GLOBAL TRENDS OF PLASMA AND PLASMA PRODUCTS DEMAND

With Focus on Emerging Markets

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The Marketing Research Bureau, Inc.

Be There for Someone Else. Give Plasma, Share Life.

Istituto Superiore de Sanita
Centro Nazionale Sangue

International Federation of Blood Donor Organizations

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www.marketingresearchbureau.com

SOURCE OF THE DATA

The data used to develop the charts and tables shown in this presentation have been compiled from the Marketing Research Bureau's database, scientific articles, congress proceedings, companies' annual reports, publications and statistics published by national and international organizations, as well as by various plasma industry stakeholders, including patients groups.

GENERAL INFORMATION

All the data and information come from sources generally available to the public. Their accuracy is not guaranteed, and the Marketing Research Bureau assumes no liability for their use.

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Table of Contents

Table of Contents

PLASMA FRACTIONATION

WHOLE BLOOD

- Plasma
- Platelets
- Cryoprecipitate
- Buffy Coat
- Red Blood Cells

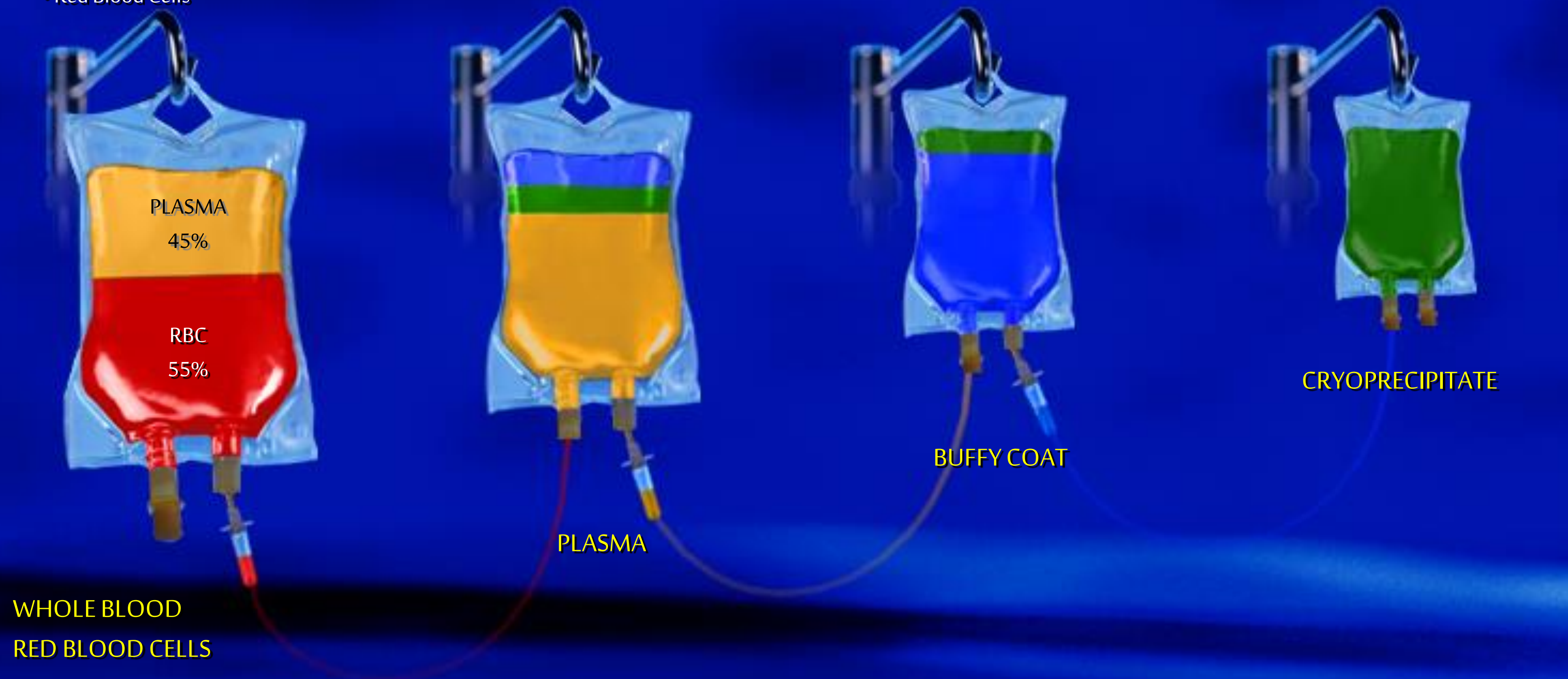
PLASMA

- Platelets
- Cryoprecipitate
- Buffy Coat

BUFFY COAT

- Platelets
- Cryoprecipitate

CRYOPRECIPITATE



PLASMA FRACTIONATION

Fraction V

Albumin
(25 grams)

Factor VIII
200 IUs

Factor IX
275 IUs

Fraction IV

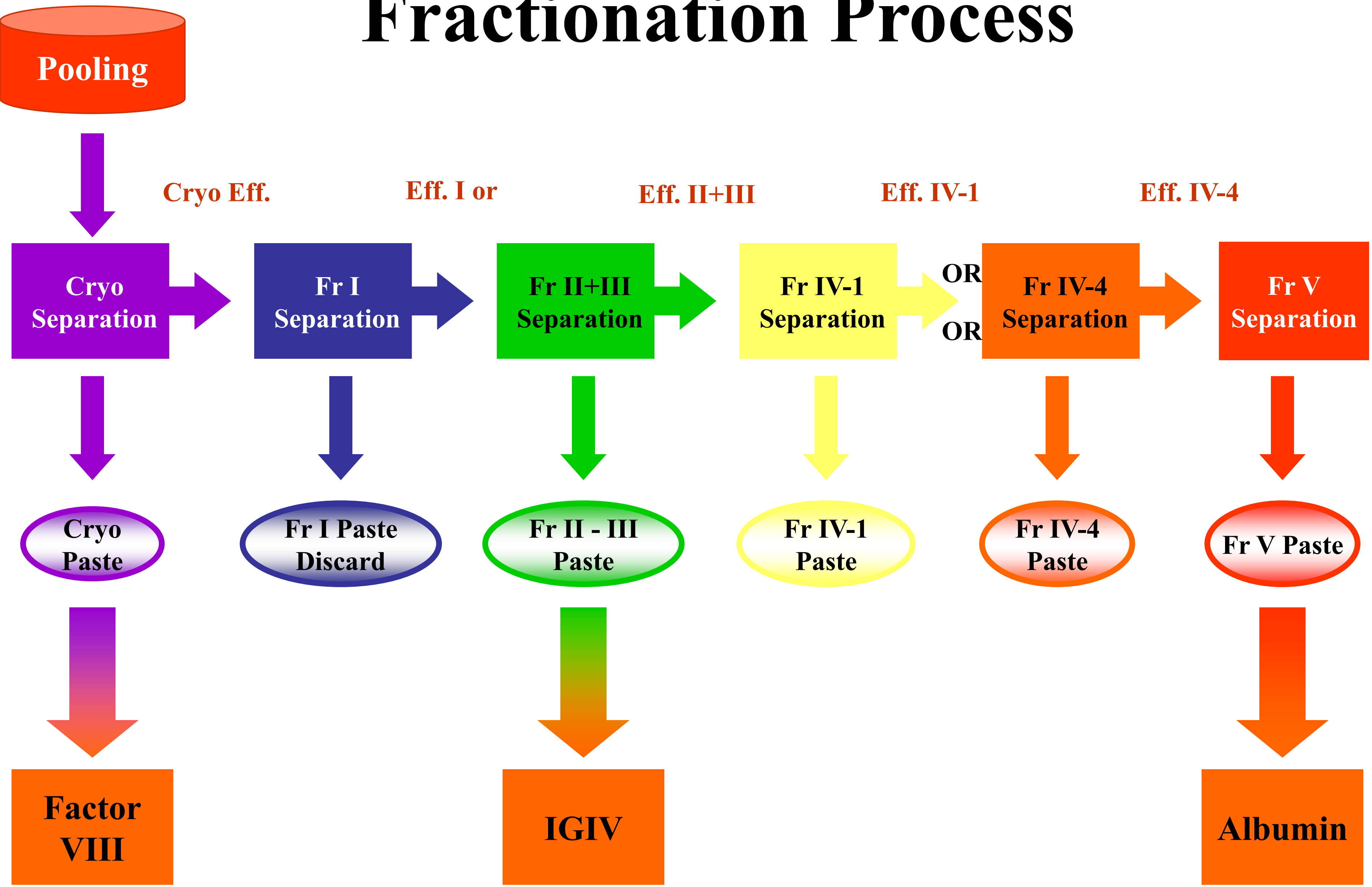
ATIII
(250 IUs)

Alpha-I Antitrypsin
(0.25 grams)

Fraction II

Polyvalent IGIV
3-5 grams)

Fractionation Process



The Plasma Fractionation Process

- Plasma is separated into five fractions, each of which is used to make a different product: immune globulin, albumin, antithrombin III, etc.

