Past, Present, and Future European Experience to Meet Required Needs of PDMPs

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ATMF/IPFA Joint Webinars

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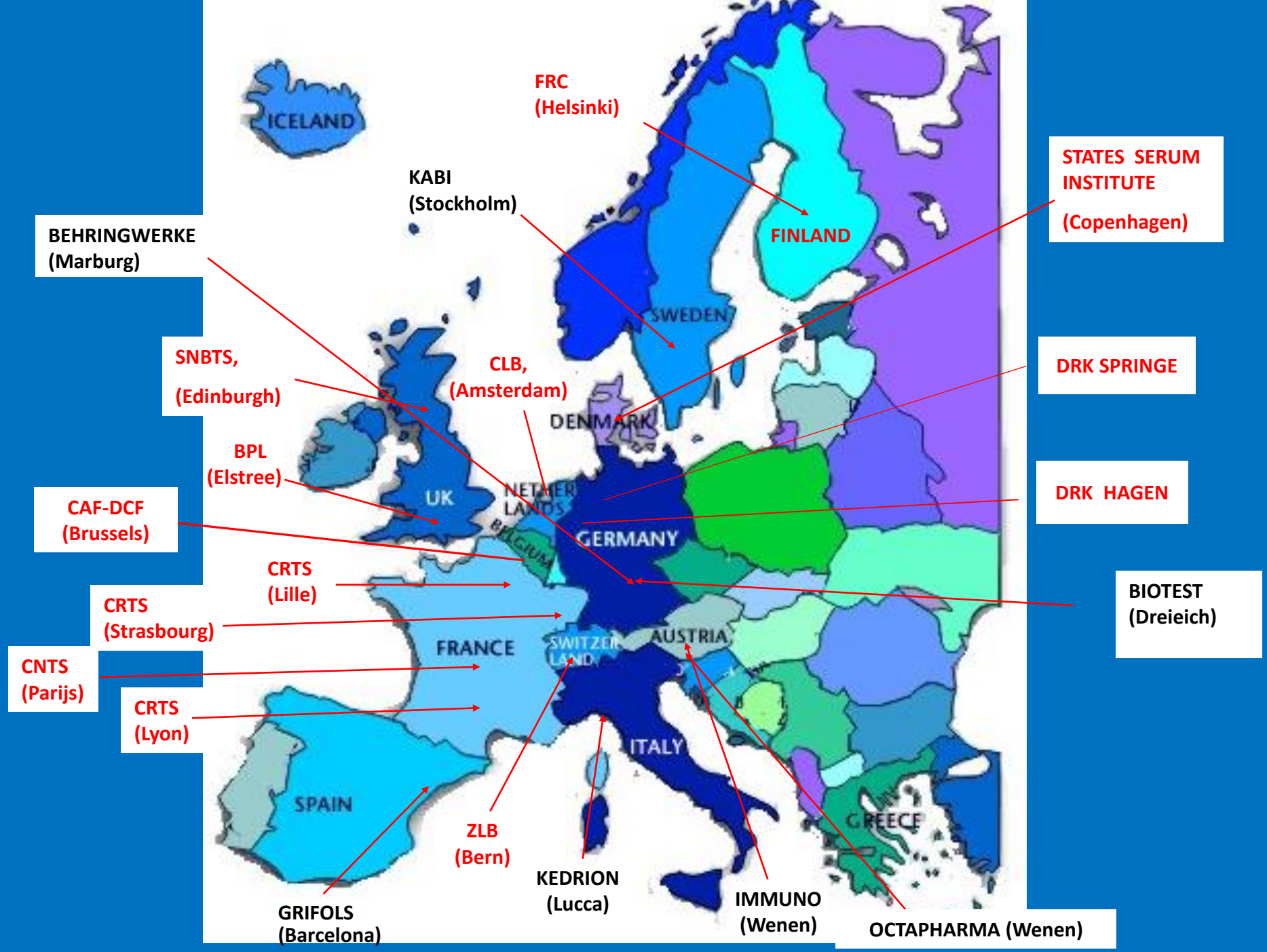
European Experience, the Past

- Protective national environment
- Mainly not-for-profit organisations
- Part of blood transfusion systems
- Plasma from local donors
- Products had national registrations
- Limited or no clinical scientific support
- Optimal costs efficiency ?

