Plasma collection and fractionation in Europe Past, Present, and Future

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Conflict of interest

Consultancy and advisory to

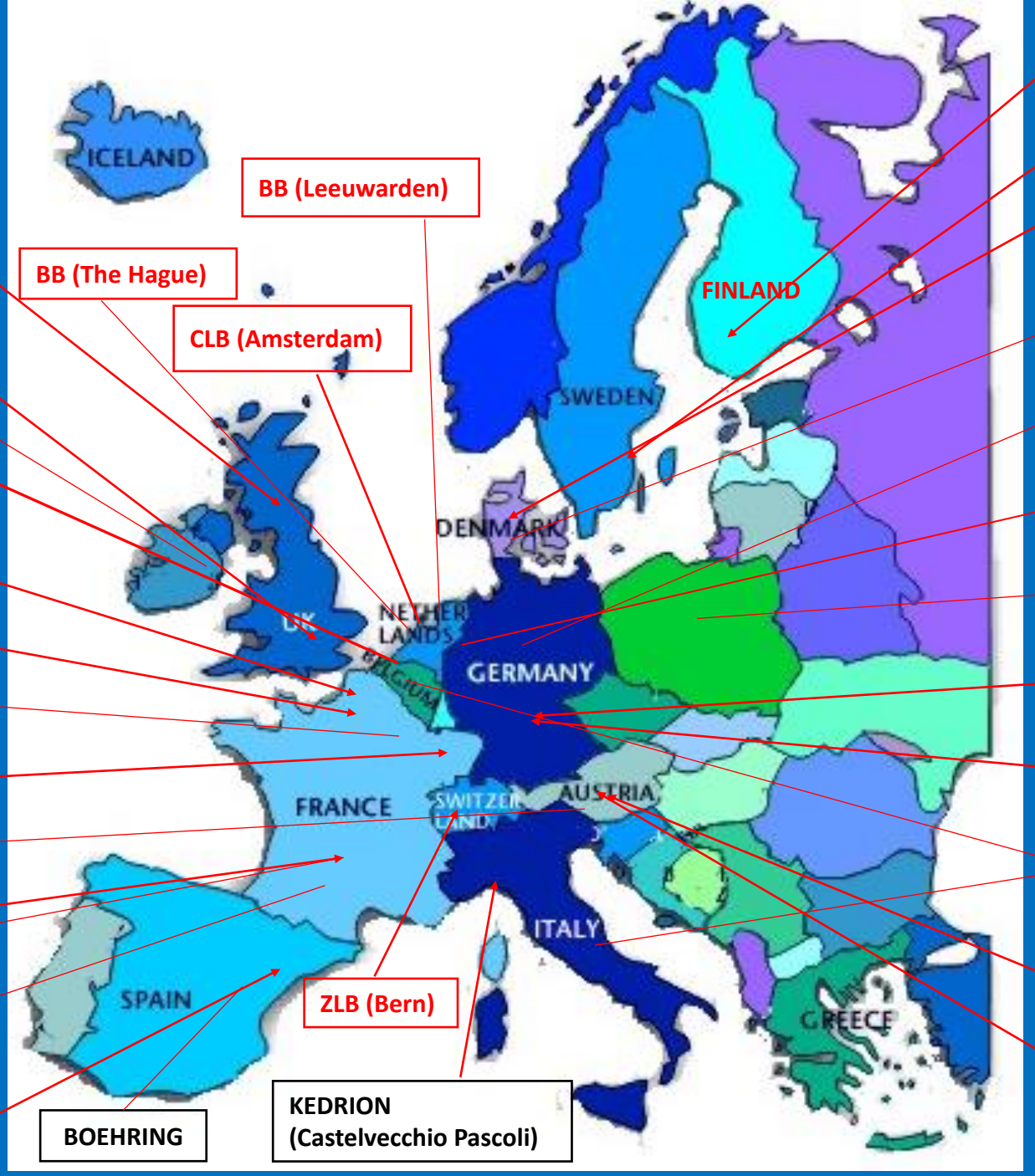
- IPFA
- Dutch Ministry of Health, Welfare and Sports
- Cerus Global Health Policy
- European Hematology Association
- WHO ECBS and Regional Office Egypt
- UK Blood Inquiry