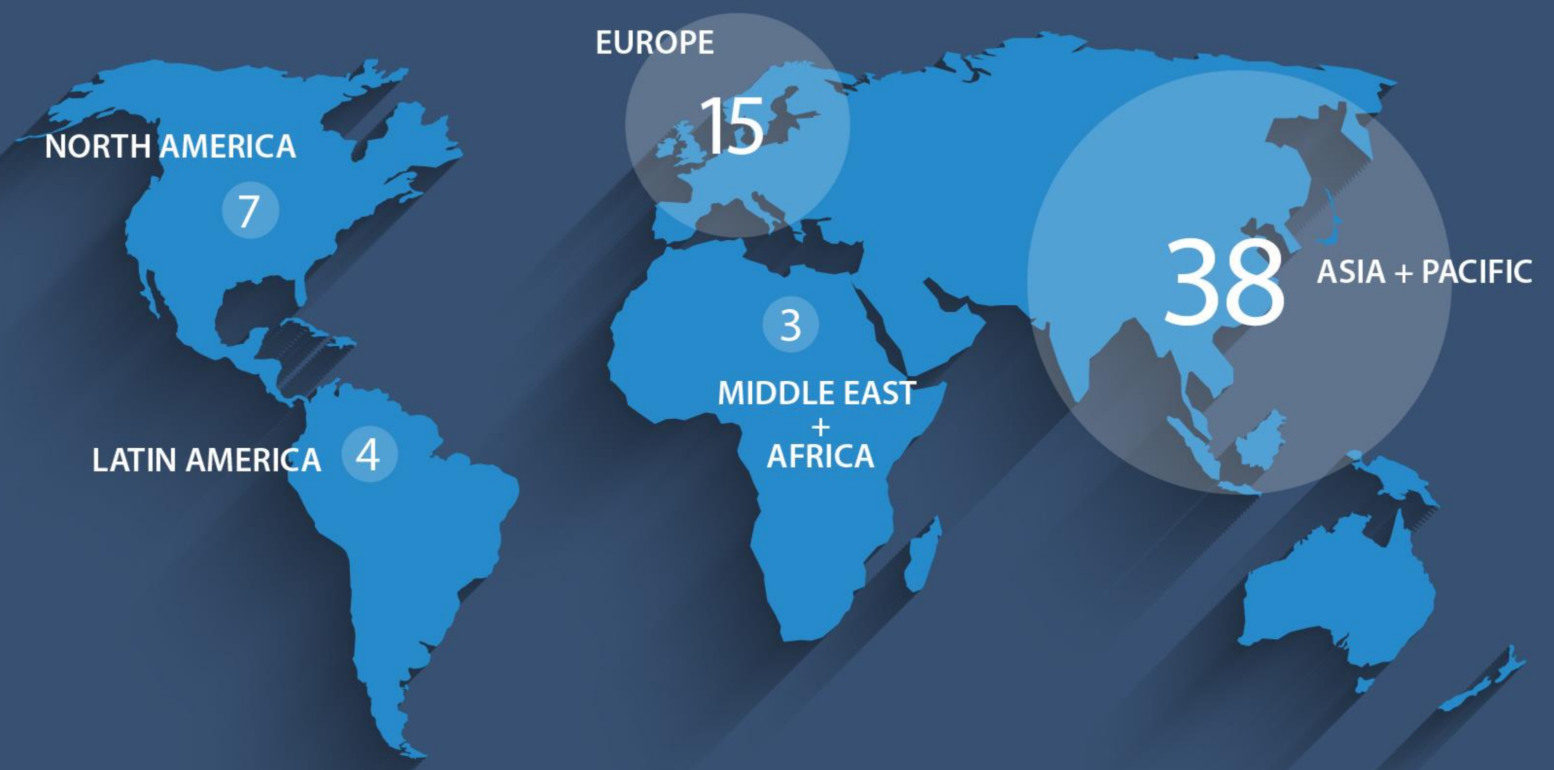
- Coagulation factor VIII is made from cryoprecipitate, a plasma component which is extracted before the fractions

- The fractionation process is a sequence of several treatment of the plasma: addition of alcohol, temperature change, change of acidity, etc. Each of these sequences generates a distinct component (effluent) which is separated from the remaining plasma until the last fraction, which is fraction V. Fraction V is used to make albumin

Plasma Fractionation

Courtesy CSL Behring

REGIONAL DISTRIBUTION OF FRACTIONATION PLANTS 2014



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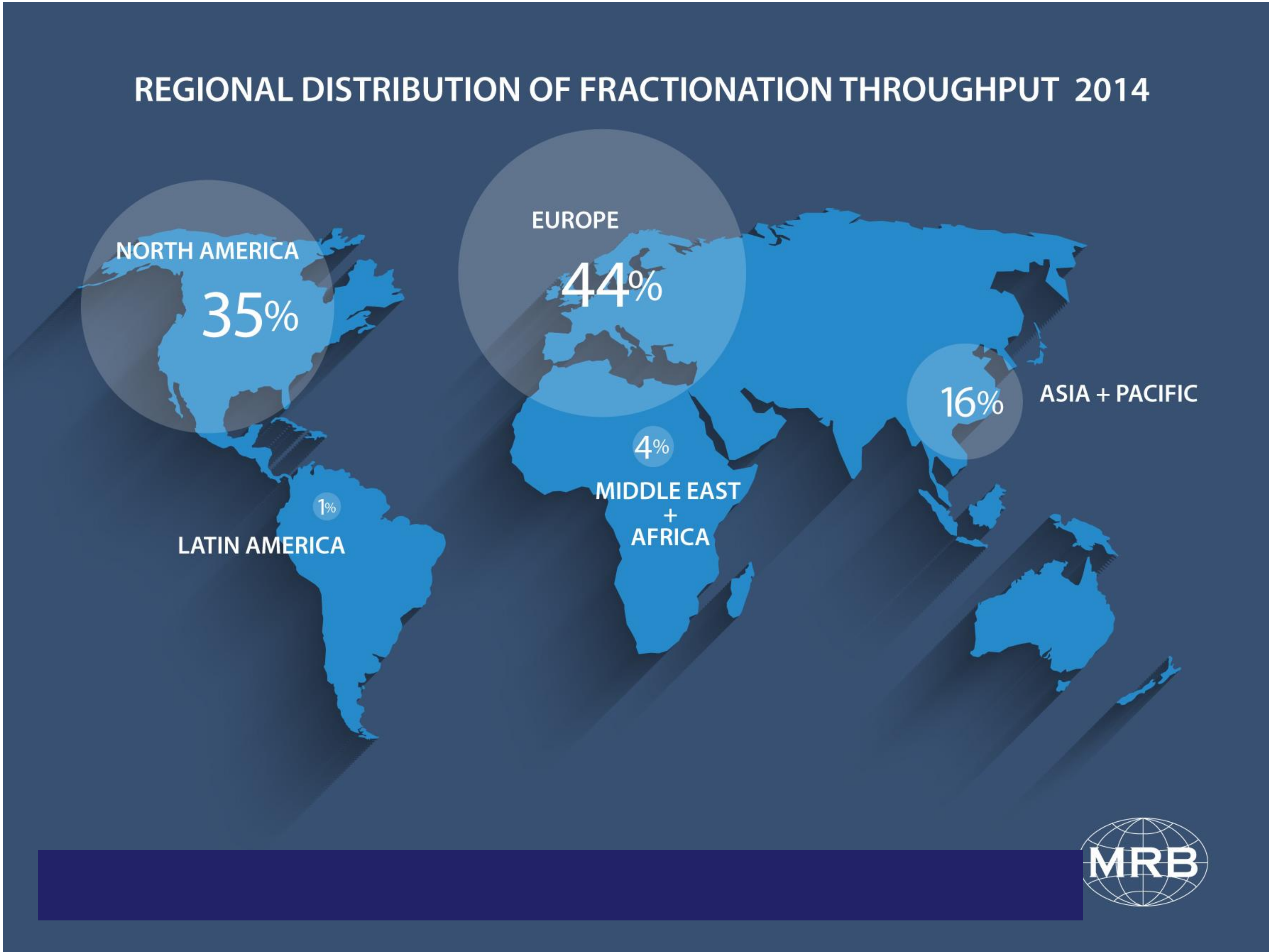
REGIONAL DISTRIBUTION OF FRACTIONATION THROUGHPUT 2014
NORTH AMERICA
35%
EUROPE
44%
16%
ASIA + PACIFIC
4%
MIDDLE EAST
+
AFRICA
1%
LATIN AMERICA
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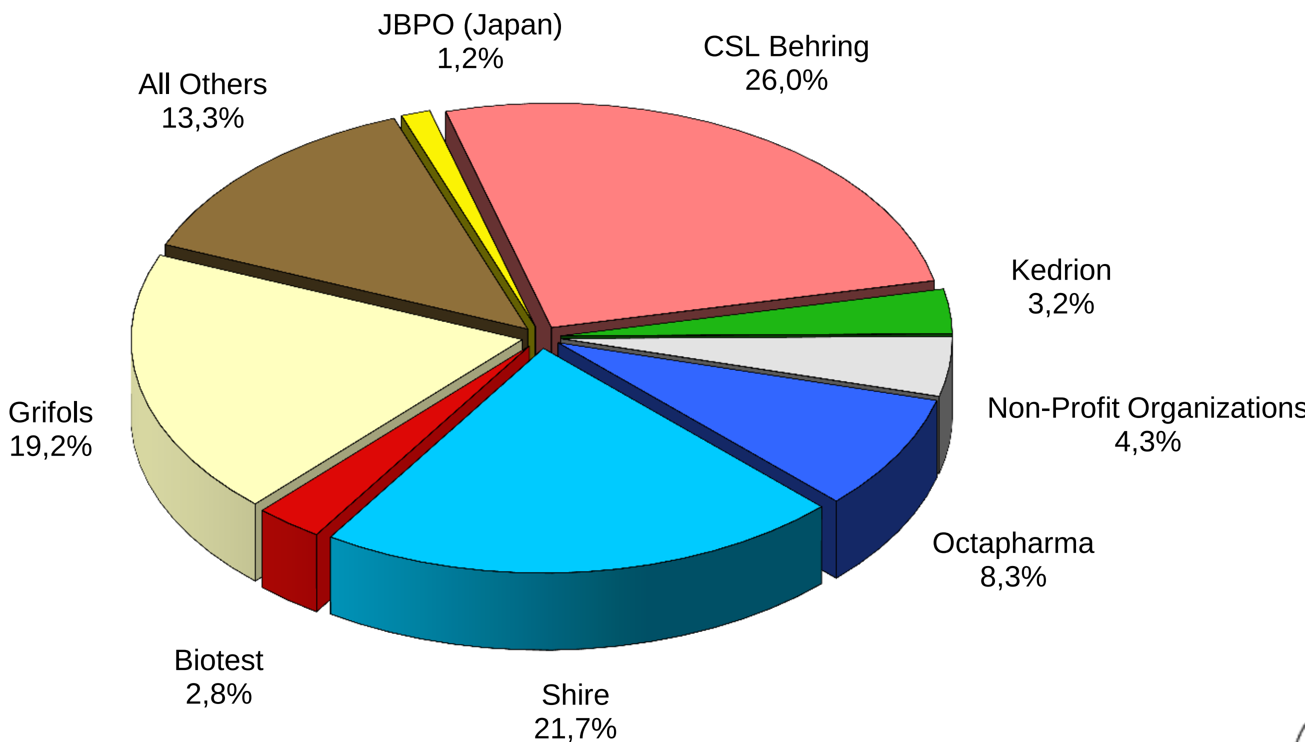
THE WORLDWIDE PLASMA PROTEINS MARKET BY COMPANY - 2016

