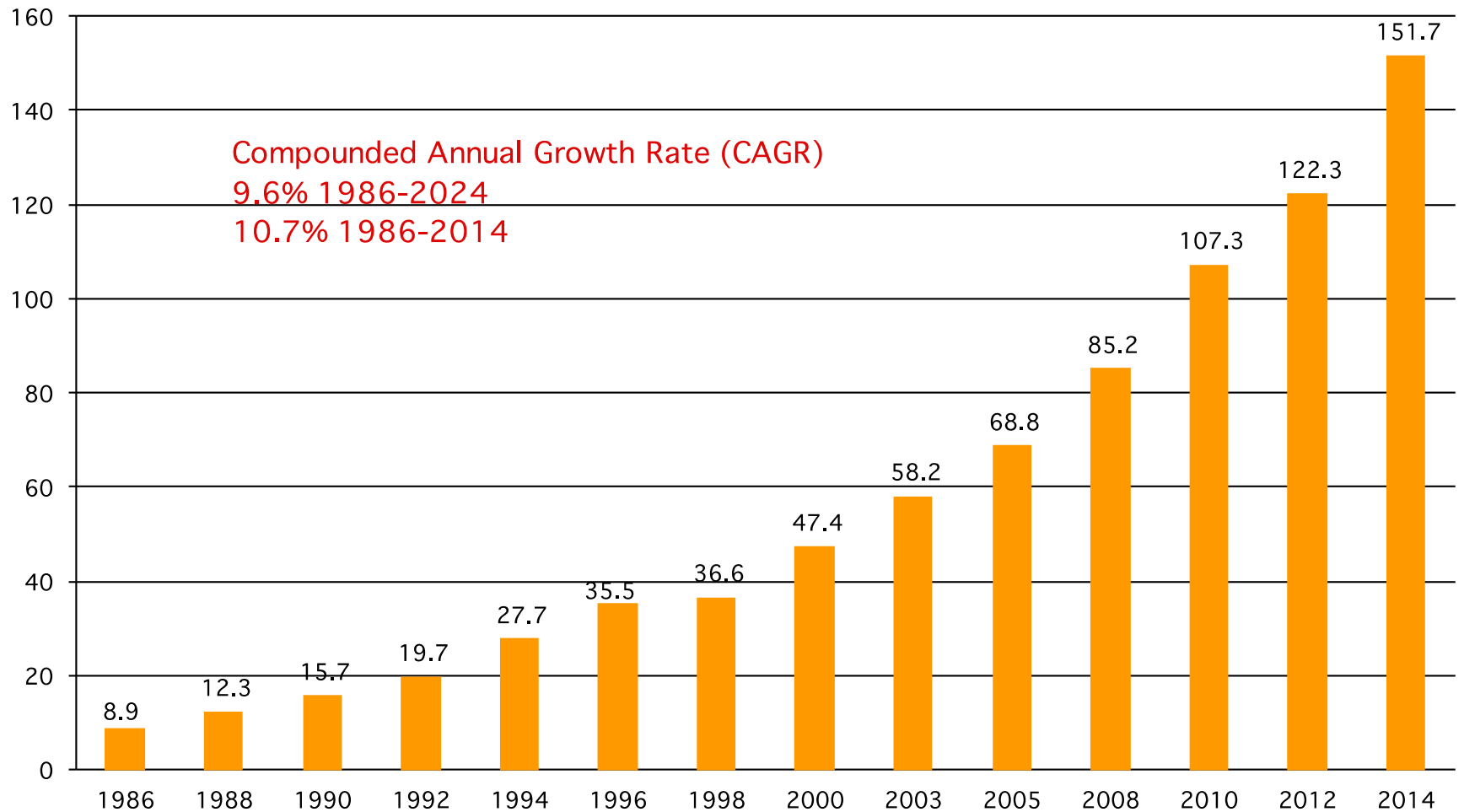
Patients discharged from U.S. Hospitals 2012

Medical Specialty	Indication by Medical Specialty	Patient Population
ALLERGY IMMUNOLOGY	Primary Immunodeficiencies (1)	34,609
	Chronic Sinusitis	12,764
	Bronchitis	24,480
	Bronchopneumonia	26,824
	Chronic Fatigue Syndrome	896
	Asthma	605,551
	Autoimmune Neutropenia (Agranulocytosis)	46,891
	Systemic Vasculitis (Severe Vasculitis)	2,193
	Systemic Lupus Erythematosus (SLE)	21,264
RHEUMATOLOGY NEPHROLOGY	Rheumatoid Arthritis- Juvenile (Still's disease)	1,941
	Lupus nephritis	92
	Polyarteritis nodosa (Churg-Strauss syndrome)	846
	Autoimmune Blistering Skin Diseases (2)	2,657
	Bullous and Oral Pemphigoid	1,882
DERMATOLOGY	Pemphigus Vulgaris, foliaceus	340
	Dermatomyositis (Idiopathic inflammatory myopathy)	1,097
	Toxic Epidermal Necrolysis (Stevens Johnson syndrome)	8,186
	Guillain Barré Syndrome (GRS)	6,511
	Chronic	22,348
	Multifocal	26,889
	Multifocal	2,075
	Diabetes with Neurological Manifestations (Diabetic Neuropathy)	64,089
	Neuropathic Pain (3)	5,963
	Acute, Parainfectious, Disseminated Encephalo-myelitis (ADEM)	3,777

The multiplication of indications brings more patients to IgG therapy

Source: Proquest/Dialog data and literature reports on prevalence data

THE WORLDWIDE POLYVALENT IgG MARKET
FROM 1986 TO 2014
(Metric Tons)



Between 2005 and 2014, IgG unit sales grew annually at the rates of:

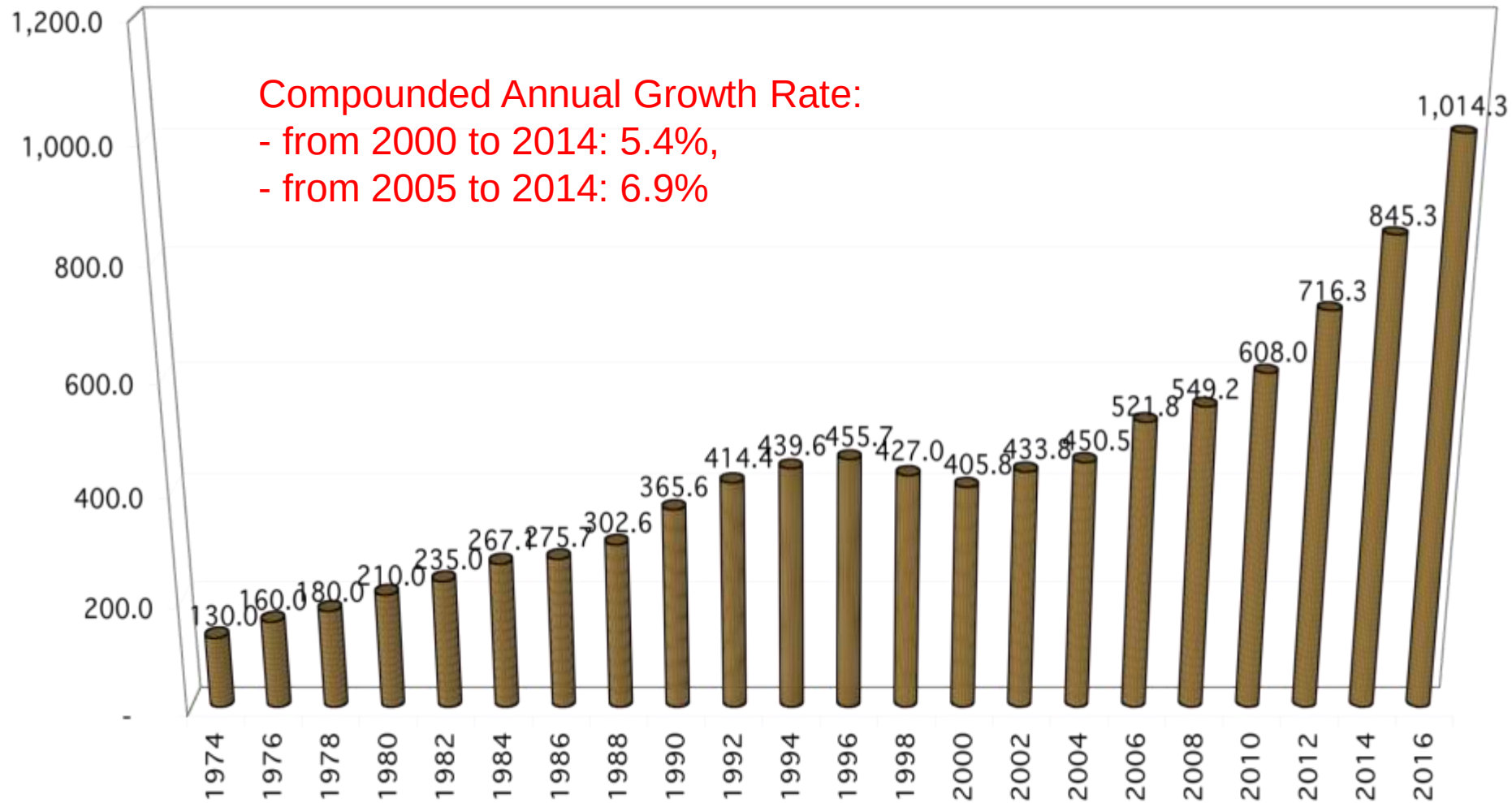
- - 9.2% in North America,
- - 8.2% in Europe,
- - 10% in Asia & Pacific, and
- - 11% in the rest of the world.

Going forward, IgG global consumption is forecast to grow over 6% per year.

This growth rate may need to be revised as new therapies emerge and compete with IgG in some indications, and the basic market demand is met in an increasing number of countries.

WORLDWIDE ALBUMIN DEMAND 1974 - 2016

Metric Tons



The global albumin market has expanded due to the Chinese demand, which grows at about 10% annually in units. Medical practice causes a higher demand than in the west

WORLDWIDE ALBUMIN UNIT SALES BY REGION

Approximately 850 Metric Tons in 2014



Albumin is used in every continent in a more balanced proportion to the population than IgG. Albumin drives the Asian markets (China), while IgG drives the western markets