Europe until 1993

- Plasma: - collected mainly as recovered plasma from local donors
- Cryo production and plasma fractionation:
  - mainly at not-for-profit organisations (BTS)
- Plasma derived products: - exempted from regulations on medicines
  - national licences
- Clinical evidence based on small clinical trials and limited scientific support

  Guidance and guidelines from WHO, Council of Europe, national organisations
- Protective national environment

- 1993



SNBTS (Edinburgh)

BPL (Elstree)

BTSB (Dublin)

CAF-DCF (Brussels)

CRTS (Lille)

CNTS (Paris)

CRTS (Nancy)

CRTS (Strasbourg)

CRTS (Bordeaux)

CRTS (Lyon)

MERIEUX (Lyon)

CRTS (Montpellier)

GRIFOLS (Barcelona)

BB (Leeuwarden)

BB (The Hague)

CLB (Amsterdam)

ZLB (Bern)

BOEHRING

KEDRION (Castelvecchio Pascoli)

FRC (Helsinki)

KABI-PHARMACIA (Stockholm)

STATEN SERUM INSTITUTE (Copenhagen)

NOVO NORDISK (Copenhagen)

DRK SPRINGE (Springe)

DRK HAGEN (Hagen)

INST. of HAEMATOLOGY (Warsaw)

BIOTEST (Dreieich)

BEHRINGWERKE (Marburg)

BAXTER (Rieti Italy, (Lessines, Belgium)

OCTAPHARMA (Vienna)

IMMUNO (Vienna)

Extra plasma supply from VNRBD

"Euroblood program" (1972-2002)

- Whole blood collections by Swiss Red Cross, Dutch CLB, RC Belgium, DRK Springe, DRK Hagen.
- Red cells for New York Blood Center, NBTC Athens, UN Support Programs
- Recovered plasma for manufacturing (albumin, factor VIII, immunoglobulins)

NYBC imported +/- 250,000 units/year (40% of its supplies)	(+/-125,000 L plasma)
In 1990, SRC delivered 150,000 units to NYBC and NBTC in Athens	(+/- 75,000 L plasma)

- 2002: US-FDA ban on European blood (risk on vCJD contamination)

Piet J. Hagen. Blood transfusion in Europe: a "White paper" Council of Europe Press 1993
Starr D. Blood An epic history of medicine and commerce. Alfred Knopf. New York .1998

Until 1993

- Critical situation : Transfusion Transmitted Infections (HIV, HAV, HBV, non-A non-B/HCV)
- TTI via plasma (paid plasma, plasma from inmates, plasma from VNRBD)
- TTI via PDMPs (factor VIII/IX, IVIG, anti-D IgG)
- Public hearings and court cases (Ireland, Germany, France, Scotland, UK, Switzerland)

- Exclusion of donors at risk (conflicting with the emancipation of gay persons)
- Introduction of screening and testing

- Plasma supply not sufficient to meet the demand (shortages of IgGs)

From half-1980s on

- Increasing demand for improvement of efficacy, quality and safety

- EC level: Exemption lifted: PDMPs became medicinal products
  Encouragement of more rational use
  More competition and transparancy on pricing and social security
  Better European authorisation system: European Medicines Agency
  EU Directive 89/381/EC (1989) to be imposed in national legislations
  January 1993 : open market