WITHOUT RECOMBINANT FACTORS

Total Market 21,174 Million



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THE GLOBAL PLASMA INDUSTRY CONSOLIDATION
NORTH AMERICA AND EUROPE (COMMERCIAL SECTOR - #1)

1996	1999	2002	2008	2015
Aima (Italy)	Baxter-Plasmitalia			
Baxter-Hyland (US)	Baxter	Baxter	Baxter	Baxalta
Immuno (Austria)				
Immuno (US)	Baxter (Rochester)	Baxter (Rochester)		
Sclavo (Italy)	Bayer Biological Products	Bayer Biological Products	Talecris	
Bayer Biological Products				
Vitex (Melville, US)	Vitex (Melville, US)	Precision Pharma		Grifols
Alpha Therapeutics	Alpha Therapeutics	Grifols	Grifols	
Grifols (Spain)	Grifols (Spain)			
Human (Hungary)	Human (Hungary)	Teva (Hungary)		
Farma Biagini	Marcucci Group	Kedrion	Kedrion	Kedrion
Istituto Sieroterapico Italiano				
Ortho Clinical Diagnostics	Ortho Clinical Diagnostics	Ortho Clinical Diagnostics	Ortho Clinical Diagnostics	
Omrix	Omrix	Omrix	J & J (Ethicon)	J & J (Ethicon)

Note: High degree of consolidation particularly between 1996 and 2002

THE GLOBAL PLASMA INDUSTRY CONSOLIDATION
NORTH AMERICA AND EUROPE (COMMERCIAL SECTOR - #2)

1996	1999	2002	2008	2015
Probifasa (Mexico)	Probifasa (Mexico)	Probifasa		
DRK Springe (Germany)	DRK Springe	DRK Springe		
Kabi (Sweden)	Pharmacia & Upjohn		Octapharma	Octapharma
Octapharma (Austria)	Octapharma (Austria)	Octapharma		
Centeon (France)	Octapharma (France)			
Centeon (Spain)	Aventis Behring (Spain			
Centeon (Austria)	Aventis Behring (Austria)			
Centeon (Marburg, Germany)	Aventis Behring (Marburg)			
Centeon/Armour (Kankakee)	Aventis Behring (Kankakee)	ZLB Behring	CSL Behring	CSL Behring
ZLB Swiss Red Cross (Bern)	ZLB Swiss Red Cross (Bern)			
CSL Bioplasma (Australia)	CSL Bioplasma	CSL Bioplasma	CSL Bioplasma	
Biotest (Germany)	Biotest	Biotest	Biotest	Biotest
	Nabi (Florida)	Nabi		
Berna (Switzerland)	Berna	Berna		

Note: High degree of consolidation particularly between 1999 and 2002

The Human Factor

- The plasma industry differs from the blood collection sector in the following ways:

- Technical: the fractionation of plasma is a heavy industrialized process,

- Economic & political: “plasma economics” play an important role, as do the development of new proteins, the production yields and market forces,

- Social: The patients’ organizations play a vital role by advocating for product access, safety and supply worldwide. They exercise a strong influence on the fractionation industry.

Logos of some Patient's Advocacy Groups involved with plasma products

Immune Deficiency Foundation

National Hemophilia Foundation
for all bleeding disorders

IPOPI

WFH
WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

Jeffrey Modell Foundation | Curing PI. Worldwide.

The Plasma Fractionation Industry

- Plasma fractionation is a highly concentrated industry: CSL Behring, Grifols, Shire (Baxter), Octapharma, Kedrion, Biotest, LFB, Sanquin, Japan Blood Products Organization control over 86% of the world's Plasma-Derived Medicinal Products (PDMPs) market.

- The global market is about €17.9 billion ($21.2 billion)

- None of the six largest fractionation companies is American. They are Australian, Japanese, Spanish, Swiss, German and Italian. Kedrion is in sixth position.

- In 2017, approximately 55 million liters of plasma were fractionated worldwide by some 80 plants which a total capacity of about 72 million de liters annually.

Table of Contents

- Introduction to the Plasma Fractionation Industry
- The Plasma-Derived Medicinal Products (PDMPs) Market: Factor VIII, Albumin, and IgG (Polyvalent intravenous and subcutaneous Immunoglobulins)
- Plasma for Fractionation: Volume and Origin
- Conclusion: Optimizing the demand the Supply and Demand of Plasma

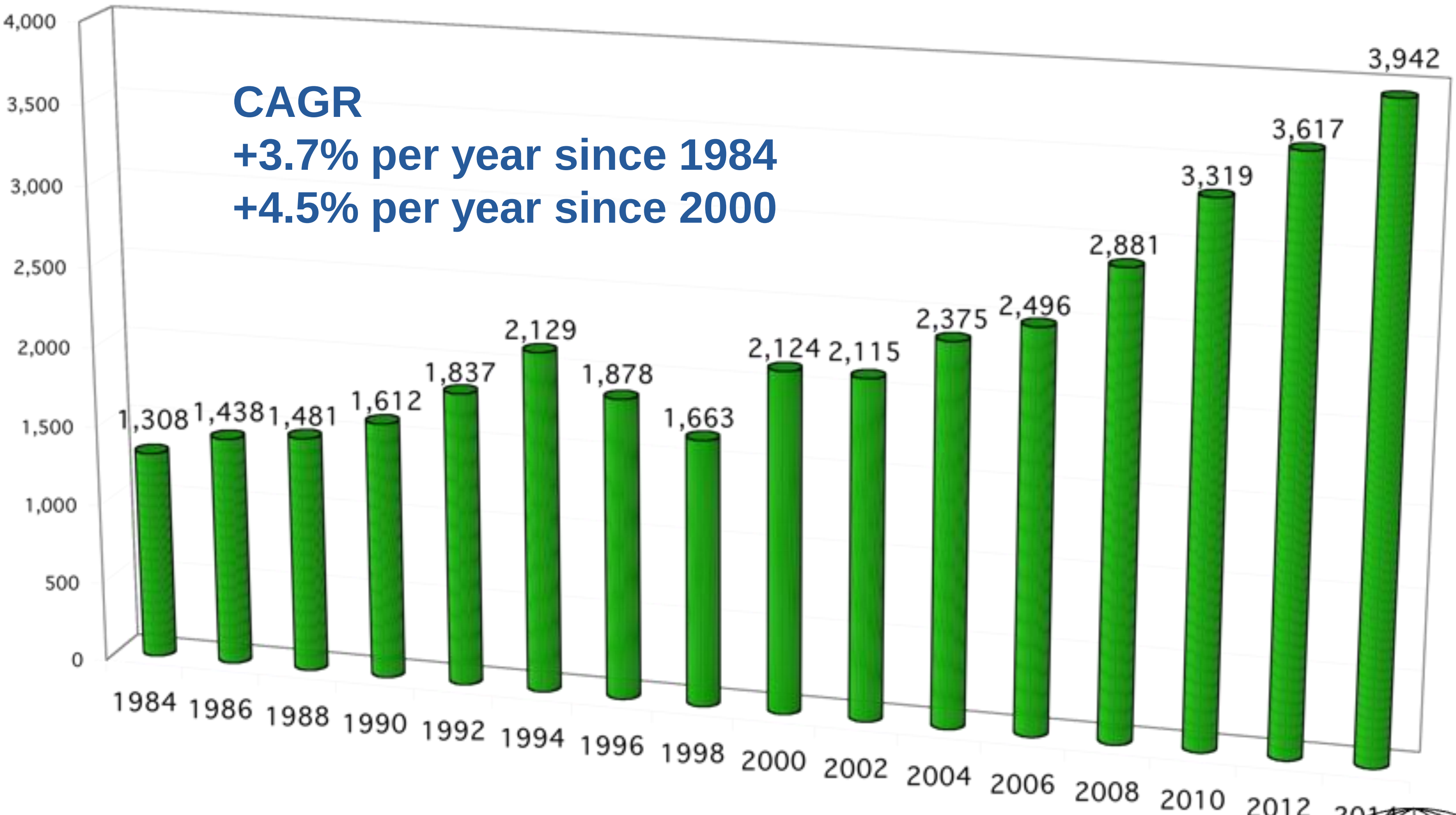
The Plasma-Derived Medicinal Products (PDMPs) Market

- Factor VIII was the industry driver in the 1980s and 1990s, as it strong demand determined the volume of plasma to be processed. Since the mid-1990s, it has been gradually replaced by a recombinant equivalent made from genetic engineering, particularly in the high income countries.

- Today, plasma-derived factor VIII is mainly used in the low income countries where sales generate less revenues for the fractionation companies. Consequently, they must offset this revenue loss with other products.