- 1990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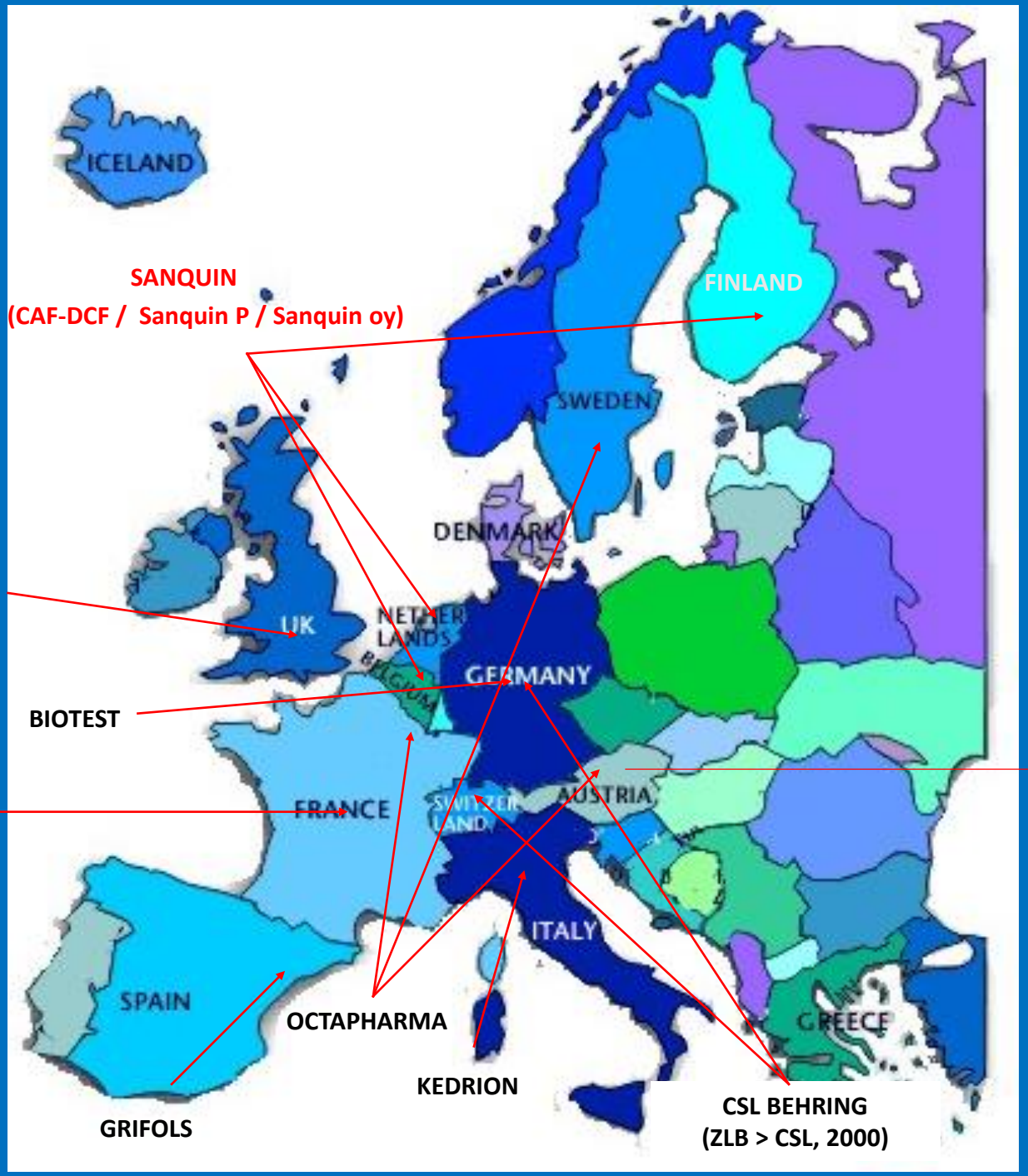
Plasma fractionation in Europa:1970-1995