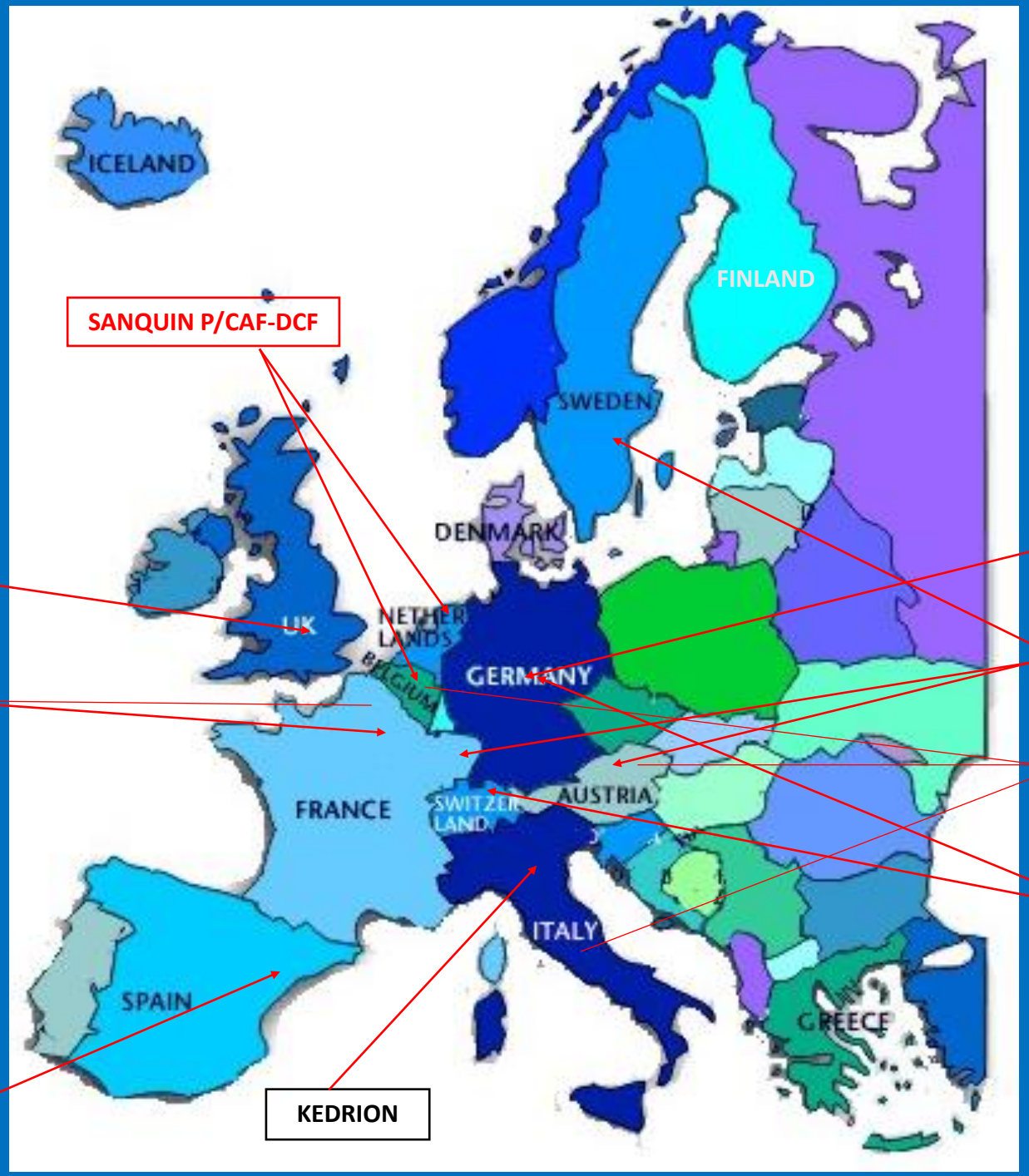
- Organisation of plasma collections remain a matter for national authorities to decide

- Response of not-for-profit sector: founding of EPFA/IPFA in 1990

Fractionation facilities

- New and more requirements on efficacy, quality, safety and controls
- Increasing costs
- Red Cross organisations concerned because of the risks on liability

1990 - 2000



SANQUIN P/CAF-DCF

BPL

LFB

GRIFOLS

KEDRION

BIOTEST

OCTAPHARMA

IMMUNO -> BAXTER (1996)

ZLB BEHRING (ZLB -> CSL, 2000)

Further developments I

- Competent authorities

  - Commission Directives on Blood and Blood Components.
  - centralised EMA procedures: PMF, mutual recognition procedures, and others
  - Notes for Guidance of Clinical Trials for licencing
  - improved communication with EMA, EU Commission, CD-P-TS/EDQM
  - EU Treaty of Amsterdam (1999).

  Art. 168: setting high standards of quality and safety of … blood and blood derivates.