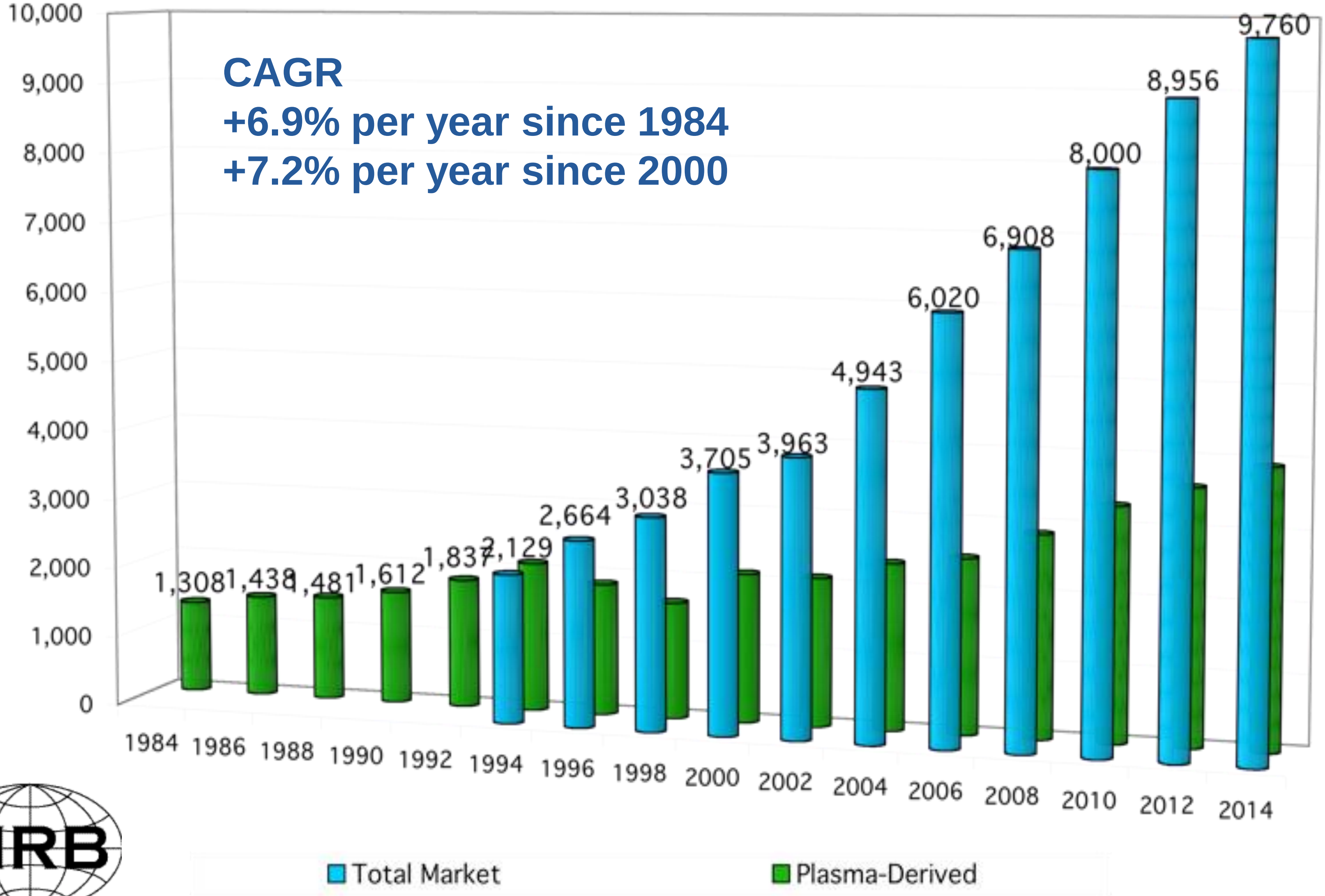
- In the coming years, plasma-derived factor VIII will not be completely replaced by recombinant factor VIII and other treatments because it is still the preferred product in some clinical circumstances, and it is much less expensive than its alternatives. Its global sales continue to increase, although more slowly than those of recombinant factor VIII.

WORLDWIDE DEMAND FOR FACTOR VIII 1984 - 2014
Plasma-derived, Million International Units



By 2020, a global consumption of about 10.5 billion factor VIII units is forecasted, including 6.2 billion units of recombinant products (Standard and Extended Half-Life).

WORLDWIDE DEMAND FOR FACTOR VIII 1984 - 2014
Plasma-derived & Recombinant - Million International Units



The Plasma-Derived Medicinal Products (PDMPs) Market

- The main function of albumin is to help the body maintain intravascular colloid osmotic pressure. It is primarily used in the treatment of shock. Other non-plasma-based fluids can be used in its place but they are less efficacious and not as well tolerated by the human body.

- In the future, the albumin demand will continue to grow as health care services improve in many emerging countries, and its price and supply are stable. By 2020, a global consumption of about 1,200 tons of albumin is forecasted, about half of it in Asia.

- In China, albumin is prescribed as a nutrient, in addition to its other indications, and its demand grows faster than in most other countries.