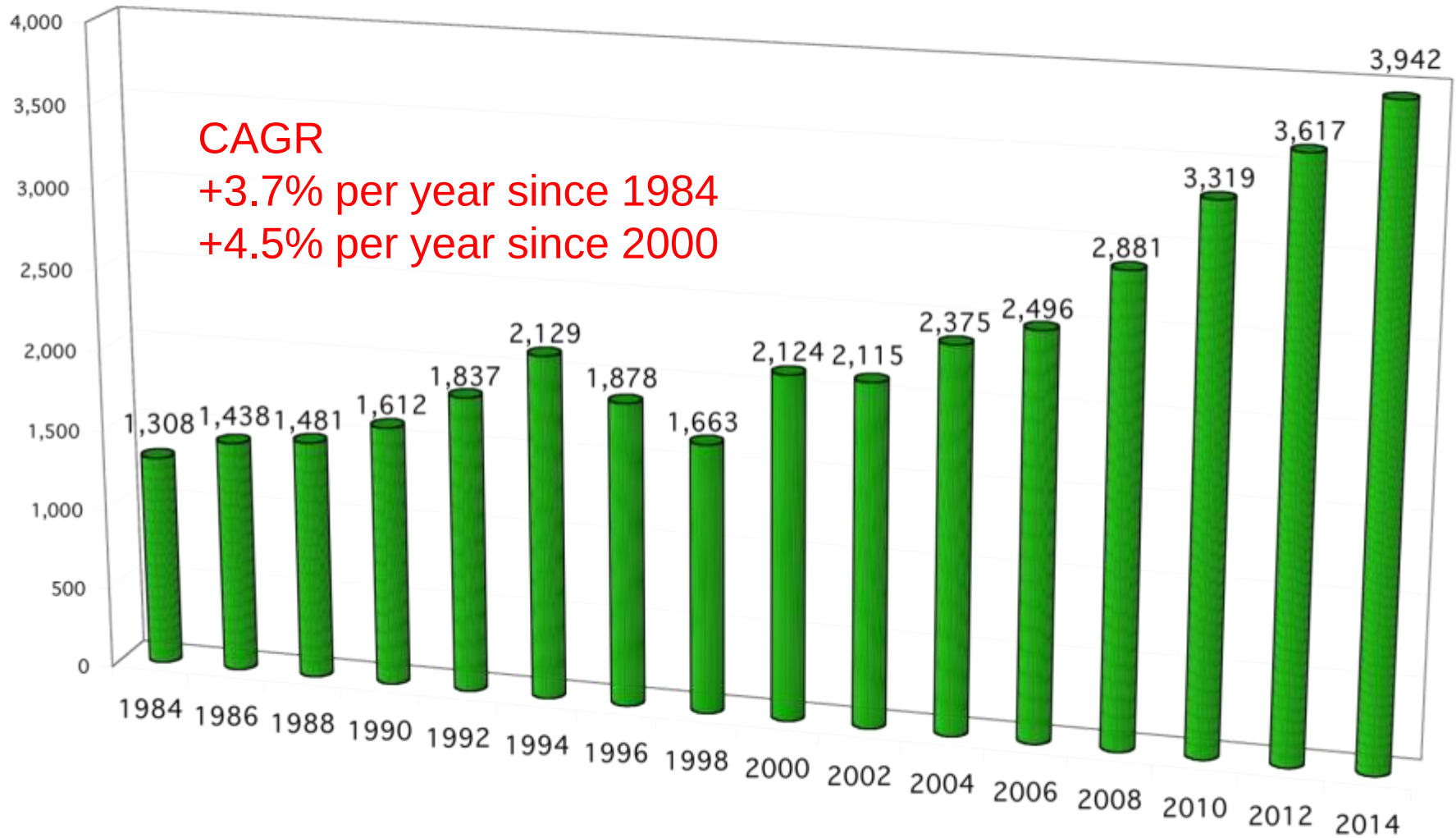


Albumin sales are forecast to grow over 5% per year to the year 2024, due to:

- Continued demand growth in China,
- New emerging markets,
- Population aging,
- New indications,
- Stable price, reliable supply, and
- Limited competition from colloids (hetastarch) or recombinants.

WORLDWIDE DEMAND FOR FACTOR VIII 1984 - 2014

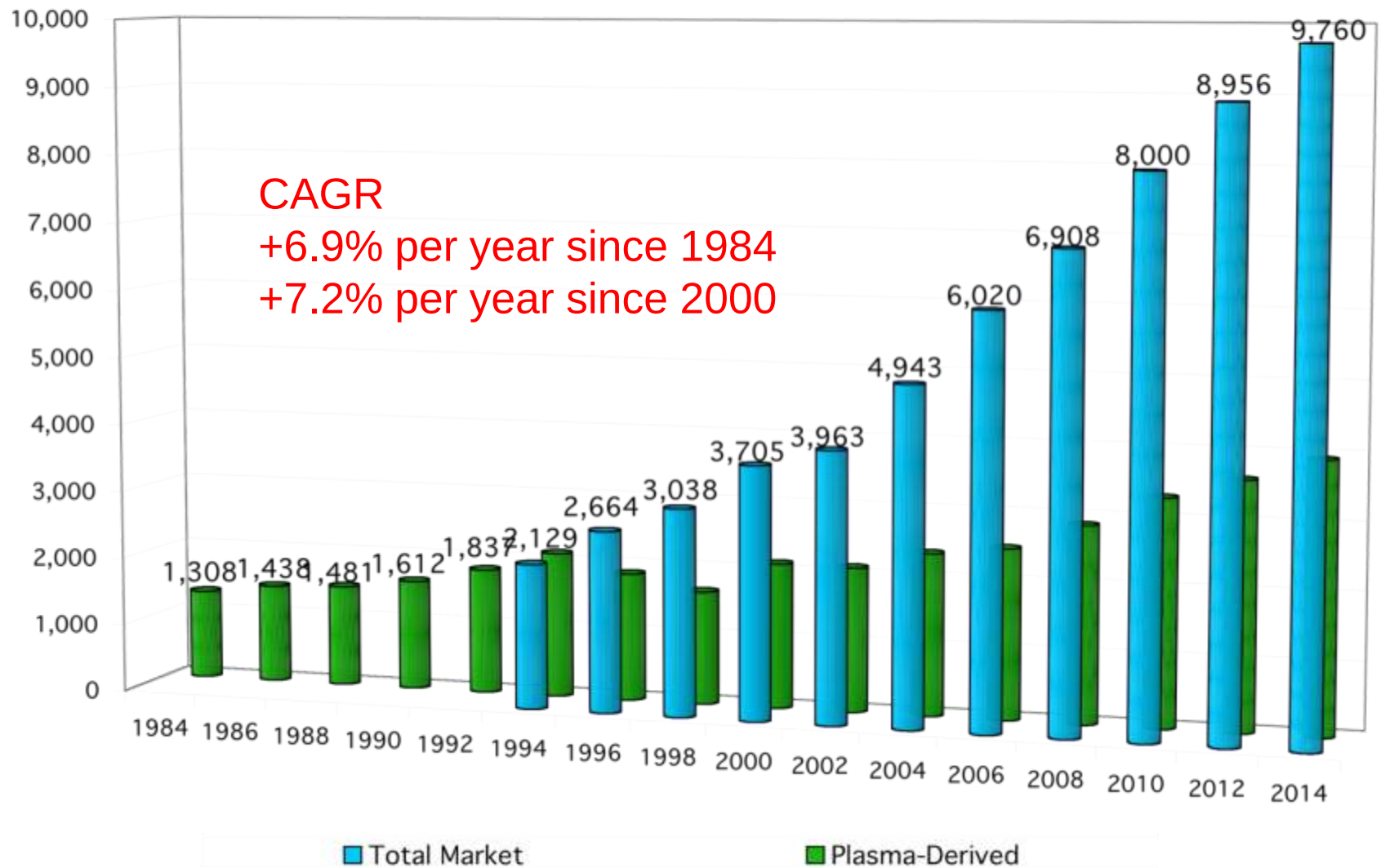
Plasma-derived, Million International Units



In 1998, manufacturing problems linked to the non-compliance with GMPs caused several companies to reduce production levels

WORLDWIDE DEMAND FOR FACTOR VIII 1984 - 2014

Plasma-derived & Recombinant - Million International Units



Since 1994, recombinant factor VIII has expanded the supply, a trend which will accelerate going forward, relegating plasma-derived factor VIII to niche markets and low income countries

Plasma-derived factor VIII consumption is forecast to grow at an annual rate below 5% in the next few years, due to:

- Continued market adoption of standard recombinants,
- Introduction of Extended Half-Life (EHL) recombinant factors and novel treatments, including gene therapy,
- Declining prices and improved product access,
- Continued lobbying of governments by patient groups,
- New markets opening for low-priced factors.