- Open EU market with presence of all players

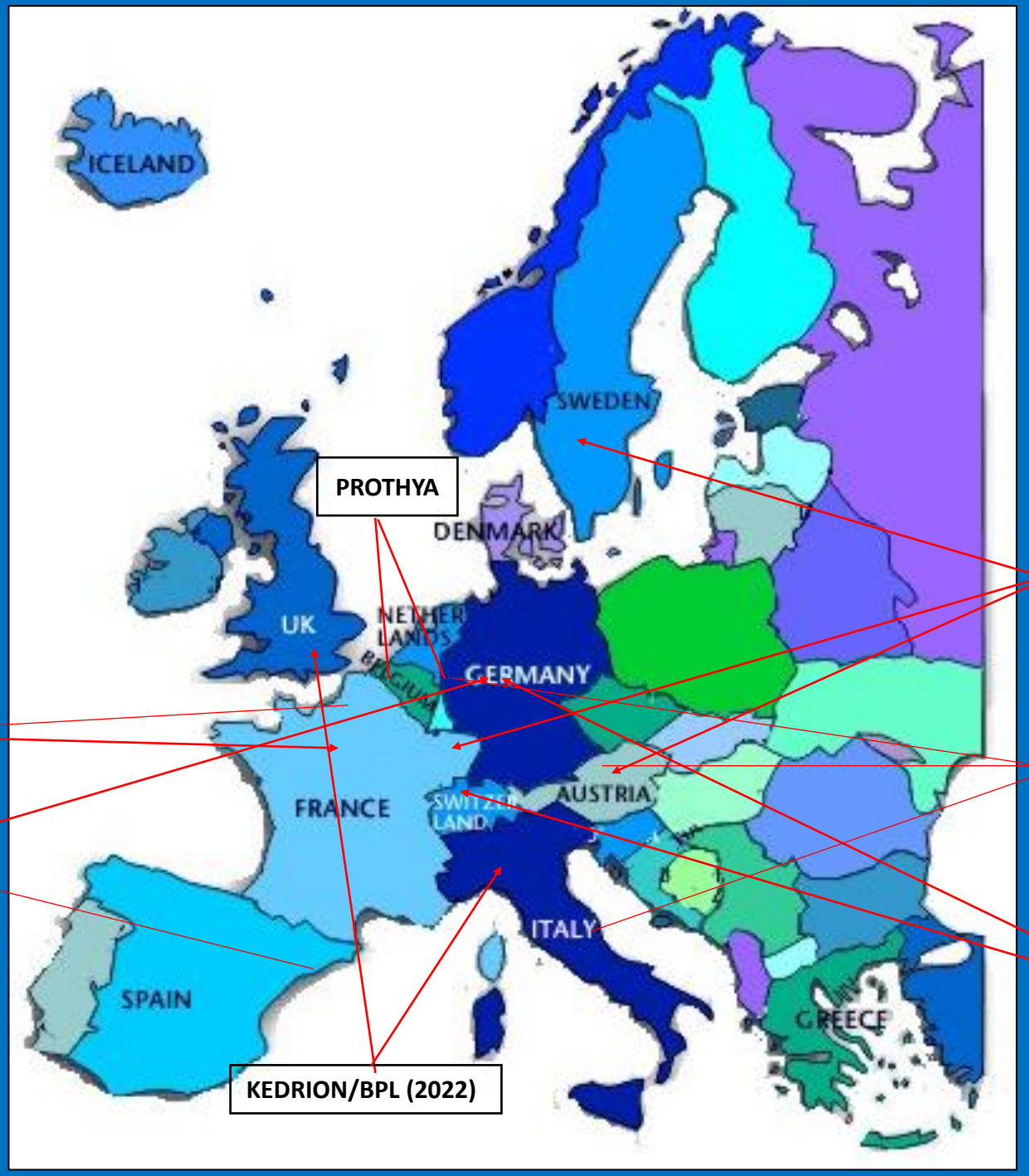
Further developments II

- Markets of PDMPs
  - compliance to medical marketing regulations
  - limited access to prescribing physicians

- Financial pressure
  - some products considered as generics
  - price reductions due to competition
  - insufficient financial compensation due to limited product pipelines.
  - higher costs and risks for new product development
  - costs of health care under pressure

- Small companies <---> big companies active in international overseas markets with higher margins

2000-2022



OCTAPHARMA

LFB

BAXTER -> SHIRE -> TAKEDA

GRIFOLS/BIOTEST (2021)

CSL BEHRING (2007)