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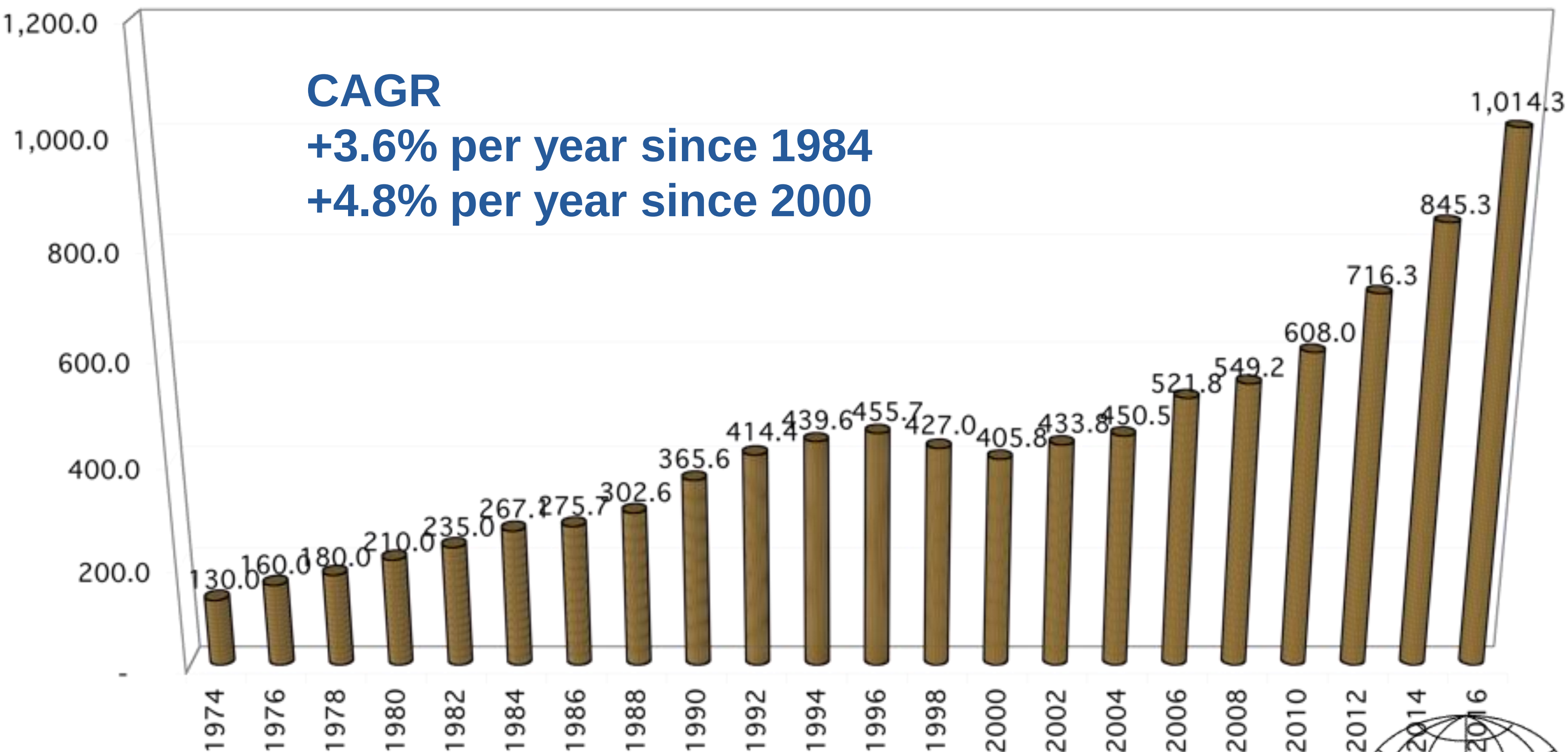
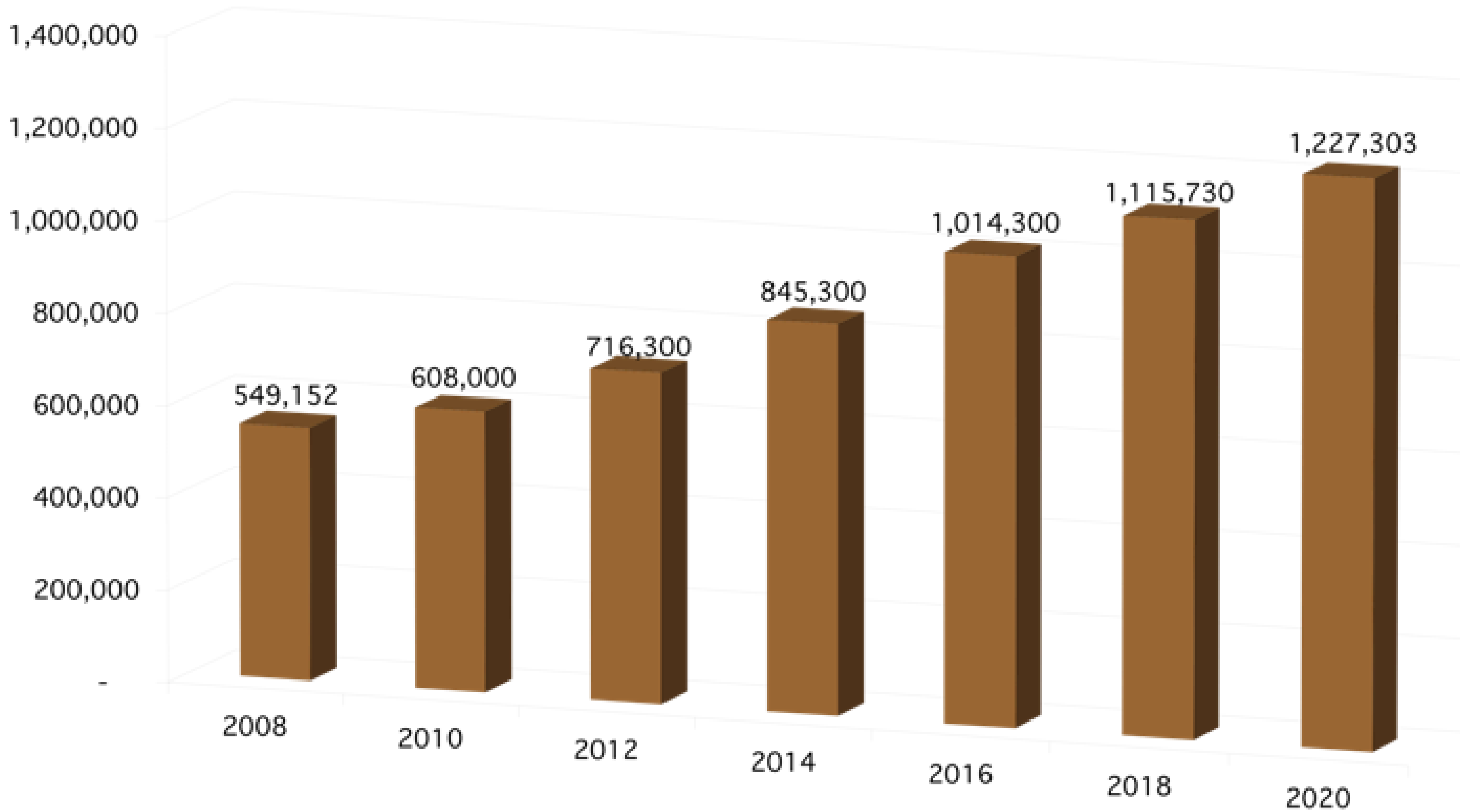
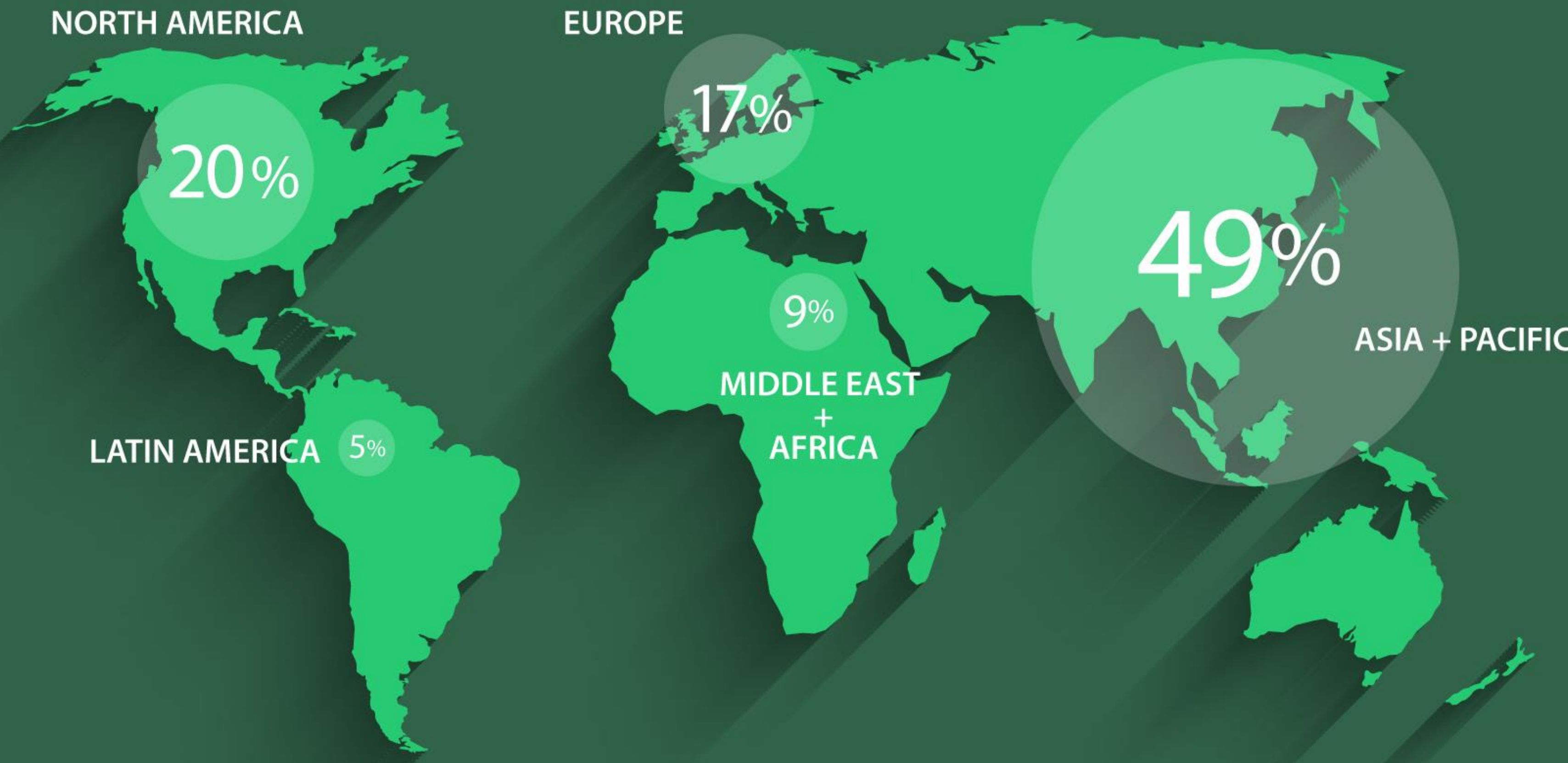
WORLDWIDE ALBUMIN DEMAND 1974 - 2016
Metric Tons



THE GLOBAL ALBUMIN MARKET FROM 1986 TO 2020 (Kilograms)