Plasma derived factor VIII will be sold in more low income countries than ever, and in high income countries as immune tolerance treatment for inhibitor patients.

Going forward, the market will no longer be measured in international units, which do not apply to new therapies (monoclonal antibodies, gene therapy).

In the past thirty years, the product mix has evolved: new products have become commercially significant, while the use of others has declined, either posting tumbling sales or reduced market share.

“Growing” products include:

- Alpha-1 Antitrypsin
- C-1 Esterase Inhibitor
- Prothrombin Complex Concentrate (PCC)
- Fibrinogen

“Declining” products include:

- Plasma-derived factors VIII and IX
- Antithrombin III
- Hyperimmune globulins

New proteins are still in development and some may become commercially viable in the future

THE WORLDWIDE PLASMA PROTEINS MARKET BY PRODUCT 1986 - 2016

(Market Shares of Plasma-derived Products only - No Recombinant)

PRODUCT	1986	1990	1998	2003	2008	2012	2016
IGIV/Subcutaneous IG	21.2%	19.0%	27.6%	39.3%	43.0%	46.7%	46.8%
Hyperimmune Globulins *	13.7%	11.2%	10.1%	9.8%	7.7%	5.8%	4.7%
Albumin	45.0%	33.9%	29.0%	15.1%	13.6%	13.3%	16.3%
Factor VIII	16.8%	25.1%	15.4%	15.7%	13.1%	10.6%	8.1%
Factor IX **	1.9%	2.3%	4.4%	3.4%	2.8%	2.5%	1.7%
Act. Prothrombin Complex (aPCC)	1.4%	1.5%	2.4%	2.7%	3.8%	3.7%	4.3%
Antithrombin III	-	2.9%	4.2%	3.0%	3.0%	1.9%	1.0%
Factor XIII	-	0.9%	0.6%	0.2%	0.1%	0.2%	0.4%
Alpha-1 Antitrypsin	-	0.7%	1.6%	3.0%	3.7%	3.9%	4.5%
Fibrin Glue	-	2.4%	4.1%	4.4%	3.8%	2.9%	2.1%
von Willebrand Factor	-	-	0.1%	1.8%	2.8%	3.0%	2.7%
Prothrombin Complex (PPSB/PCC) **	-	-	-	1.1%	1.9%	1.9%	2.2%
Thrombin	-	-	-	-	0.1%	1.0%	0.1%
C1 Esterase Inhibitor	-	-	-	-	-	-	4.0%
Factor VII	-	-	-	-	-	-	-
Factor XI	-	-	-	-	-	-	-
Fibrinogen	-	-	-	-	-	-	-
Protein C	-	-	-	-	-	-	-
Haptoglobin	-	-	-	-	-	-	-
All Other Products***	0%	0.1%	0.7%	0.4%	0.6%	2.6%	1.1%
Total Market	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

* Includes intramuscular and intravenous IgG, Polyvalent IMIG, "FSME" (Tick Borne), Hepatitis A, Measles, Mumps, and Pertussis.

** Combined with Factor IX before 2000

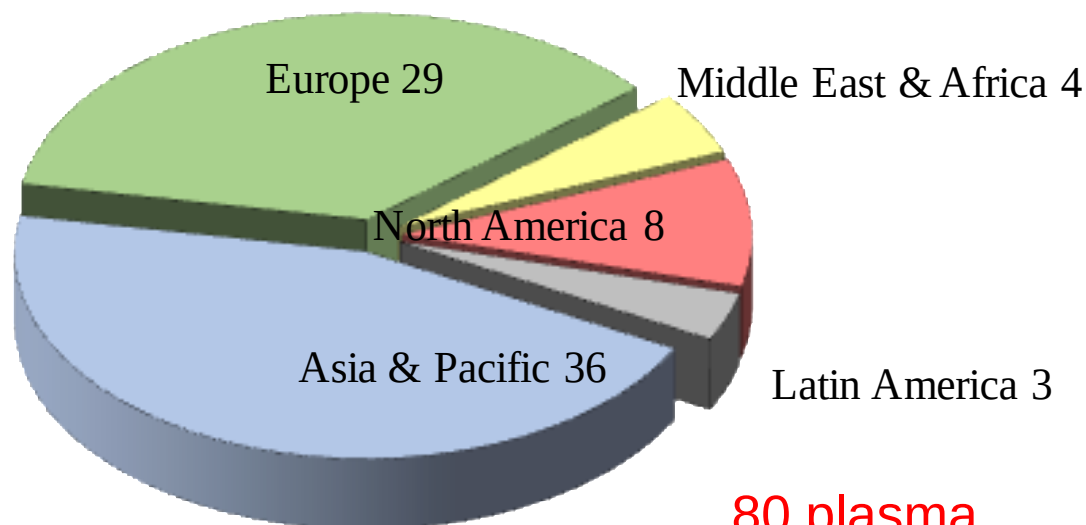
*** Factor VII, Factor XI, Fibrinogen, C1 Esterase Inhibitor, Protein C, Haptoglobin, etc