Challenges

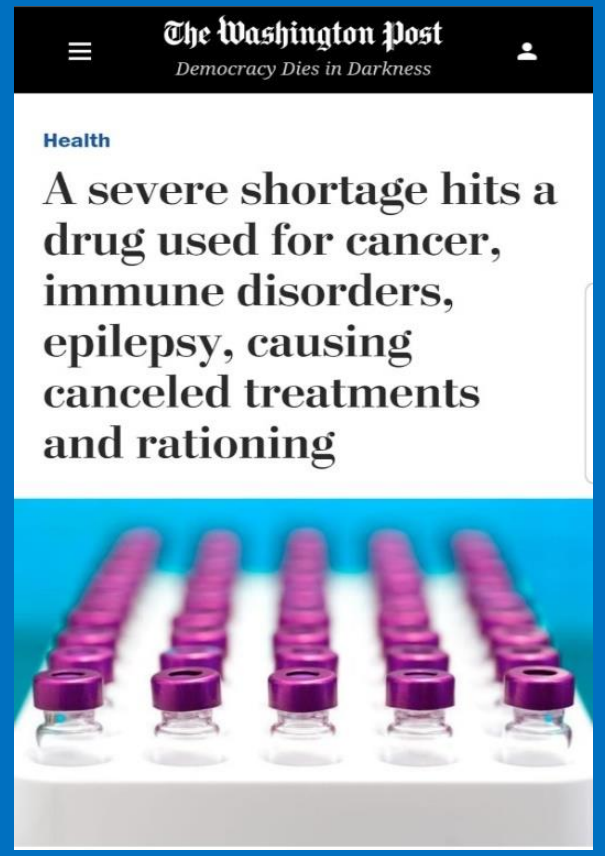
- Unequal distribution of PDMPs over the world
- Prices of PDMPs are rising
- Two products - IgG (IVIG and SubCu) and albumin - determine the demand for plasma

- Strategic Independence : 70% of world' plasma supply is sourced in one country – USA
  Europe is for 37 % dependent on this plasma

- Plasma supply under pressure
- Shortages of PDMPs

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:**	Supply tensions. Special meeting in 2021 with Paul Ehrlich Institut
2019-2021	**USA:**	Severe shortages.



The Washington Post
November 1. 2019

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

Concerns

What has NOT (yet) been achieved?

✓ Regulatory harmonisation worldwide

✓ Sufficient supplies

15-20 % shortage of plasma due to pandemic with (expected) severe shortages of IVIG

✓ Developments on plasma wastage linked to blood transfusion systems in emerging health care systems

✓ Access to all patients, including in the developing world

Future : treatments I

- Patient population
  - Increase of patients' population worldwide
  - Differences in treatments based on gender and age

- New generation recombinant products: extended half-life, less immunogenic, more resistant to inactivation, ….

- New recombinant substitutes: human albumin; C1 esterase inhibitor; Covid-19 polyclonal hyper IgG

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

- Continuous growth of global polyvalent immunoglobulin markets: role of guidelines

Guidelines on IVIg usage

- Comité d' experts IgIV de l' Assistance Publique . Recommandations de bon usage de imunoglobulins intra veineuse polyvalents. March 2000
- National Blood Authority Australia. Report on the use of IVIg for 2009-2010
- Policy Recommendations. Use of therapeutic exchange in neurological conditions in Australia 2018
- Canadian Guidelines for the use of IVIG for hematological and neurological conditions. *Transf. Med. Rev. April 2007*
- Health Canada. Protecting access to immunoglobulins for Canadians. 2018
- Department of Health UK. Demand management plan for immunoglobulin use
- Department of Health UK. Clinical Guidelines for immunoglobulin use. May 2008 and July 2011
- European Dermatology Forum. Guidelines on the use of high-dose IVIG in dermatology. 2018
- KCE Report. Polyvalent immunoglobulins – part 2: use in Belgium. December 2020
- Cochrane Library : 73 reviews on clinical use in single indications, 6 protocols, 3148 trials. *View date 11/03/2022*
- Brand A, de Angelis V, Vuk T, Garraud O, Lozano M and Politis D. Narrowing the gap between IG supply and demands by appropriate indications: a prerequisite for self-sufficiency? *Transfus Clin Biol. 2021 28(1): 96-122*

Do IVIG-guidelines work ?