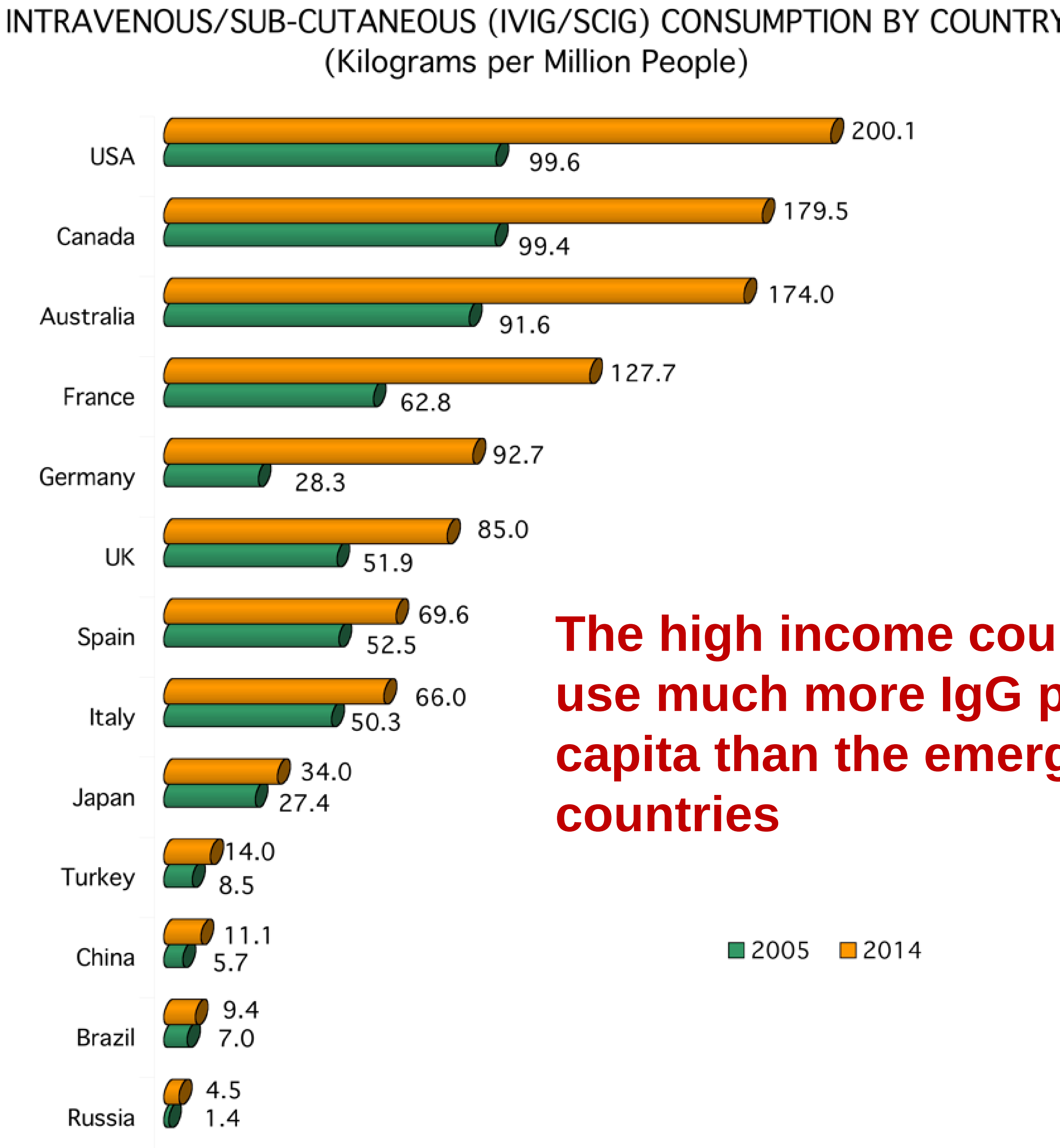


WORLDWIDE ALBUMIN UNIT SALES BY REGION

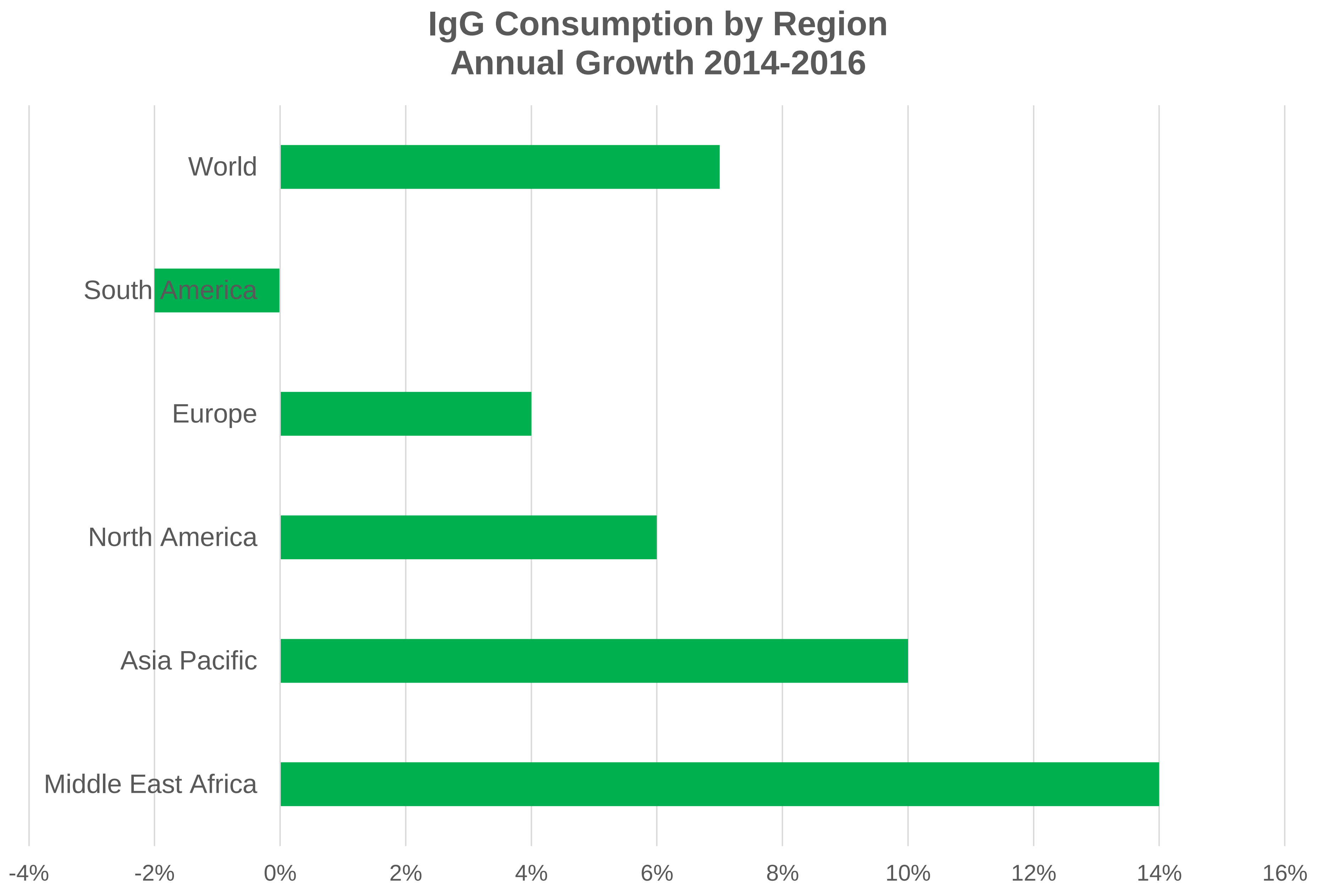


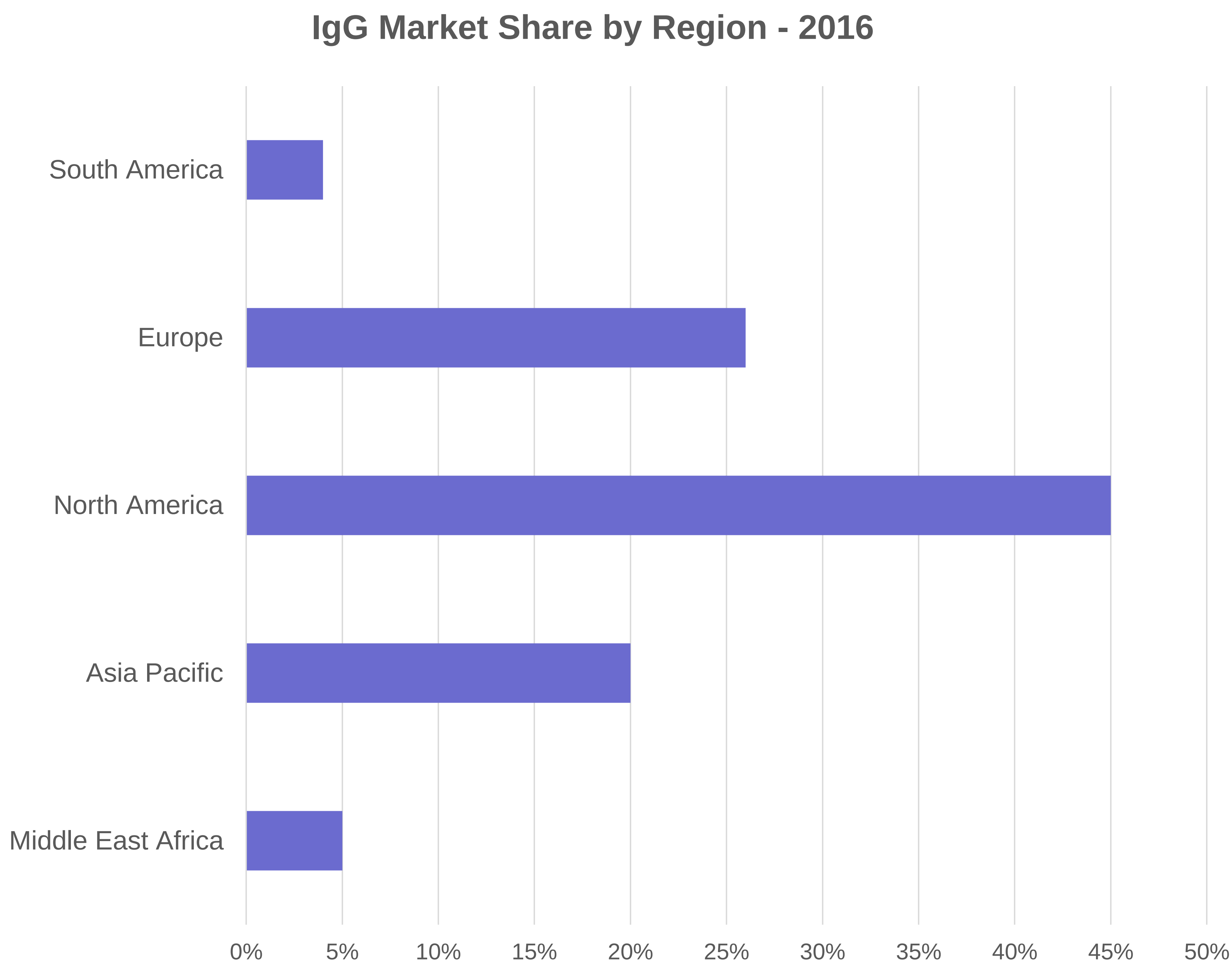
THE WORLDWIDE POLYVALENT IgG MARKET FROM 1986 TO 2024 (Metric Tons)