*** Includes von Willebrand Factor until 1999

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REGIONAL DISTRIBUTION OF FRACTIONATION PLANTS IN 2015



Number of Fractionation Plants 80

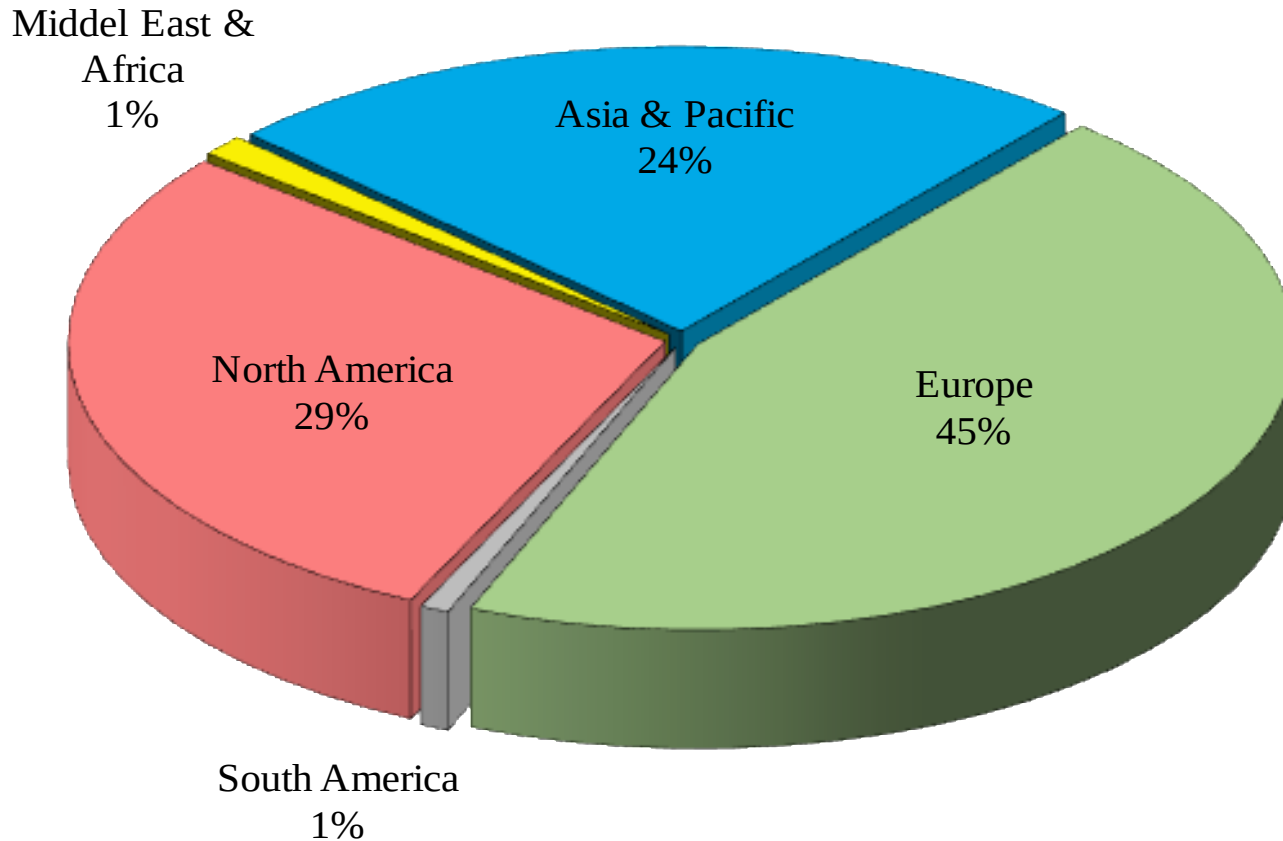
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The six largest companies fractionate about 75% of the world's plasma and capture approximately 78% of the global market.

80 plasma fractionation companies were operating worldwide in 2015, ca. 58 commercial and 22 non-profit

Asia has the highest number of fractionation plants (36) followed by Europe (29). North America has the largest plants in terms of processing capacity

REGIONAL DISTRIBUTION OF THE FRACTIONATION CAPACITY IN 2015 (Thousand Liters)



Global Fractionation Capacity: 66.3 million liters

The Marketing Research Bureau, Inc.

Europe has the world's highest fractionation throughput. The multinational companies move paste from site to site across continents

TYPE OF PLASMA FRACTIONATED WORLDWIDE FROM 1996 TO 2015 COMMERCIAL COMPANIES & NON-PROFIT ORGANIZATIONS

(Thousand Liters)