- IVIG indicated for autoimmune and inflammatory diseases of which pathology is mostly unknown
- Working mechanism of IVIG unknown or hypothesised in some indications
- Evidence based RCTs do not seem to be not feasible in rare diseases

- Treatment with IVIG relatively effective. Confirmation bias? Is disease self-limmiting?
- No or few alternatives for effective treatment
- Low rate of side effects of IVIG

- Pressure from well educated patients and patient organisations
- Compliance not imposed when guidelines are not followed

Future : treatments II

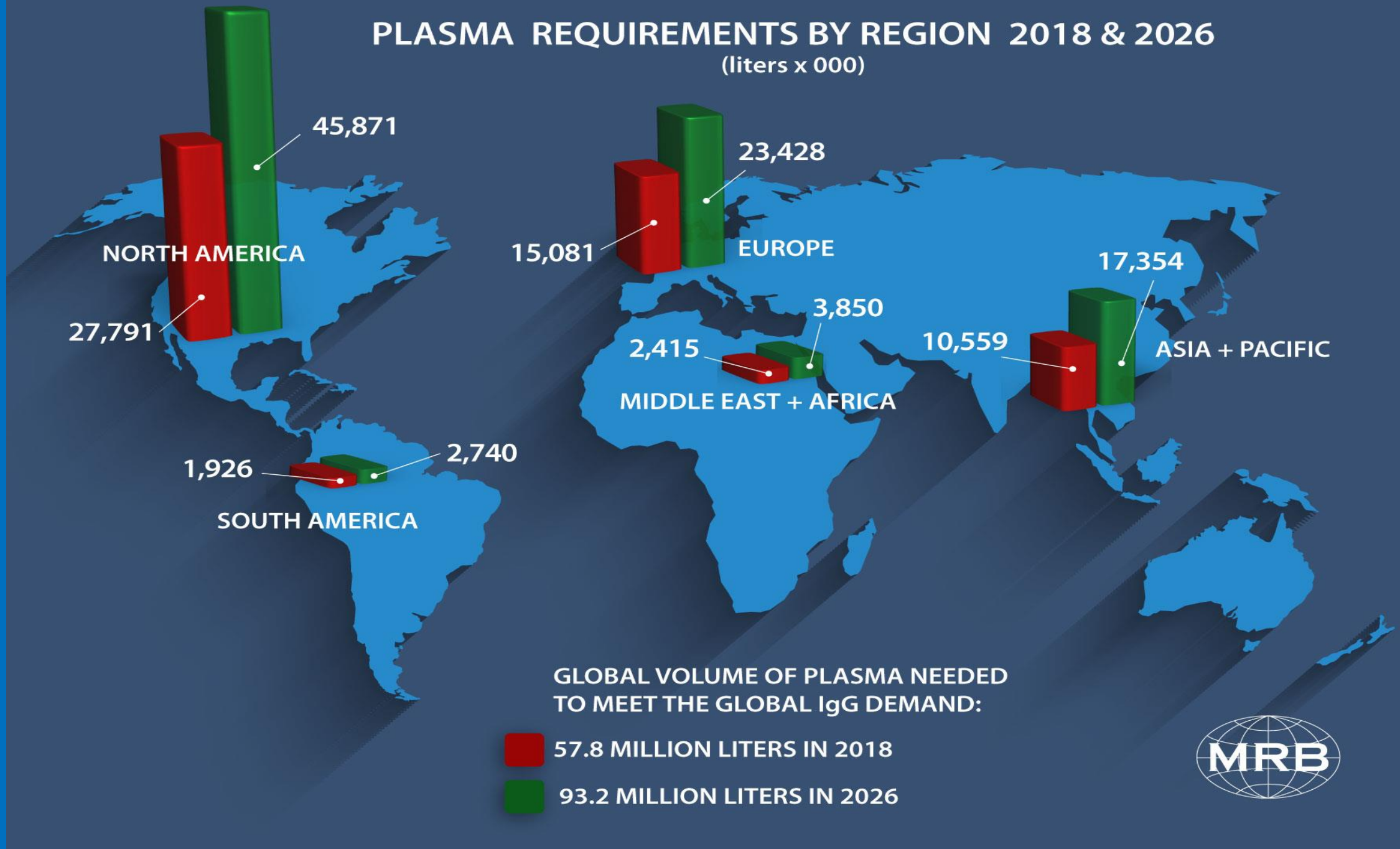
- New therapies: e.g.
  - gene therapy for PID;
  - gene therapy for hemophilia A and for hemophilia B
  - FVIII bypass products (emicizumab)
  - PerClot polysaccharide hemostatic system
  - FcRn antagonists (alternative for IVIG immune modulation treatment)

- Transgenic substitutes: larger supplies ? cheaper ?