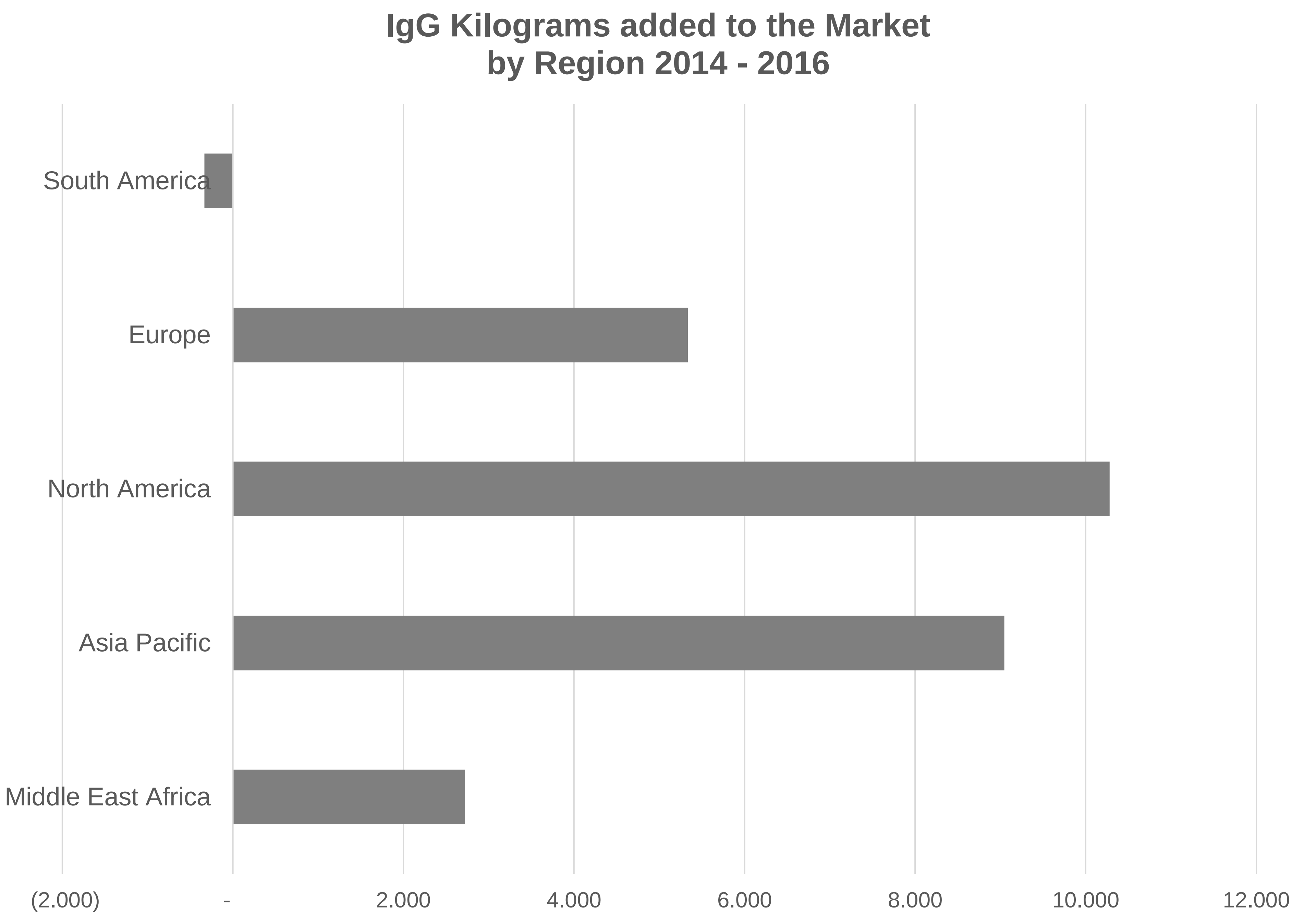
In 2024, 290 tons of immunoglobulins will be produced from 75 millions de liters of plasma, based on a production yield of 3.9 grams per liter.



The high income countries use much more IgG per capita than the emerging countries


IgG Consumption by Region
Annual Growth 2014-2016
World
South America
Europe
North America
Asia Pacific
Middle East Africa
-4%
-2%
0%
2%
4%
6%
8%
10%
12%
14%
16%

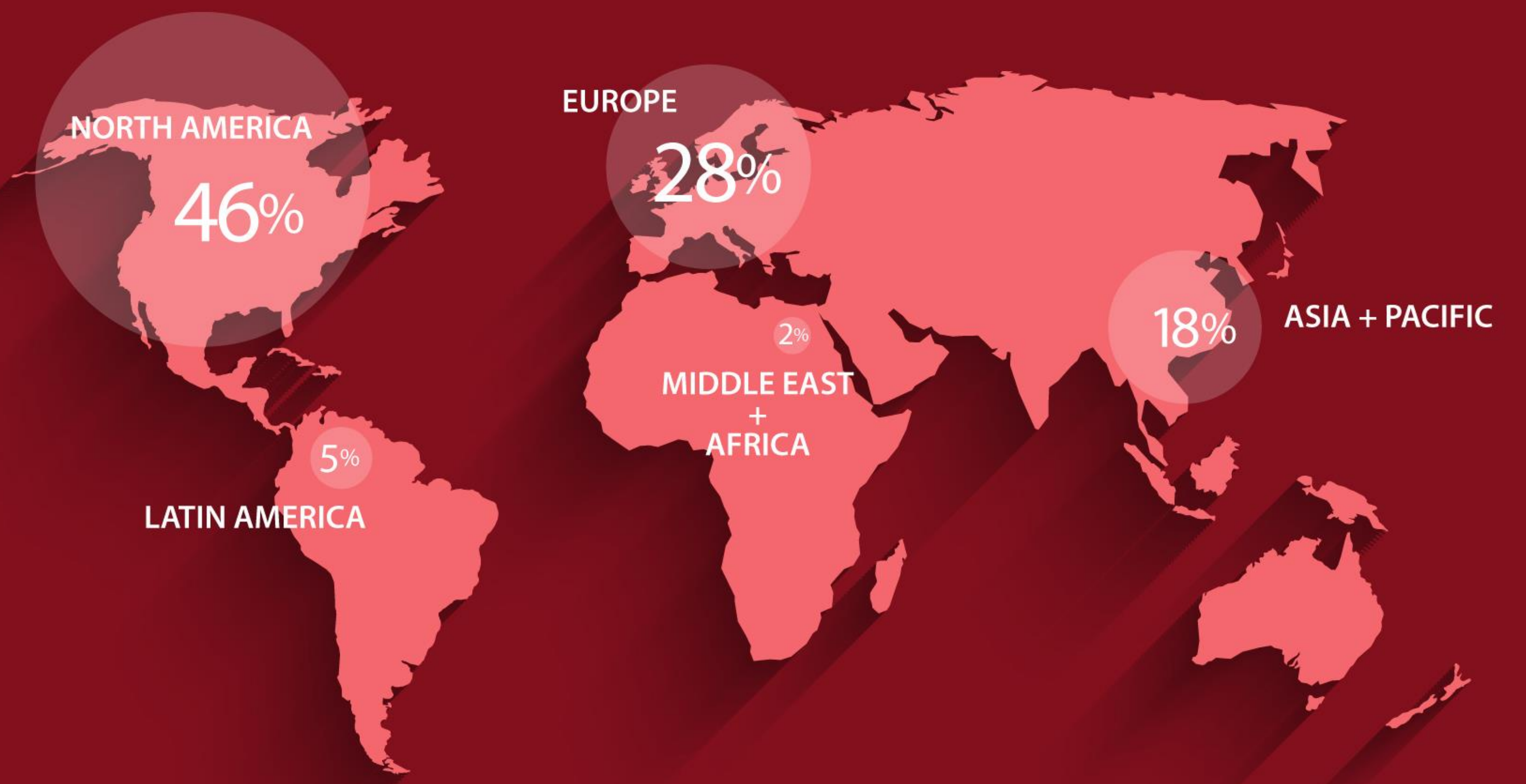

IgG Market Share by Region - 2016
South America
Europe
North America
Asia Pacific
Middle East Africa
0%
5%
10%
15%
20%
25%
30%
35%
40%
45%
50%


IgG Kilograms added to the Market
by Region 2014 - 2016
South America
Europe
North America
Asia Pacific
Middle East Africa
(2.000)
-
2.000
4.000
6.000
8.000
10.000
12.000

IgG Consumption in selected Countries 2014-2016

- Argentine, Brazil and Mexico 2016: 5.1 tons
- Australia, China, India, Japan 2015: 34.8 tons
- Algeria, Saudi Arabia, Iran, Turkey 2016: 5.1 tons
- France, Germany, Italy, Spain, UK 2014: 29.6 tons
- USA, Canada 2015/2016: 80.0 tons

WORLDWIDE IVIG/SCIG UNIT SALES BY REGION



The Plasma-Derived Medicinal Products (PDMPs) Market

- The demand for IgG grows faster than the demand for albumin and plasma-derived factor VIII. IgG is now the market driver.

- May new patients are prescribed IgG in emerging countries, where it is used mainly for acute conditions. The relatively high cost of IgG therapy is an impediment to market expansion in the emerging markets, even though

- The demand for IgG grows faster in the emerging markets (Asia & Pacific, Middle East and Latin America (than in Europe and North America).

•The Role of Emerging Markets in IgG Demand

- The emerging markets use less IgG per capita than the high income countries. Therefore, going forward, the demand growth will still come primarily from the high income countries

- China is not expected to have a major impact on the global IgG demand because of the country’s self-sufficiency policy. The country have a necessary resources to meet its IgG needs in the years to come.

- New market are likely to emerge in the next decade, notably in Africa, due to the population explosion.

