AN EVOLUTIONARY TALE OF THE PLASMA PROTEIN INDUSTRY

What has evolved and what has not

Presentation at Plasma Product Biotechnology Meeting
Sicily

May 16, 2019

Do we remember 1975?

Betamax Tape

Betamax
SONY

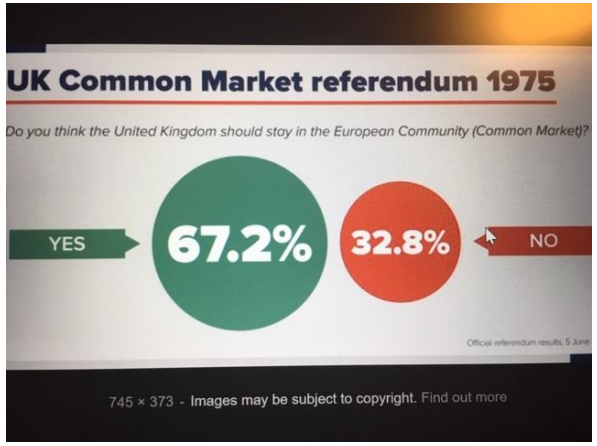
Global expertise plasma proteins

Are we still living in 1975?

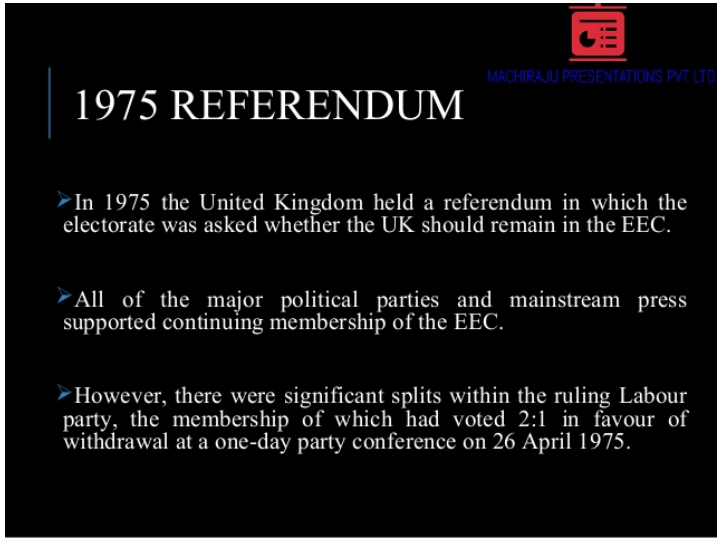
Or have we moved on?

Sometimes it does not seem to be the case

1975


UK Common Market referendum 1975
Do you think the United Kingdom should stay in the European Community (Common Market)?
YES
67.2%
32.8%
NO
Official referendum results, 5 June
745 × 373 - Images may be subject to copyright. Find out more


YES!
Britain is where she Belongs... in Europe
Build Bridges — Not Barriers
You will be voting for our future on June 5th — don't let us down.
620 × 429 - Images may be subject to copyright. Find out more


MACHIRAJU PRESENTATIONS PVT LTD
1975 REFERENDUM
In 1975 the United Kingdom held a referendum in which the electorate was asked whether the UK should remain in the EEC.
All of the major political parties and mainstream press supported continuing membership of the EEC.
However, there were significant splits within the ruling Labour party, the membership of which had voted 2:1 in favour of withdrawal at a one-day party conference on 26 April 1975.


Conservatives say
YES
The Guardian

Margaret Thatcher Quote

In politics if you want anything said ask a man

If you want anything done, ask a woman

Communication in 70’s and 80’s

Do you remember:

- the time you wrote letters?
- the 5th carbon paper copy?
- that it took a week or longer to get an answer?
- Having more time to think?

Should we still want to communicate that way?