Total in 2015: 48,132,000 Liters

Compounded annual growth rates (CAGR) of
plasma for fractionation

1996 to 2015

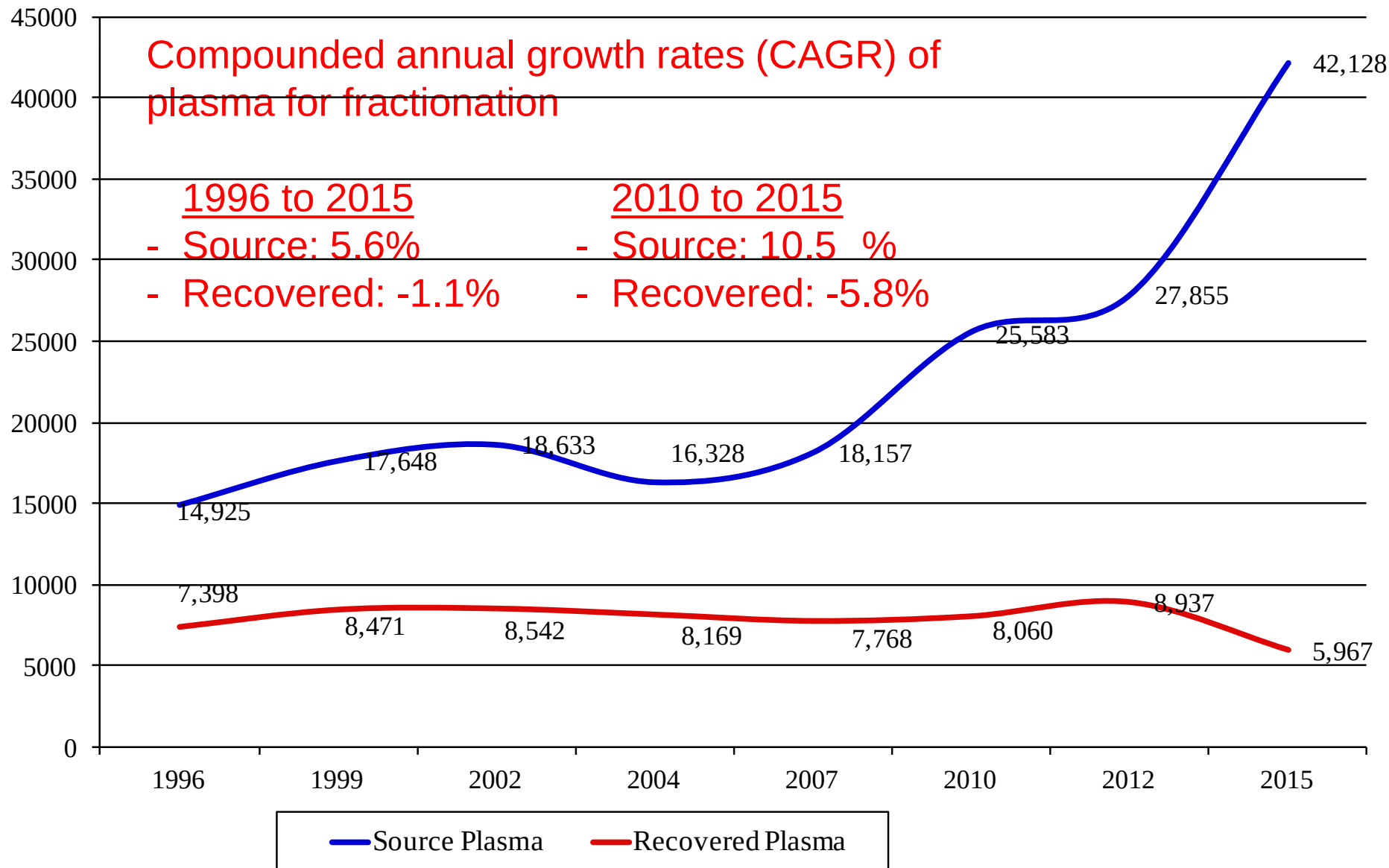
- Source: 5.6%

- Recovered: -1.1%

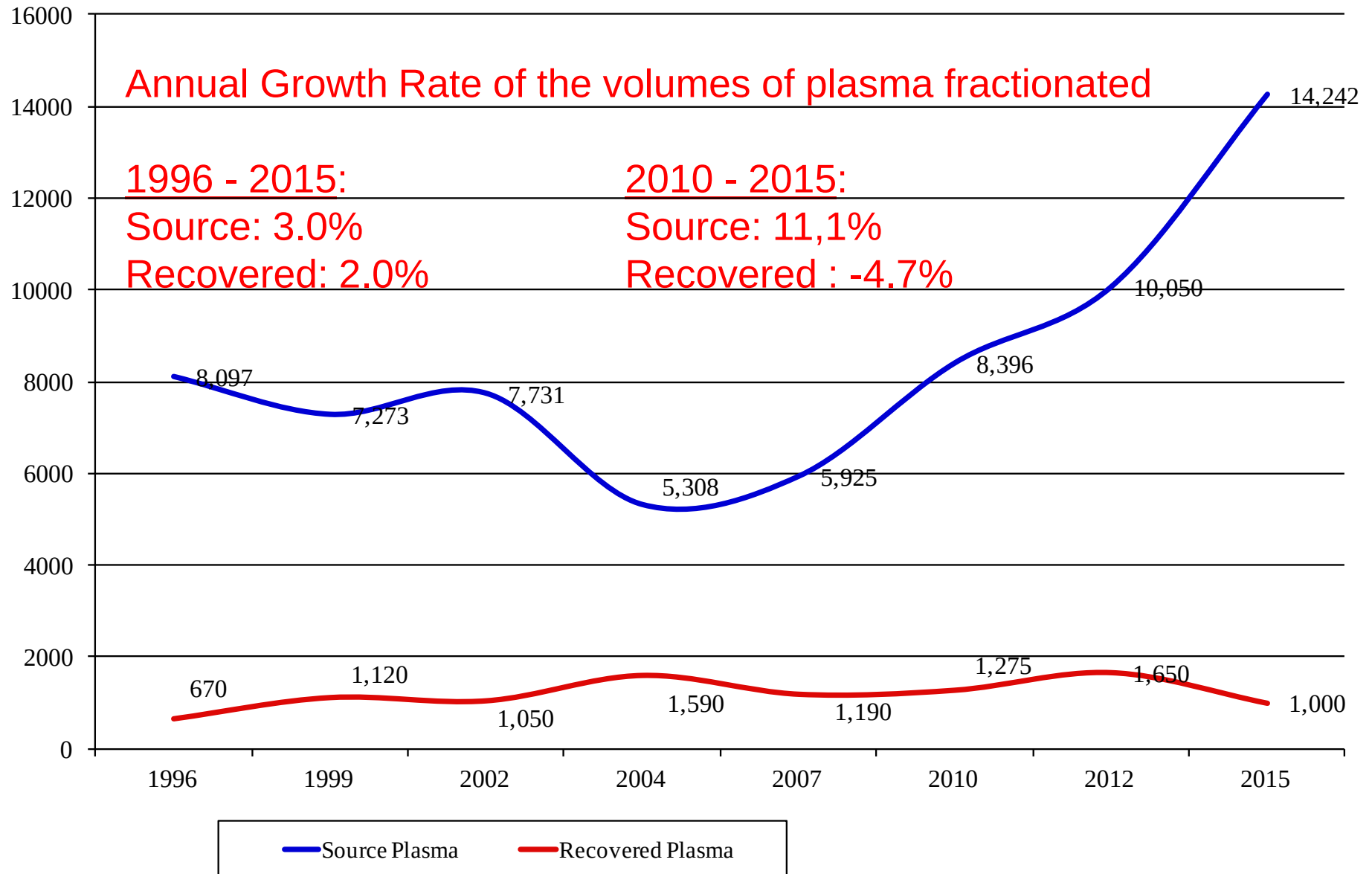
2010 to 2015

- Source: 10.5 %