Table of Contents

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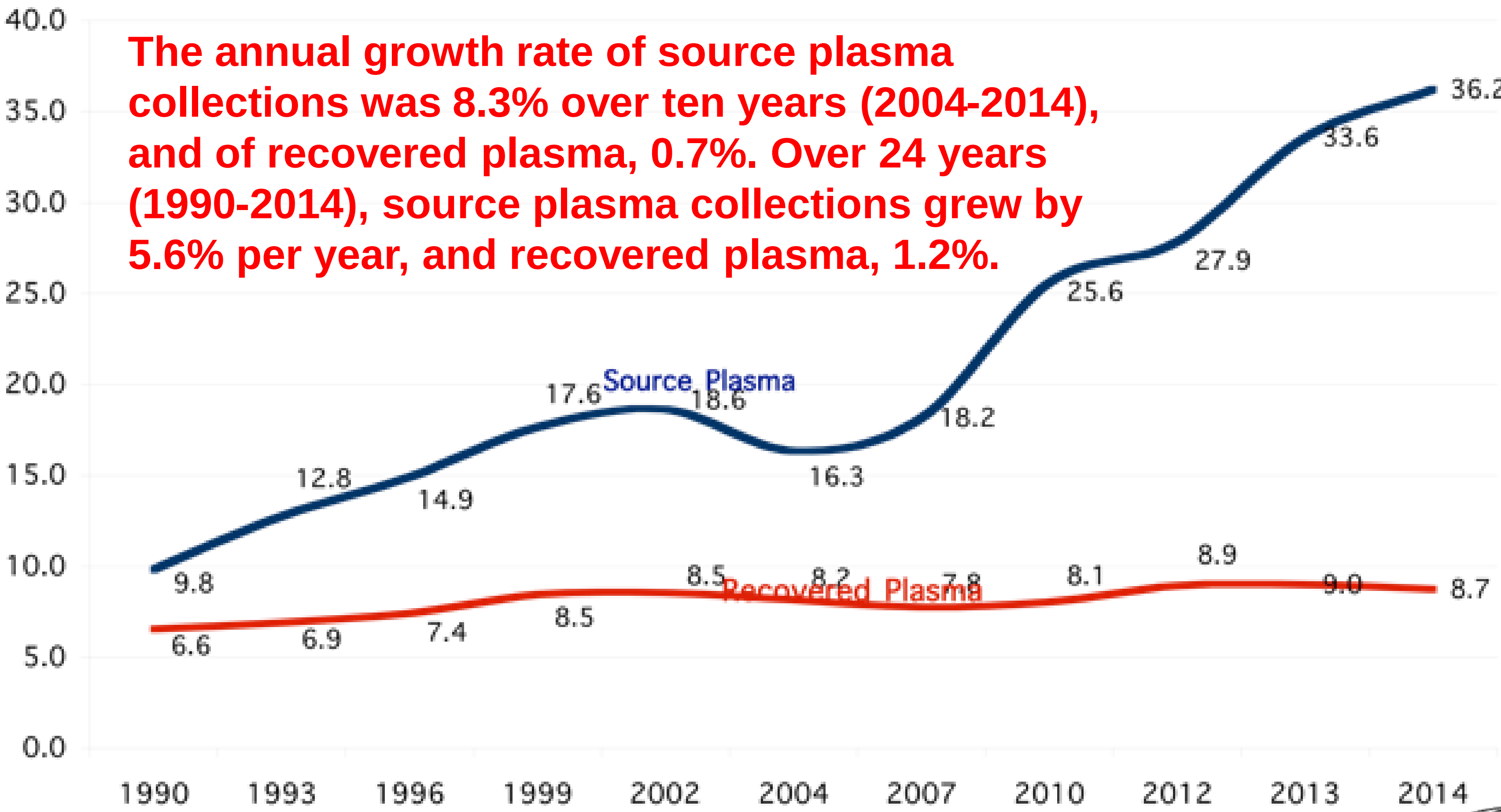
GLOBAL VOLUME OF PLASMA FOR FRACTIONATION 1990 - 2014
Recovered & Source in Liters

Global volume in 2014: 45.0 Million Liters

The annual growth rate of source plasma collections was 8.3% over ten years (2004-2014), and of recovered plasma, 0.7%. Over 24 years (1990-2014), source plasma collections grew by 5.6% per year, and recovered plasma, 1.2%.



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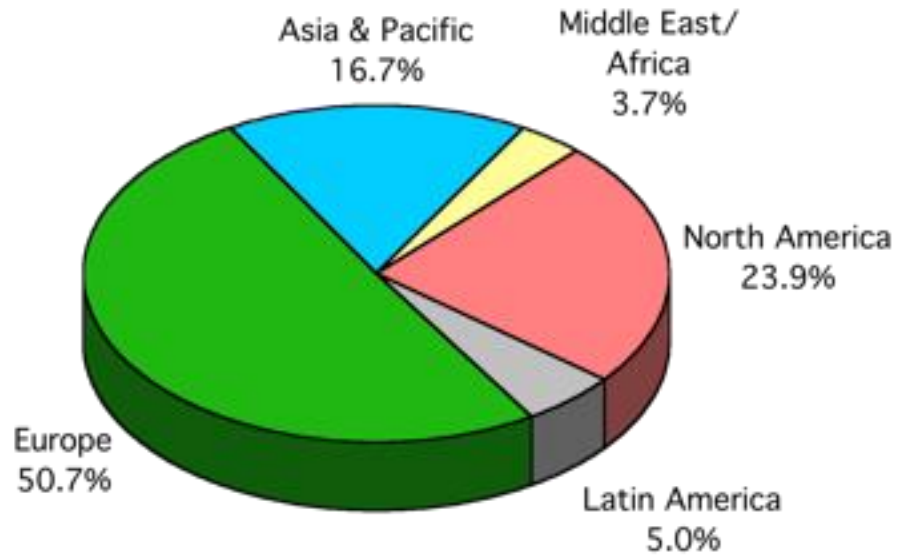
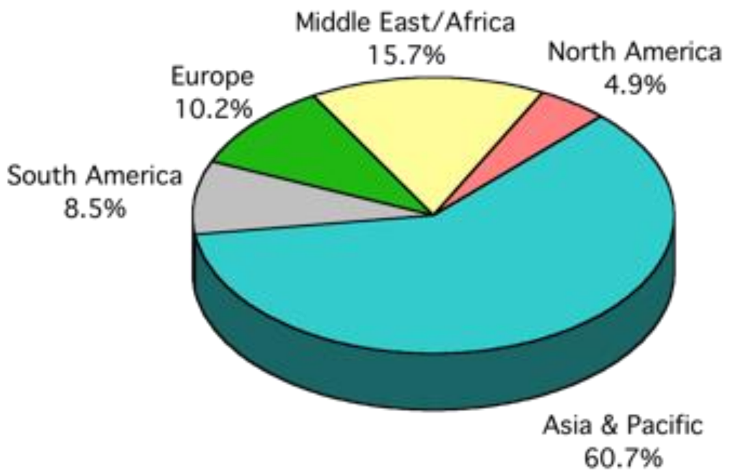
Plasma for Fractionation by Region 2014 (Recovered)



Total recovered: 8,747,000 liters

World Population by Region - 2014



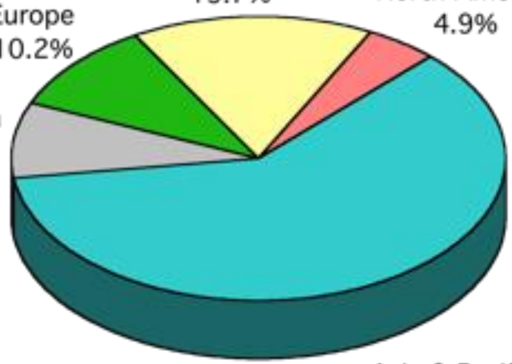
Europe has 10% of the world population and produces 51% of the world's recovered plasma for fractionation

Source: PopulationReference Bureau

Plasma for Fractionation by Region 2014 (Source)

Total source 36,212,000 liters

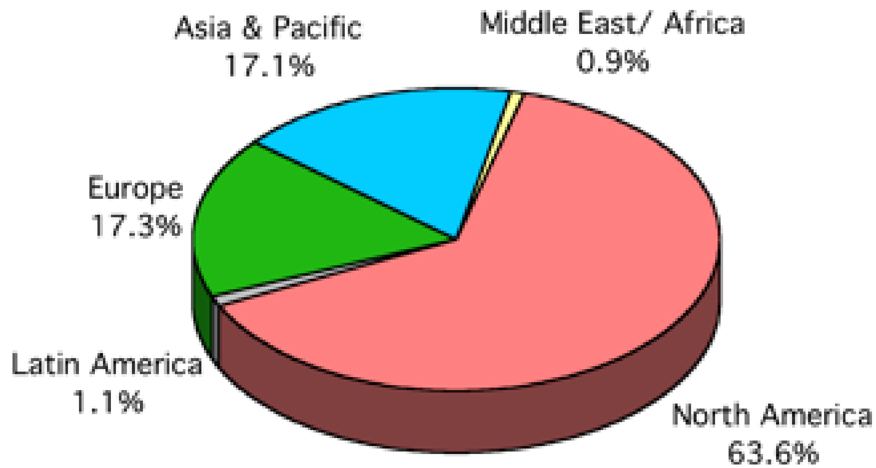
World Population by Region - 2014



North America has 5% of the world population and supplies 73% of the world's <u>source</u> plasma for fractionation

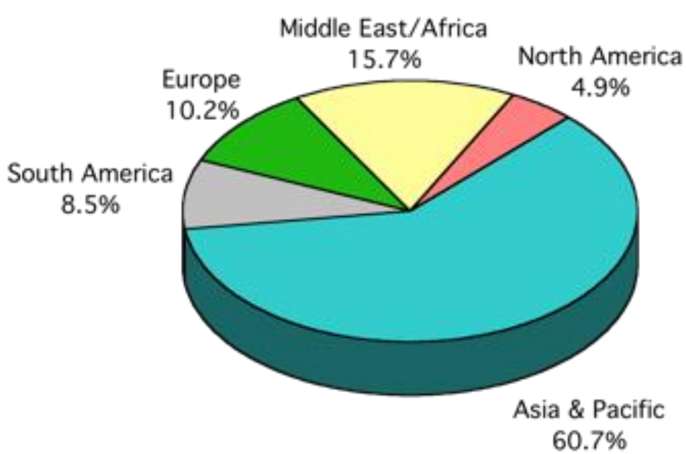
Source: PopulationReference Bureau

Plasma for Fractionation by Region 2014 (Recovered & Source)



Total recovered & source: 44,959,000 liters

World Population by Region - 2014



Asia's generates 17% to the world's plasma for fractionation and has 61% of the world population

Source: PopulationReference Bureau

•Plasma for Fractionation

- It is forecasted that between 2017 and 2024, the world will need about 20 million additional liters of plasma for fractionation (from 55 million to 75 million), assuming that the demand for IgG continues to grow at the same rate.

- Since the need for whole blood is stable or declining in some countries, the volume of plasma recovered from whole blood donations will not suffice to secure the additional volume which will have to come from plasmapheresis.

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Conclusion: Optimizing the demand

- The IgG demand grows faster in the emerging countries, but from a smaller starting base.

- IgG is an expensive therapy, which limits its penetration in emerging markets. Europe and North America will remain the main users of IgG in the foreseeable future.

- In the future, source plasma may no longer come mainly from the United States. A diversification of supply is expected to occur for political, economic and logistical reasons.

- From FIODS to FIODSP

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