Though they look the same

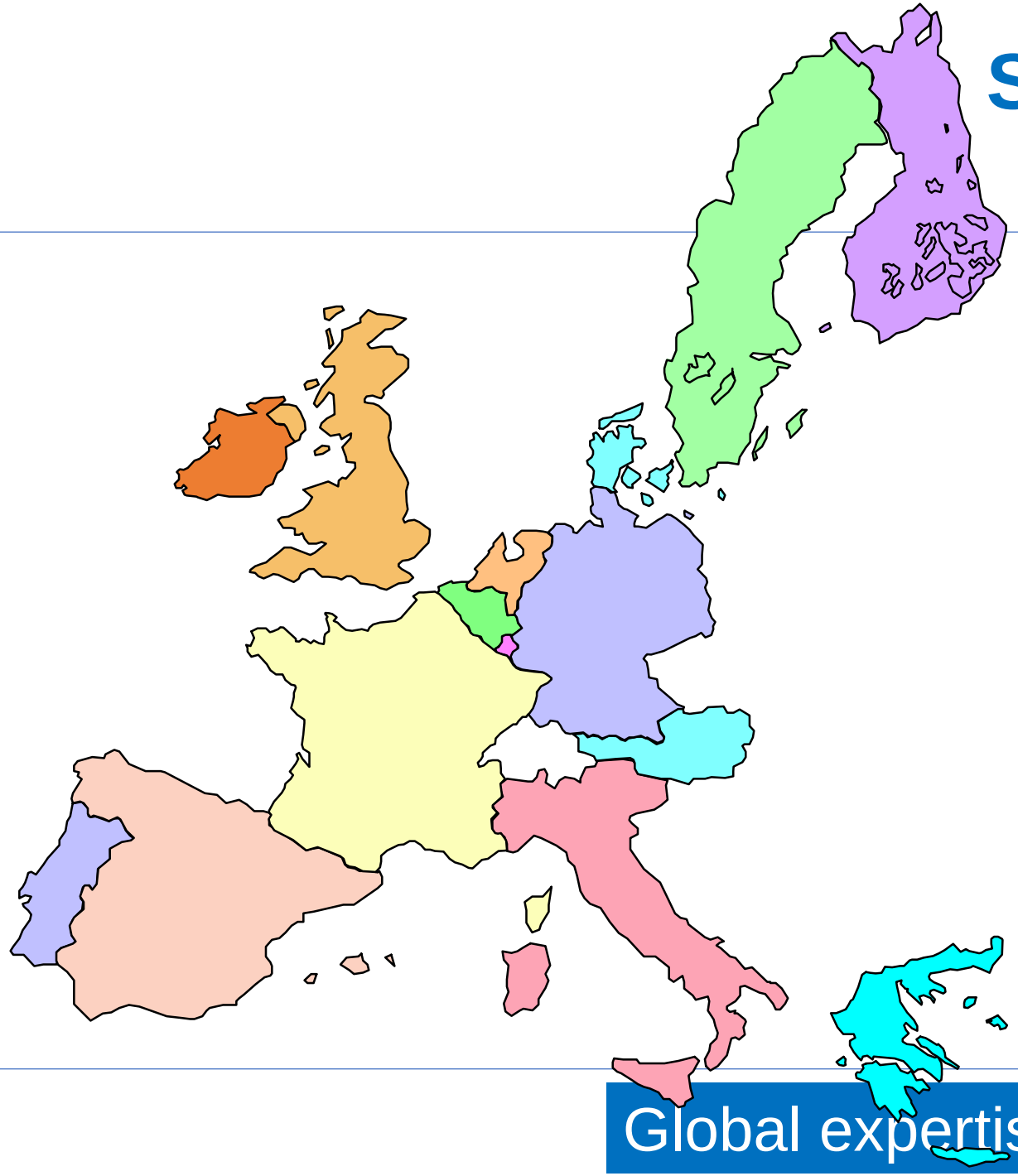
Cessna 172

They are not the same!

Do you remember?

Isn’t having a smoking section in a restaurant the same as having a peeing section in a swimming pool?

Self sufficiency



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What has happened?

National self sufficiency model of the 70’s

- one fractionation plant in each country
- using domestic plasma

Growth of fractionation plants in Europe and ROW

Time has shown that this is an unsustainable model.