- Critical situation because of TTI transmissions (HBV, HIV, HCV) with PDMPs
- Public hearings and court cases
- Demands for serious quality and safety improvements
- Demands for improvement of efficacy, quality and safety at all levels.
- Response from competent authorities:
  - Termination of special position of fractionators
  - PDMPs became medicinal products
  - Emphesis on implementation of quality requirements
- Drafting and implementation of EU Directives and National Legislations

Consequence:
termination of fractionation facilities

- New quality demands and stringent controls
- Costs for quality improvements were for a number of organisations too high
- All resources and human capital needed to be as efficient as possible.
- Some National Red Cross organisations were concerned on continuation because of risks regarding liability

1990 - 2000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CSL BEHRING
(ZLB > CSL, 2000)

Further developments

- EU Treaty of Amsterdam (1999).
  Article 168: setting high standards of quality and safety of … blood and blood derivates.

- New EU Directive and Commission Directives on Blood and Blood Components.

- Open EU market with the presence of all players

- Financial pressure
  - costs of health care
  - some products are considered as generics
  - price reductions due to competition
  - insufficient financial compensation due to limited product pipelines.

PDMPs: more changes

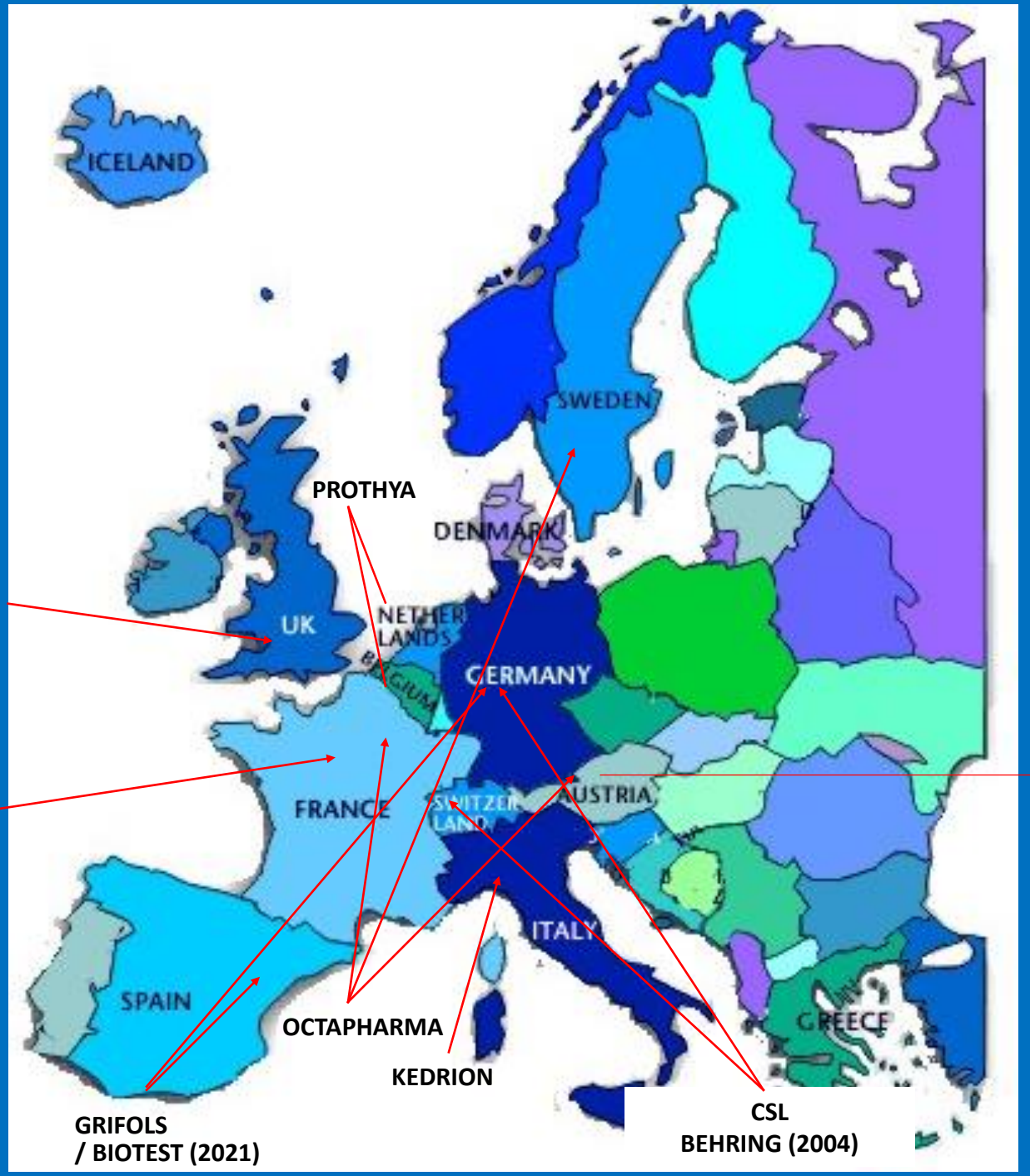
- At the level of registrations
  - centralised EMA procedures: PMF, mutual recognition procedures, and others
  - improved communication with competent authorities including EMA, EU Commission, CD-P-TS / EDQM