- Recovered: -5.8%



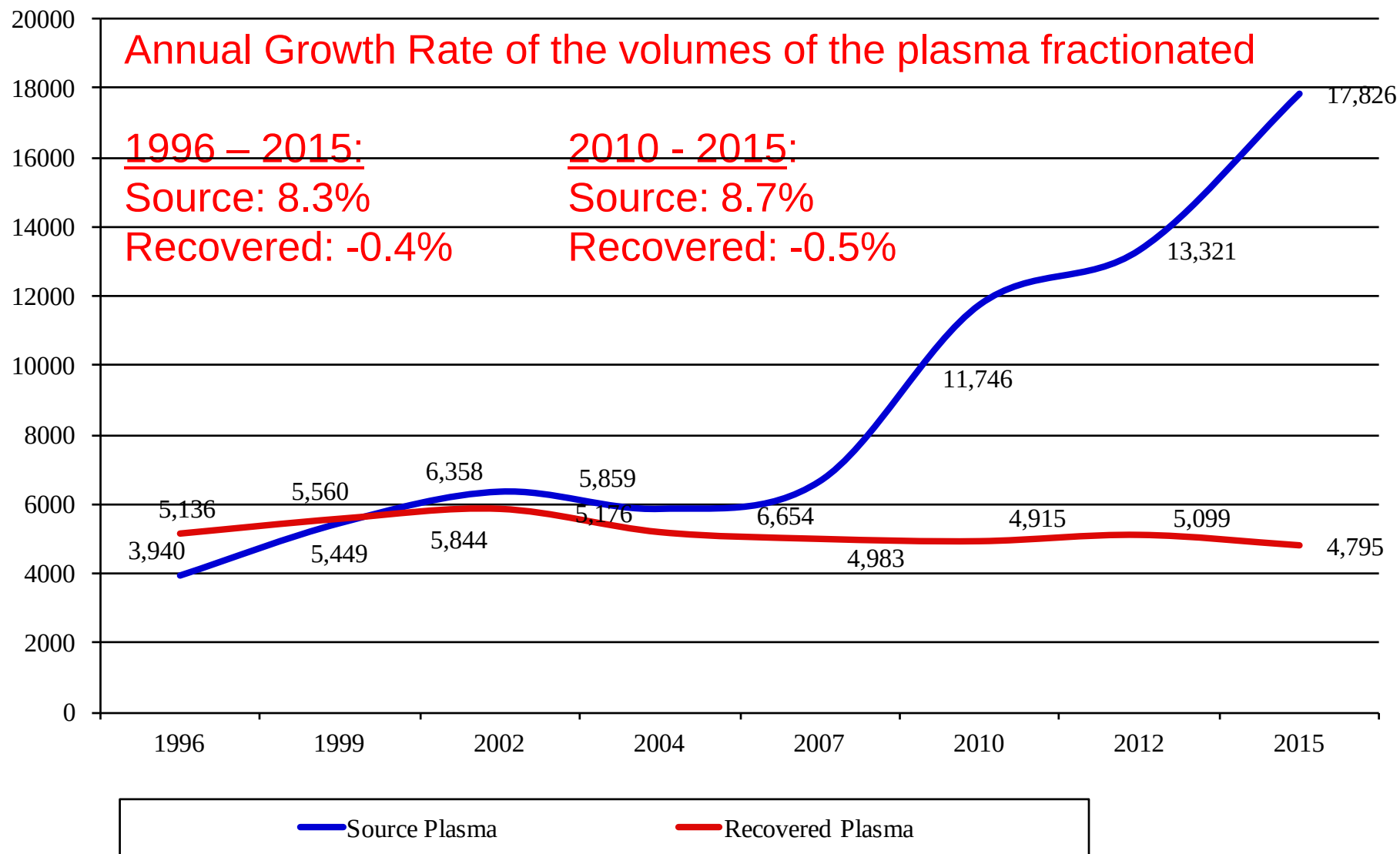
TYPE OF PLASMA FRACTIONATED IN NORTH AMERICA FROM 1996 TO 2015
COMMERCIAL COMPANIES & NON-PROFIT ORGANIZATIONS
(Thousand Liters)



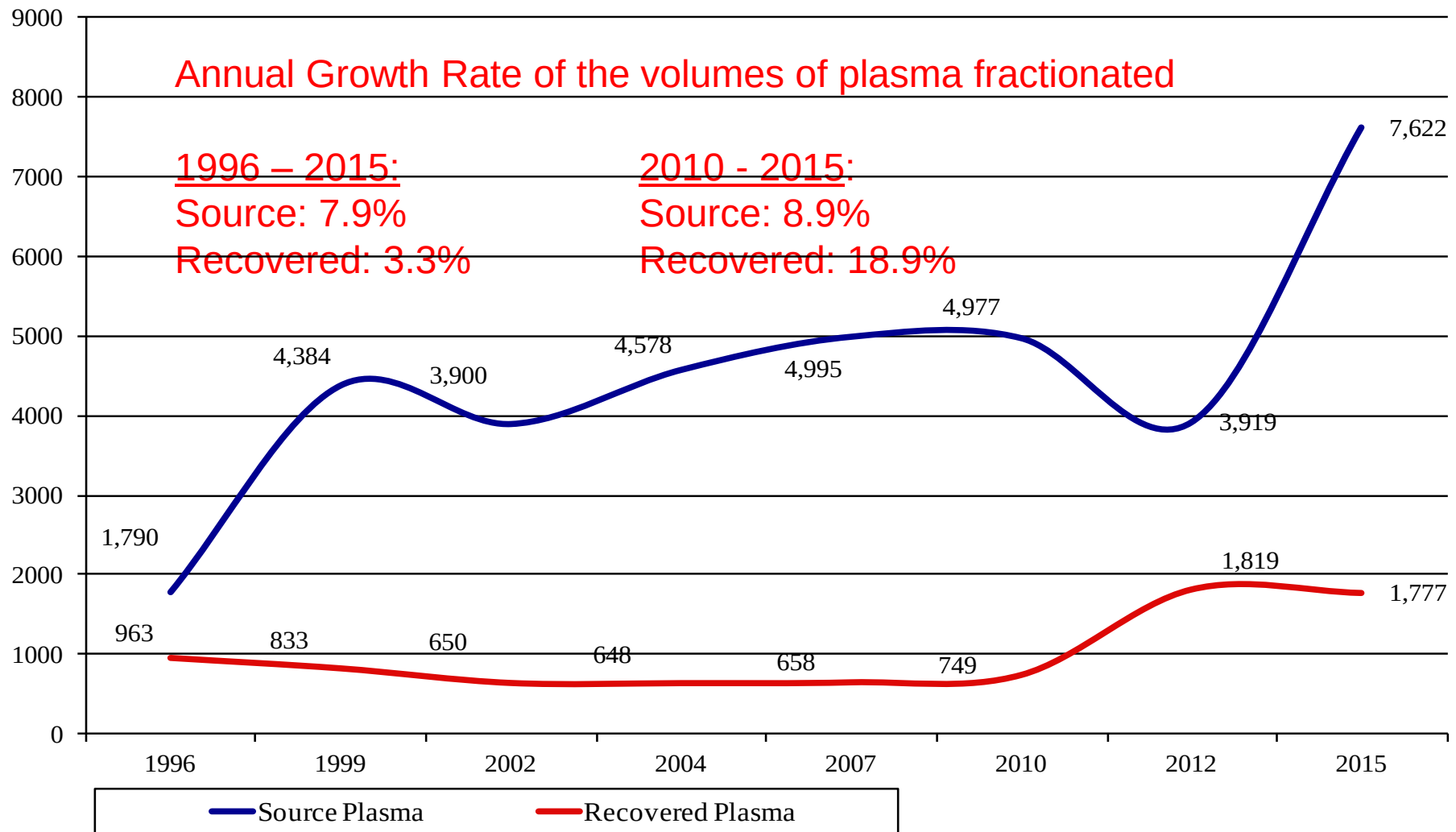
TYPE OF PLASMA PROCESSED IN EUROPE - 1996 TO 2015