WORLDWIDE DISTRIBUTION OF PLASMA FRACTION PLANTS AND CAPACITY

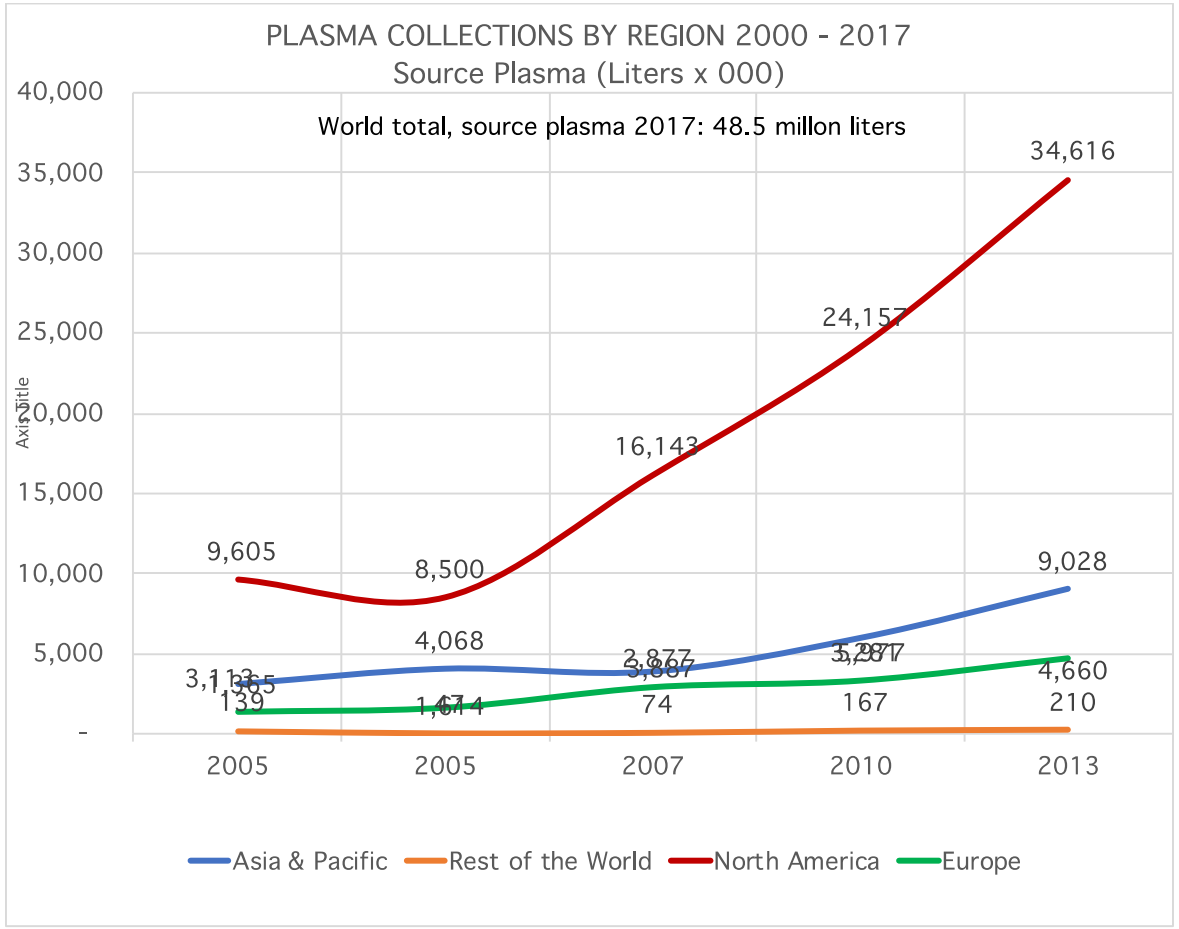
INCLUDES BOTH NON-PROFIT AND FOR-PROFIT ORGANIZATIONS AND COMPANIES

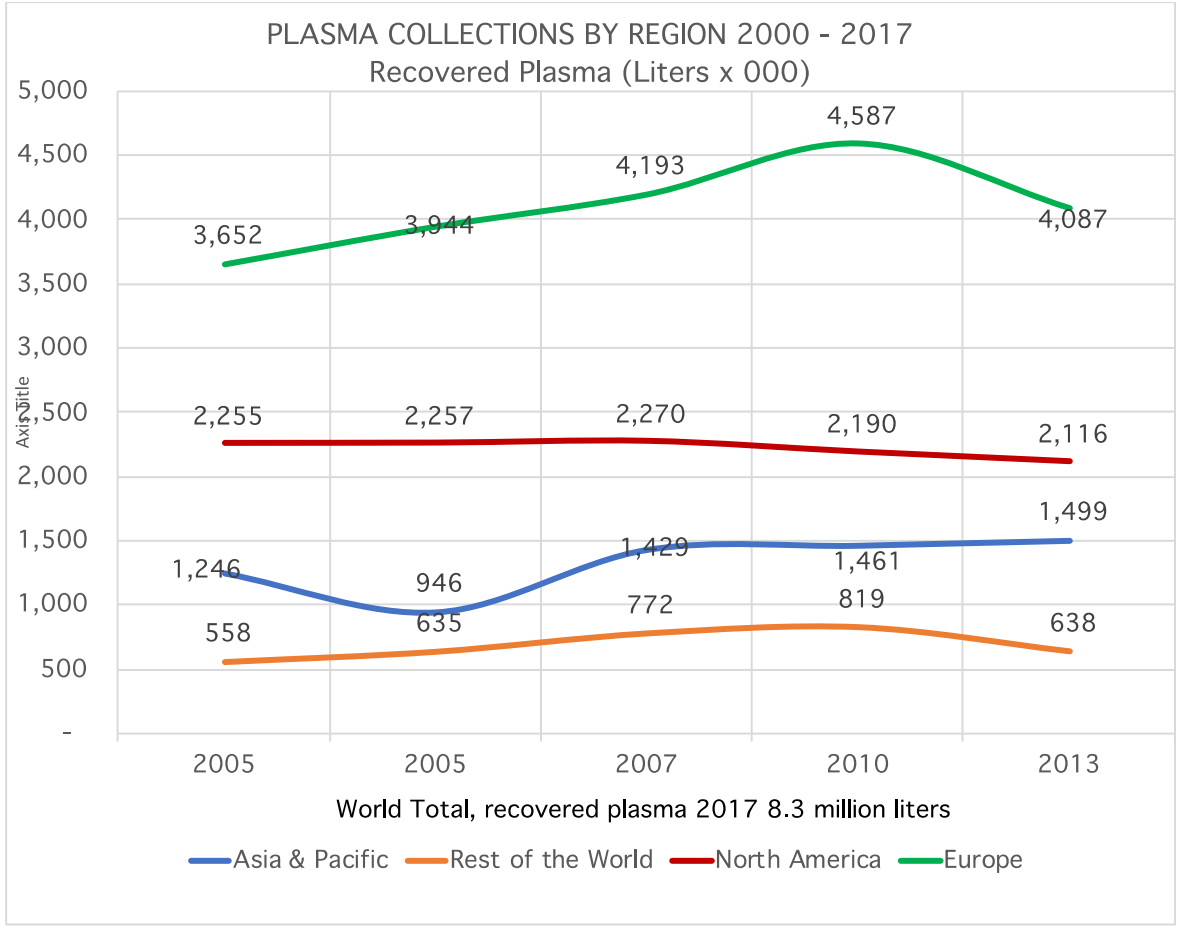
	# PLANTS	% OF TOTAL	PLANT CAPACITY (000 LITERS/YR.)	% OF TOTAL
W. EUROPE	47	58.0%	5,687	45.9%
UNITED STATES/ CANADA	13	16.1%	5,667	45.8%
JAPAN/ASIA	6	7.4%	459	3.7%
LATIN AMERICA/ MEXICO	6	7.4%	325	2.6%
OCEANIA	2	2.5%	160	1.3%
MIDDLE EAST/ AFRICA	7	8.6%	82	0.7%
TOTAL	81	100%	12,380	100%