- At the level of purchasing of PDMPs
  - medical marketing regulations and limited access to prescribing physicians

- Big companies versus some smaller companies active in specialisation in niche markets with higher margins

- Risks and costs for new product development became higher and higher

2000-2021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OCTAPHARMA
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GRIFOLS / BIOTEST (2021)
CSL BEHRING (2004)

Plasma products vs “normal”pharmaceuticals

- human plasma, source material for plasma products, is limiting
- cyclical nature of plasma product markets
- different products :… different driving forces for collection of plasma
- importance of strategic independence programmes: protection against market fluctuations (shortages, price increases, …)
- importance of developments linked to blood transfusion systems in “emerging health care systems”

Current PDMPs supply

What has NOT (yet) been achieved?

✓ regulatory harmonisation worldwide, but progress is made….

✓ sufficient supplies. Currently 15-20 % shortage of plasma due to pandemic with (expected) severe shortages of IVIG

✓ access to all, including developing world, but also rare bleeding disorders, …

✓ % diagnosed and treated patients worldwide:

- hemophilia A/B: 30 % and 25%, resp. (WFH)
- PID: < 10 % " 6 %, " (IPOPI)
- AAT deficiency: 10 % " 3 %, " (AlphaOne)

Challenges of PDMPs

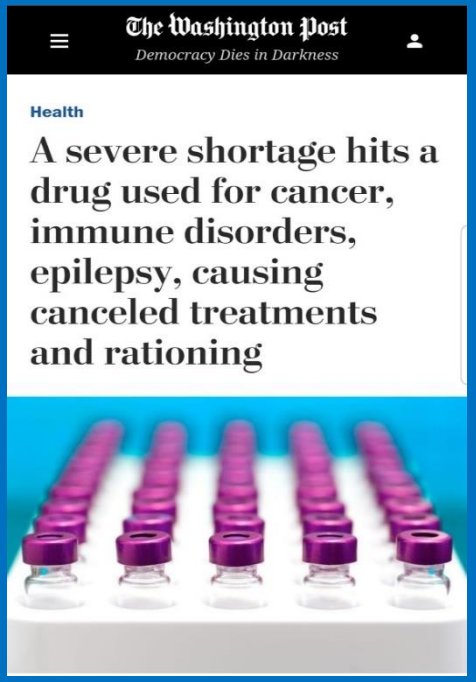
- Most PDMPs are used for treatment of rare diseases