COMMERCIAL COMPANIES & NON-PROFIT ORGANIZATIONS

(Thousand Liters)



TYPE OF PLASMA PROCESSED IN ASIA & PACIFIC FROM 1996 TO 2015 COMMERCIAL COMPANIES & NON-PROFIT ORGANIZATIONS (Thousand Liters)



The drop of the source plasma volume in 2013 was caused by the SFDA crackdown on plasma centers in China, where no recovered plasma is fractionated.

Source plasma collections depend on factors **external to the fractionation industry** while the production of recovered plasma depends on the **demand for red cells and other components**

The **annual volume allowed per donor** (15 liters vs. 44, or 85 liters) is the main factor differentiating the “performance” of a country in terms of plasma collections

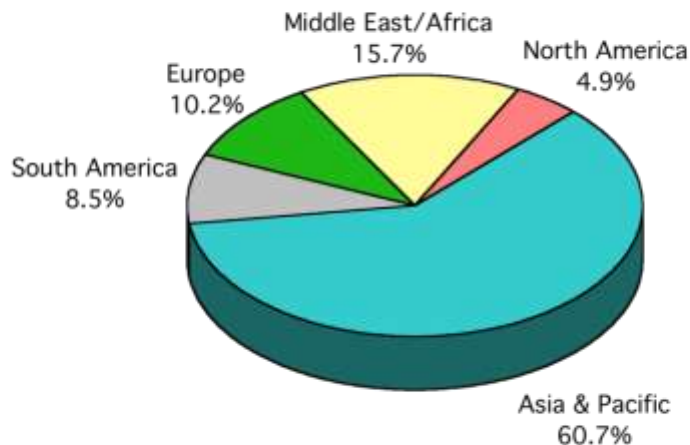
Payment is one form of donor compensation, which is determined by **tradition and culture**.

Provisional

Data!

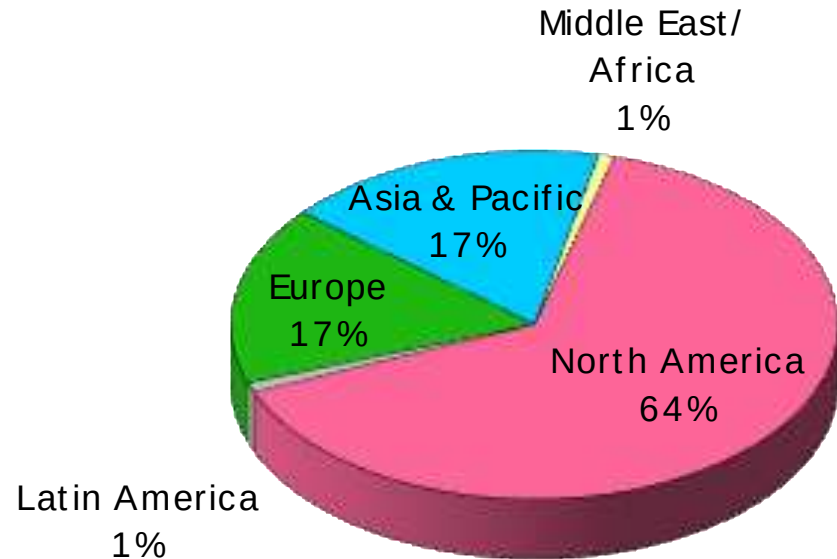
The United States generate 64% to the world's plasma for fractionation (source and recovered) with only 5% of the world population.

World Population by Region - 2014



Source: PopulationReference Bureau

Plasma for Fractionation by Region 2015 (Recovered & Source)



Total: 48,744,000 liters

Asia's generates 17% to the world's plasma for fractionation and has 61% of the world population. However most of its source plasma remains in China

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CURRENT ISSUES

- Will the U.S. be able to continue supplying plasma to the world? Is there a limit to the US plasma supply?
- Is Europe going to generate more plasma for fractionation? from compensated donors? Other regions?
- Will a substitute for IVIG/SCIG emerge and threaten their clinical supremacy?
- Will self-sufficiency become a reality, using small-scale fractionation technologies, and threaten the large fractionators' commercial domination?
- Is China going to export/import plasma products and threaten the large fractionators' commercial domination?

Thank you!



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