MRB	2010 NUMBER OF PLANTS	PERCENT	PLANT CAPACITY (000 LITERS/YEAR)	PERCENT
EUROPE	26	33%	18,874	39%
NORTH AMERICA	8	10%	11,544	24%
ASIA	34	44%	15,785	33%
SOUTH AMERICA	5	6%	790	2%
OCEANIA	1	1%	750	2%
MIDDLE EAST/ AFRICA	4	5%	620	1%
TOTAL	78	100%	48,363	100%

Source: The Marketing Research Bureau, Inc.

Plasma collections





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Observations

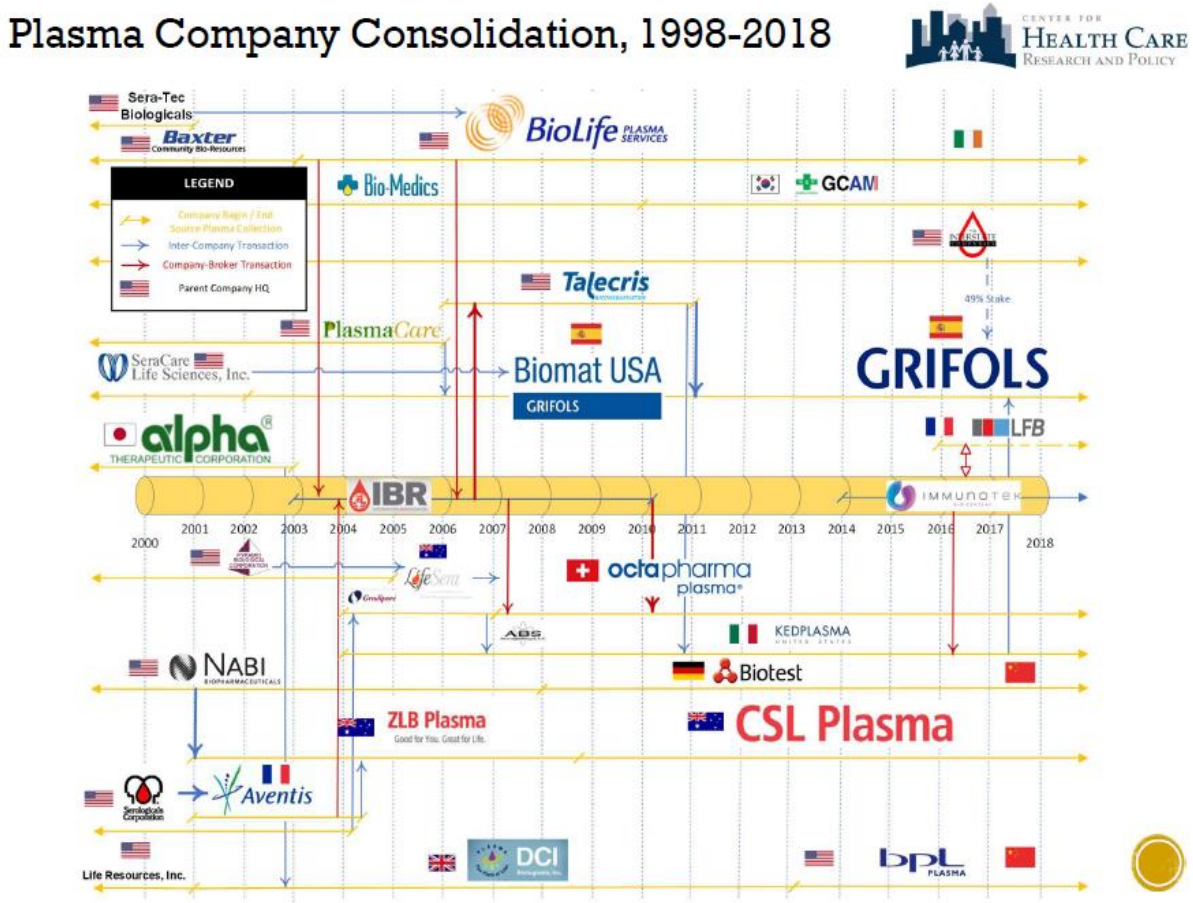
Both recovered and source plasma are important
Recovered plasma not sufficient to meet clinical need
Recovered plasma stable at best
Patient Blood Management reduces need for BTF

Private sector heavily invested in plasmapheresis
Most plasma collection centers owned by fractionators
Source plasma growth only way to obtain more plasma
Regions (exception USA) need to do more

“Old” discussion about compensation
“New” discussion on “crowding out”
Defensive approach “blood sector”

Some regulators do not see the writing on the wall
Enormous need for (ongoing) education