- Two products with high demand - IgG (IVIG and SubCu) and albumin - determine the demand for plasma
- 70% of world' plasma supply is sourced in one country – USA
- Europe is for 37 % dependent on this plasma

- Unequal distribution of PDMPs over the world
- Prices of PDMPs are rising
- Shortages of PDMPs
- More shortages to be expected (plasma supply under pressure)

Shortages of IVIG

2017-2018	**United Kingdom:**	Insufficient supply, supply instability, reduction of products commissioned, cost containment, cheapest products only, company withdrawal from market.
2018	**Romania:**	Supply withdrawal from market due to clawback tax set by government
2018 – 2021	**France:**	Supply tensions.
2021	**Germany:**	Special meeting with Paul Ehrlich Institut
2019-2021	**USA:**	Severe shortages.



Other countries with supply tensions: Cyprus, Greece, Hungary, Latvia, Lithuania, Portugal.

Future experience (1)

✓ Continuous growth of global polyvalent immunoglobulin and albumin markets

✓ New recombinant substitutes (rec. human albumin; rec. C1 esterase inhibitor; rec. Covid-19 polyclonal hyper IgG)

✓ Further clinical use of new generation recombinant products: extended half-life, less immunogenic, more resistant to inactivation, ….

✓ Transgenic substitutes: cheaper ? larger supplies ?

✓ Substitution of hyper-immunes: vaccines, antivirals, monoclonals, …..

Future experience (2)

✓ New therapies: e.g.

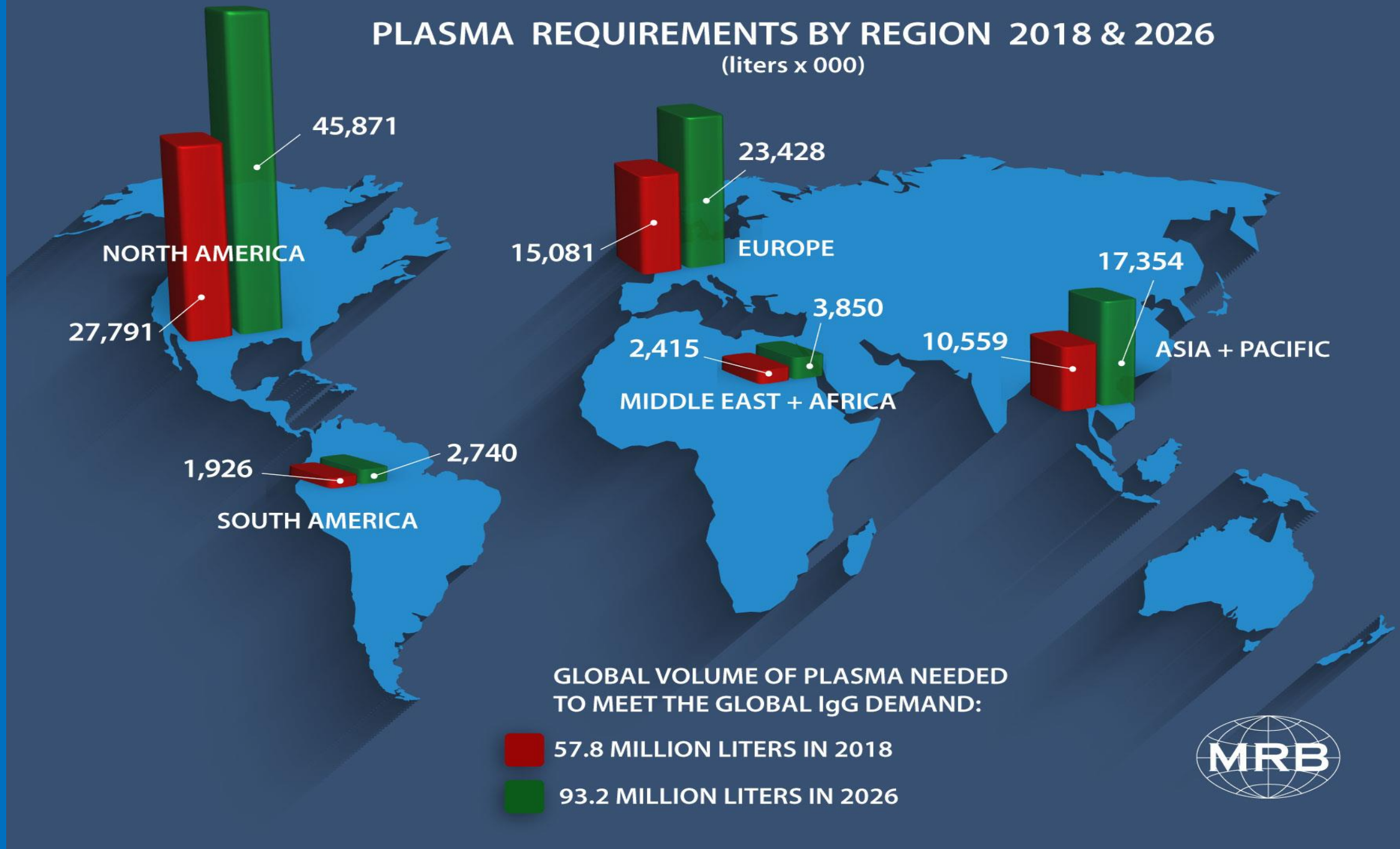
- gene therapy for PID;
- gene therapy for hemophilia A
- gene therapy for hemophilia B
- FVIII bypass products (emicizumab)
- PerClot polysaccharide hemostatic system
- FcRn antagonists (alternative for IVIG immune modulation treatment)