Consolidation



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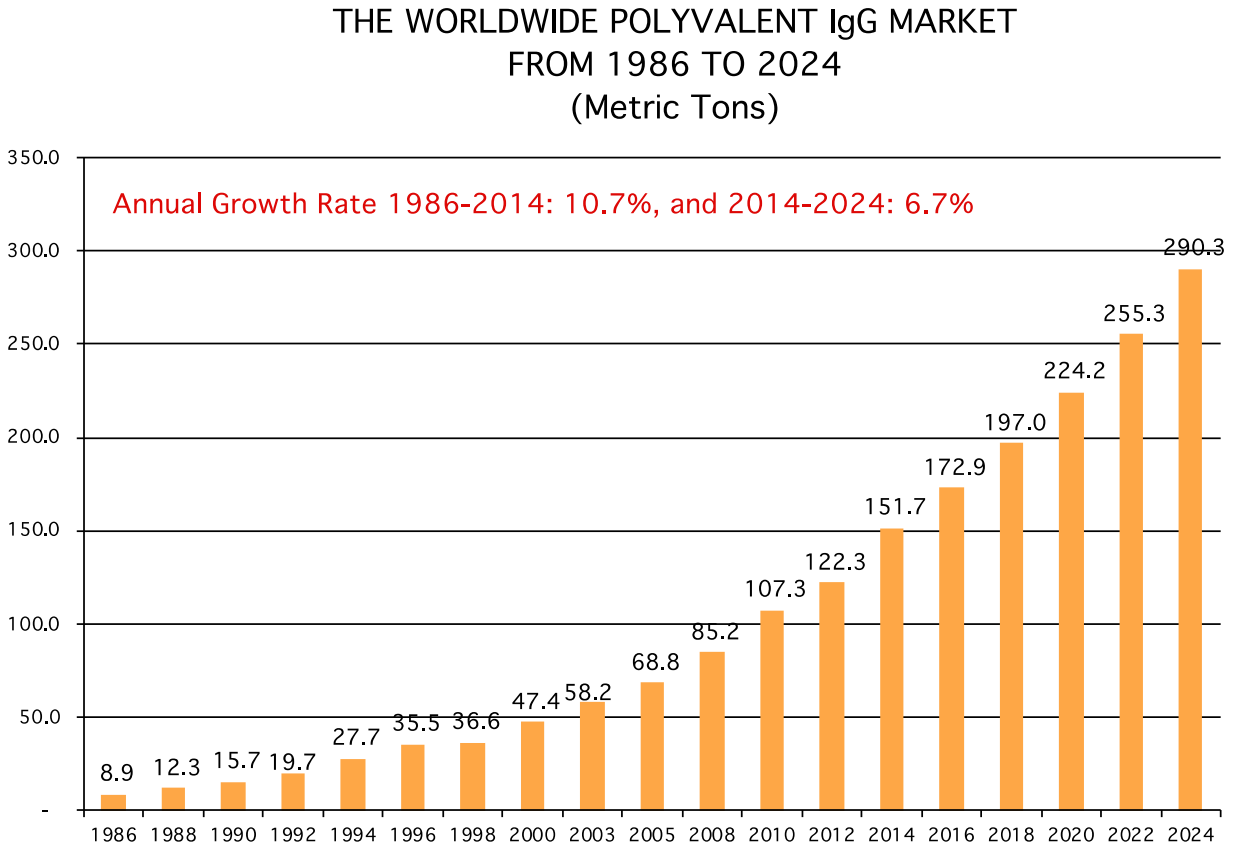
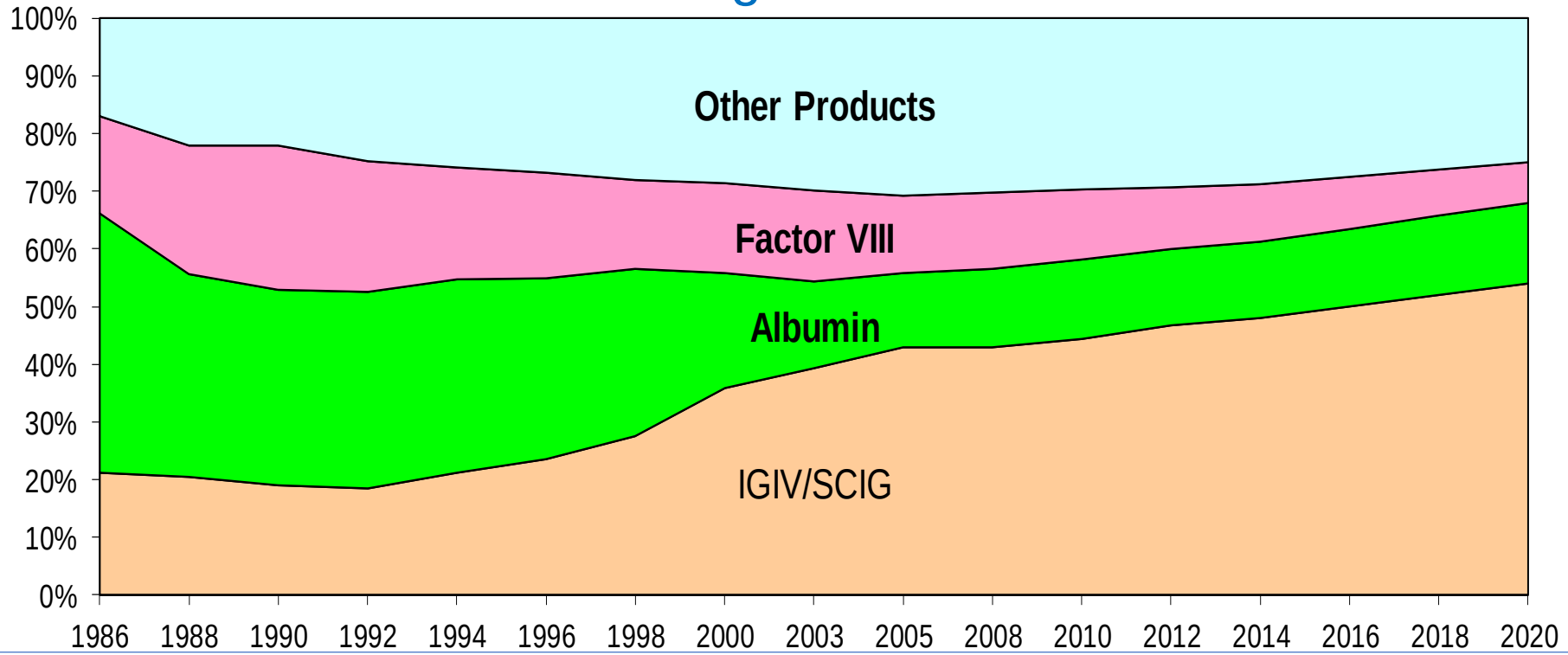
IgG Forecast