Future experience (3)

✓ Changes in patient population

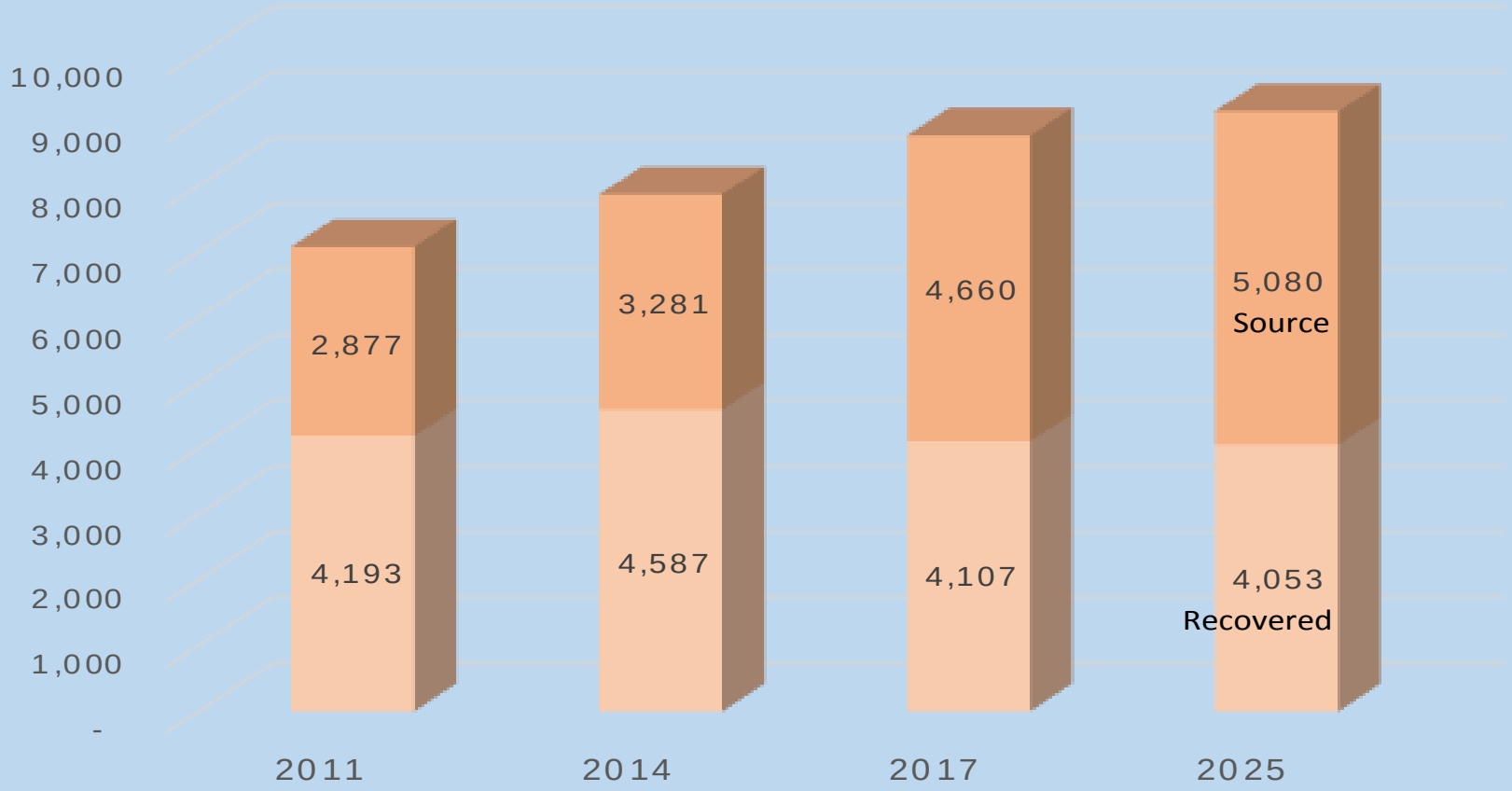
✓ Too low number of manufacturers ?
- risk of production breakdown ?
- fewer products available ?
- monopolistic behaviour ?
→ higher prices ?
→ less innovations ?

✓ Inadequate management of plasma supply


PLASMA REQUIREMENTS BY REGION 2018 & 2026
(liters x 000)
45,871
NORTH AMERICA
27,791
23,428
15,081
EUROPE
3,850
2,415
MIDDLE EAST + AFRICA
17,354
10,559
ASIA + PACIFIC
2,740
1,926
SOUTH AMERICA
GLOBAL VOLUME OF PLASMA NEEDED
TO MEET THE GLOBAL IgG DEMAND:
57.8 MILLION LITERS IN 2018
93.2 MILLION LITERS IN 2026
MRB

The Growing Discrepancy between Recovered and Source Plasma in the Domestic Supply from 2011 and 2025

The share of source plasma increases while recovered plasma's declines



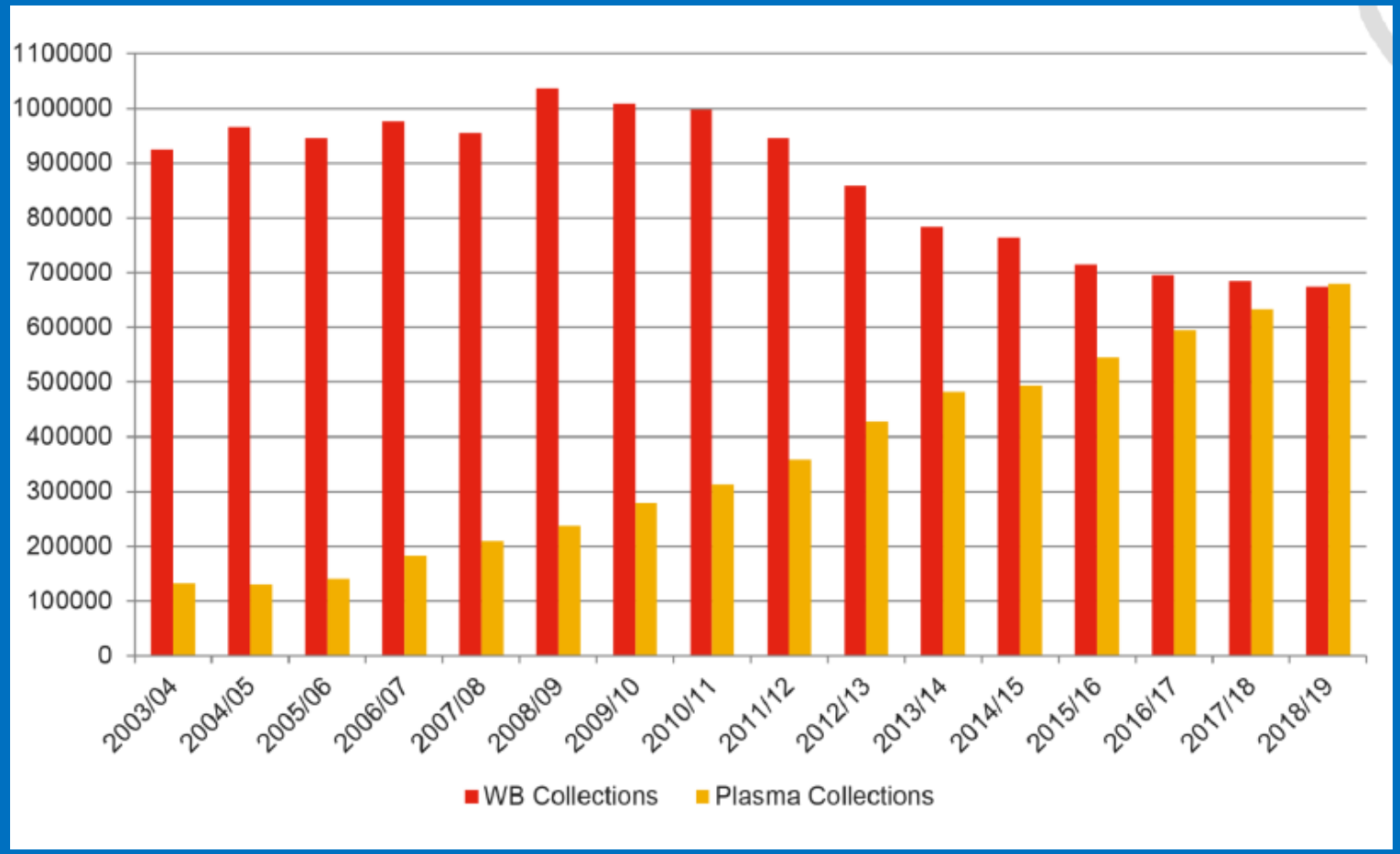
MRB

Ref. P. Robert, PLUS conference 2019, 24-01-2019

Initiatives and actions:

- Europe needs more plasma
- Corona pandemic has increased awareness on the dependency on US plasma supply and the risk on interruptions of the supply (Trump: America first, US Defence Act)
- More awareness at European blood establishments (EBA) to increase the supply of plasma in Europe
- Guidelines are required on clinical use of immunoglobulins at base line and in crises and priority for life saving indications
- EU4Health call for proposals: Actions grants on substances of human origen (SOHO) – Increase resilience, ensure continuity of supply and access to safe and high quality therapies in particular in times of crisis: SUPPLY project.

Successful approaches: ARCLife Blood is collecting more apheresis plasma than whole blood



Plasma for fractionation is Australian Blood Service's dominant product line

- Approximately 25L/'000 population

Summary

- Plasma products demand in the world will expand significantly
- Europe will face the effects
- Developing countries will become developed countries and will follow the same pattern.
- Blood safety will continue to be paramount
- COVID-19 pandemic has shown that plasma supply is not guaranteed
- Costs of production need to be addressed.
- New technologies are required in order to reduce the costs of production
- Plasma value chain = plasma donors - plasma collection centres - fractionation facilities - hospitals - physicians - authorities.
- All stake holders play a role and are important for curing the patients in need.

Thank you for your attention