The production of 290 tons of IgG will require about 75 million liters of plasma globally (3.9 grams/liter yield)

Drivers for plasma collection

Albumin
Factor VIII
Immuneglobulins



Interesting observation

-pd FVIII was driver in the early 80's

-FDA mandated each unit to be immediately frozen

-Obsolete requirement?

A lot of things have happened

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What happened in Europe?

What happened in Austria

Early legislation allowed plasma collection in larger volumes and frequencies

Austria had more plants in early years than any other country:

Immuno
Merieux Institute
Chemie-Linz
Behringwerke

Austria today

2 large fractionators

octapharma

Takeda

17 Private plasma collection centers

France

7 Plants at its peak
LFB - Ulis (CNTS), Lille
Lingolsheim (Regional BTS -> Centeon -> Octapharma
Bordeaux, Lyon, Montpellier

Merieux using plasma from placenta’s in Lyon

France today

octapharma
Lingolsheim

LFB Les Ulis
Arras?
Plasma from EFS

Centers in Austria, Czech Republic and USA

No private plasma collection centers

France current issues

LFB Website for UK only

The LFB group owns a chain of plasma collection centres (EUROPLASMA Group). Following the highest quality standards, EUROPLASMA is a member of the Plasma Protein Therapeutic Association (PPTA).* The plasma donated at EUROPLASMA centres is used to make plasma products, notably for the UK.

Operators are now confronted with a questioning of a balanced economic equilibrium, or even with significant financial difficulties, questions about their durability and a need for transformation

Vingt ans après la restructuration de la filière du sang, les opérateurs sont aujourd'hui confrontés à une remise en question de leur équilibre économique, voire à des difficultés financières importantes, des interrogations sur leur pérennité et une exigence de transformation.

Rapport public annual 2019
Cour des Comptes

Recommendations

EFS to systematically compensate apheresis plasma donations and increase the cap of donor compensation

For LFB and APE to initiate a total or partial withdrawal of LFB from biotechnology activities

For APE to contemplate every possible funding avenue to cover the costs of a new plasma fractionation plant (Including funding from private entities)

What happened in Germany

7 Plants at its peak
German Red Cross 4 fractionation plants
Baden-Baden
Springe -> Octapharma
Munich
Hagen (SD Plasma)

Behringwerke
Biotest
Pharma Dessau

Germany today

Behringwerke is now CSL Behring

Biotest is now Creat

71 Private plasma collection centers

What happened in Spain

4 private plants at its peak

Barcelona
Instituto Grifols
Behringwerke

Madrid
Laboratorio Landerlan
Hubber

Spain today

Grifols plants

Spain:	Sant Cugat
USA:	Los Angeles, Clayton

Acquired

alpha® THERAPEUTIC CORPORATION

Talecris UTICS

No private plasma collection centers

And much more happened

STATENS SERUM INSTITUT

BERNA

INSTITUT MERIEUX

bpl
Bio Products Laboratory
a commitment for life

Finnish Red Cross Blood Service

ZLB

CAF-DCF
A HUMAN TO HUMAN APPROA

SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE

Sanquin Plasma Products

PHARMACIA

Pharmacia & Upjohn

biovitrum.

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What has changed since 1975

The world has completely changed

Technology improvements

Public sector fractionators future is uncertain

Private sector has grown enormously

More patients are diagnosed and treated

Most plasma collected comes from the USA

Europe (and other regions) need to step up

The world has evolved but……

TWENTY-EIGHTH WORLD HEALTH ASSEMBLY, GENEVA, 13–30 MAY 1975
WHA28.72 Utilization and supply of human blood and blood products

Noting the extensive and increasing activities of private firms in trying to establish commercial blood collection and plasmapheresis projects in developing countries;

Expressing serious concern that such activities may interfere with efforts to establish efficient national blood transfusion services based on voluntary nonremunerated donations;

(3) to further study the practice of commercial plasmapheresis including the health hazards and ethical implications, particularly in developing countries;

(4) to take steps to develop good manufacturing practices specifically for blood and blood components in order to protect the health of both donors and recipients; and

World Health Organization

The Rome Declaration on
Achieving Self-Sufficiency in Safe Blood and Blood Products,
based on Voluntary Non-Remunerated Donation

Rome declaration

CALL ON NATIONAL AUTHORITIES TO:

-Incorporate goal of self-sufficiency based on VNRD

-Introduce labeling requirements to distinguish between VNRD and paid

-Provide financial and other resources to move towards self-sufficiency

-Put in place agreements between blood system and fractionators for the fractionation of surplus recovered plasma from VNRD

AND

-**Phase out in a programmed manner, the use of blood components for transfusion, intermediates and PDMP obtained from paid or compensated donors and family / replacement donors**

Effective stakeholder response

PPTA
Plasma Protein Therapeutics Association

Dr Marie Paule Kieny
Assistant Director General Health Systems and Innovation
World Health Organization
E-mail: kienym@who.int
Ref: WHO14003
May 16, 2014

Dear Dr. Kieny:

I am writing to you to express concerns with regard to the "Rome Declaratic Achieving Self-Sufficiency in Safe Blood and Blood Products, based on Voluntary Remunerated Donation". This Declaration was published as a WHO document a High Level Policy Makers Forum in Rome on October 8-9, 2013.

On May 19, 2014 there will be a meeting (technical event) in Geneva. This event at serving a renewed call to action in order to emphasize the commitment tak consistency with the Rome Declaration. I wrote two letters to Dr. Neelam Dinghra 9 and May 14) and requested an invitation to attend that meeting. Since I have rec no answer as of today, I am writing this letter to you.

PPTA is the international trade association and standards-setting organiz representing the manufacturers of Plasma Protein Therapies (PDMP's) recombinant analogue products, and the collectors of source plasma. These ther include clotting factors for persons with bleeding disorders, immune globulin persons with immune deficiency as well as a variety of other rare protein deficier These therapies are the safest, highest quality, and most effective treatments for indications available today and are of vital importance to patients worldwide. estimated that over 70% of the supply of these therapies in the world are coming private sector manufacturers.

The afore mentioned Rome Declaration calls on national authorities to introduce va measures which certainly are not in the interest of the many patients that deper these lifesaving therapies. Many of the recommendations are not realistic and cann achieved.

The current Rome Declaration is a document that (when implemented) can c unnecessary damage. I specifically want to point out the following:

- During the meeting in Rome in October 2013 there was no participation various stakeholders whose voice should have been heard like:
  - Patients who depend on the lifesaving therapies
  - Regulatory agencies who regulate these therapies
  - Countries that collect plasma from compensated donors
  - Private sector industry

147 Old Solomons Island Road · Suite 100 · Annapolis, MD 21401 USA
tel: 202.789.3100 · 410.263.8296 · fax: 410.263.2298 · e-mail: ppta@pptaglobal.org · www.pptaglobal.org
PPTA Offices in Washington · Annapolis · Brussels · Tokyo

Ref. IP-14-155

IPFA
international plasma fractionation association

Dr. Marie Paule Kieny,
Assistant Director General Health Systems and Innovation
World Health Organization
Sent by email: kienym@who.int

Amsterdam, 15 May 2014

Subject: IPFA position on the WHO Rome Declaration of October 2013

Dear Dr. Kieny,

I am writing to you on behalf of the Board of the International Plasma Fractionation Association (IPFA) to express our grave concerns regarding the "Rome Declaration on Achieving Self - Sufficiency in Safe Blood and Blood Products, based on Voluntary Non - Remunerated Donation" which we understand was the outcome of the WHO High - level Policy Makers Forum, October, 2013, Rome, Italy, and which has been published as an official WHO document.

The IPFA is the international umbrella organization representing both not-for-profit plasma fractionators from all over the world which manufacture and supply plasma derived medicinal products (PDMP) that are life saving essential medicines for the treatment of eg patients with clotting factor deficiencies, immune disorders and inflammatory diseases, and not-for-profit blood transfusion organizations that collect blood and plasma from voluntary non-remunerated blood and plasma donors.

It is widely known and acknowledged that the global supply of plasma for fractionation is currently dependent largely (70-80%) on plasma from paid plasma donors mainly from the US, Germany, Austria and the Czech Republic. Although this situation is not in line with WHO resolutions and recommendations, the reason that a paid donor system still exists and is expanding is an inadequate supply of plasma suitable for fractionation from national blood establishments. There is little evidence of a reversal of this trend toward the aspirational WHO resolutions.
However, the WHO has developed a very important initiative called "Achilles Project" which seeks to increase the supply of high quality plasma for fractionation from blood establishments, particularly those in developing countries where limited access to PDMP's is most acute. This initiative is supported by the WHO Expert Committee on Biological Standardization (ECBS) and the WHO Blood Regulators Network (BRN). IPFA supports this initiative fully because it combines both quality activities at blood establishment level to create a sustainable plasma supply and input from regulators who audit on the compliance of the quality and GMP procedures which are prerequisites for the supply of suitable plasma and the subsequent manufacture of the essential plasma derived medicines from this source.

PLUS
Platform of Plasma Protein Users

21 May 2014

Dr. Margaret Chan
Director General
World Health Organisation
Geneva, Switzerland
chanm@who.int

CC:
Dr. Marie-Paul Kieny
Assistant Director General, Health Systems & Innovation
kienym@who.int
Mr Cees de Joncheere, Director Essential Medicines
& Health Products
dejoncheerec@who.int

Subject: Rome Declaration on Achieving Self-Sufficiency in Safe Blood and Blood Products, based on Voluntary Non-Remunerated Donation

Dear Dr. Chan,

We are writing to you on behalf of PLUS, the Platform of Plasma Protein Users, to express our serious concerns regarding the Rome Declaration on Achieving Self-Sufficiency in Safe Blood and Blood Products, based on Voluntary Non-Remunerated Donation (see enclosed) and request a meeting to further discuss.

PLUS is a consortium of several patient organisations representing people living with treatable rare plasma related disorders such as haemophilia, primary immunodeficiencies and alpha1 anti-trypsin deficiency among others.

We are extremely concerned with the Rome Declaration which in our view puts forward dangerous recommendations that could seriously impact access to treatments for patients relying on life-saving and life-enhancing plasma derived medicinal products, several of which are classified by WHO as essential medicines both for adults and children.

Today, the majority of safe and effective plasma derived medicinal products is produced from plasma obtained through apheresis (paid plasma donations), whilst a minority of these products is produced from plasma recovered from blood (unpaid blood donations). Irrespectively of their source material (whether they are produced from apheresis or recovered plasma), plasma derived medicinal products are crucially needed and life-saving treatments which undergo strict regulatory approval processes. The European Medicines Agency considers that there is no difference between products made from apheresis or recovered plasma both from an efficacy and safety standpoint (CPMP Position Statement on Non-Remunerated and Remunerated Donors: Safety and Supply of Plasma-Derived Medicinal Products, EMEA/CPMP/BWP/1818/02/Final).

Please reply to: johan@ipopi.org, PLUS, Firside, Main Road, PL11 3LE Downderry, United Kingdom

PLUS
AMERICAN PLASMA USERS COALITION

May 29, 2014

Dr. Margaret Chan
Director General
World Health Organization
Geneva, Switzerland
chanm@who.int

Subject: Rome Declaration on Achieving Self-Sufficiency in Safe Blood and Blood Products, based on Voluntary Non-Remunerated Donation

Dear Dr. Chan,

The American Plasma Users Coalition (APLUS) is a coalition of national patient organizations created to address the unique needs of patients with rare diseases that use life-saving plasma protein therapies. Together our coalition represents more than 125,000 Americans living with chronic disorders who depend upon plasma protein therapies to lead healthy, productive lives.

We are writing to express concerns regarding the Rome Declaration on Achieving Self-Sufficiency in Safe Blood and Blood Products, based on Voluntary Non-Remunerated Donation. We also stand in support of statements by our counterpart, the Platform of Plasma Protein Users (PLUS), in PLUS's letter dated May 21, 2014.

We agree with PLUS that the Rome Declaration recommendations may seriously and adversely impact access to treatments for patients relying on life-saving and life-enhancing plasma derived medicinal products, several of which are classified by WHO as essential medicines both for adults and children.

In the United States there is no policy restricting remunerated voluntary donations of plasma. The majority of safe and effective plasma derived medicinal products are produced from plasma obtained through apheresis of remunerated plasma donors. There is no evidence that remunerated plasma donations have increased safety risks for patients in the United States. Rather, there is a robust and safe supply of plasma products for the ever-increasing demand for such products to treat various rare and chronic disorders.

While we support the importance of voluntary blood and plasma donation for labile products, we believe that if recommendations in the Rome Declaration are implemented, there will be a serious decline in the supply of plasma-derived medicinal products, which will leave patients who need life-saving plasma treatments at severe risk of not having access to their treatments. On several occasions we have indicated our support for the importance of and necessary coexistence of both voluntary and remunerated systems as essential.[abc]

According to estimates of the Market Research Bureau, in 2010, 32.8 million liters of plasma (recovered and apheresis) will be collected worldwide. Of this amount, 20.4 million liters (62%) will be collected in North America;[d] the vast majority of this amount is collected in the United States. Plasma derivatives made from United States source and recovered plasma are essential if we are to meet patient needs globally. Without these products, there will be a global shortage

Global expertise plasma proteins

Where do we go from here?

Path forward

Paramount: Patient centeredness
Donor health

Stop living in the past but embrace current environment

- Time to review context of WHA 1975 resolution
- Rethink system of donor incentives
- Change World Blood Donor Day to World Donor Day

Recognition of private sector industry

- Stop complaining but accept contributions
- Stop fighting expansion plasma collection activities

Path forward

Focus on area of expertise

- Plasma experts: Talk about plasma and not about blood
- Blood experts: Talk about blood and not about plasma
- Involve industry experts in policy developing meetings

Be realistic

- Economy of scale is important for sustainable fractionation
- Not for profit has its own challenges

Self sufficiency

- National self sufficiency for blood and components
- Global sufficiency for finished products

Contact information

Jan M Bult

Website: jmbconsultancy.nl

Email: info@jmbconsultancy.nl

+1 443 454 5301

+31 6 2511 4198