Future : supply

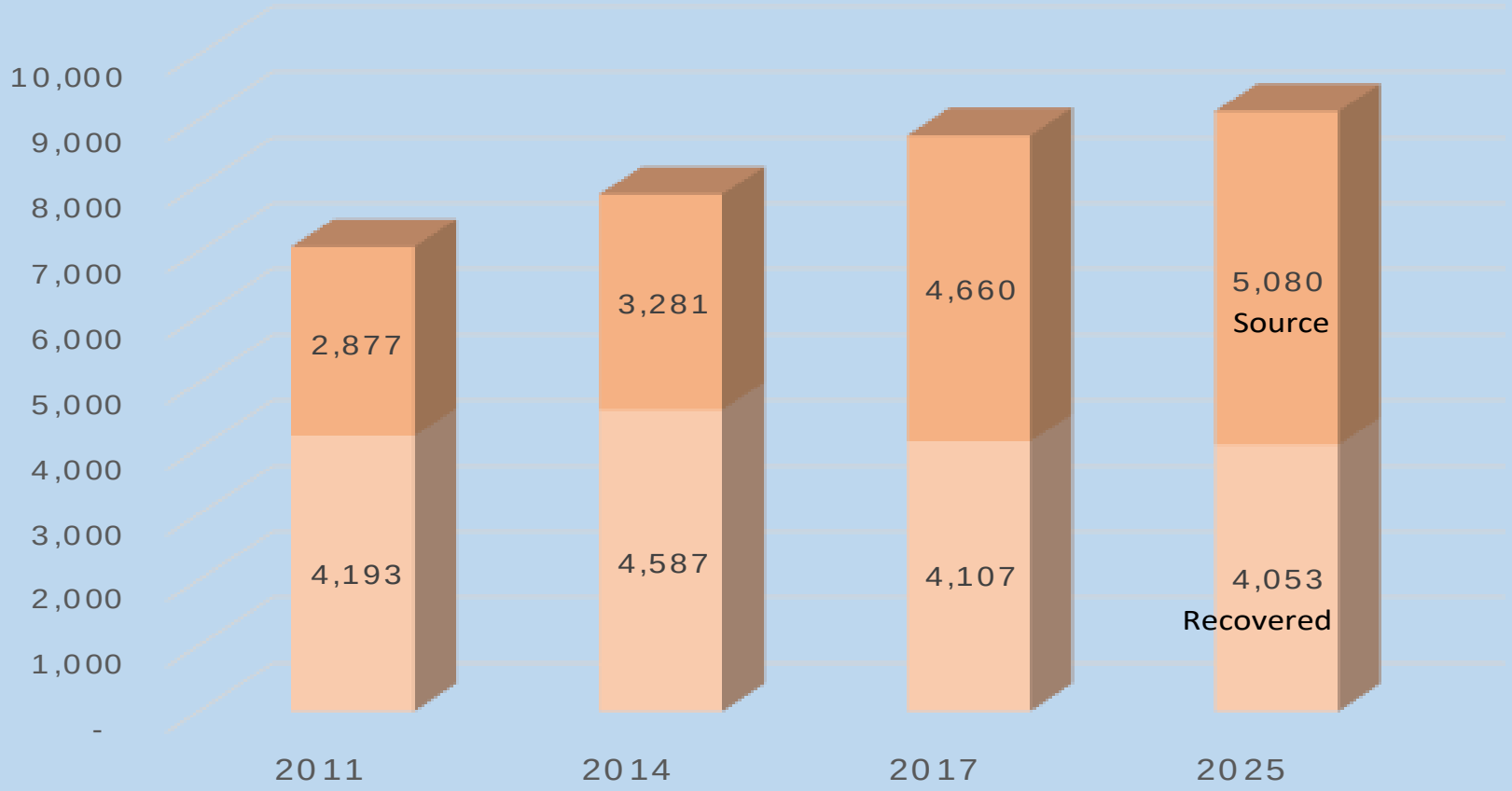
- Small number of manufacturers:
  - risk of production breakdown ?
  - fewer products available ?
  - monopolistic behavior ?
  → higher prices ?
  → less innovations ?
  - risks for selected markets: non-introduction/withdrawals

- 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:

- SARS-Cov-2 pandemic emphasised the need for balanced global plasma supply and the risk on interruptions (Trump' America first and US Defence Act, reduction of US plasma supply)

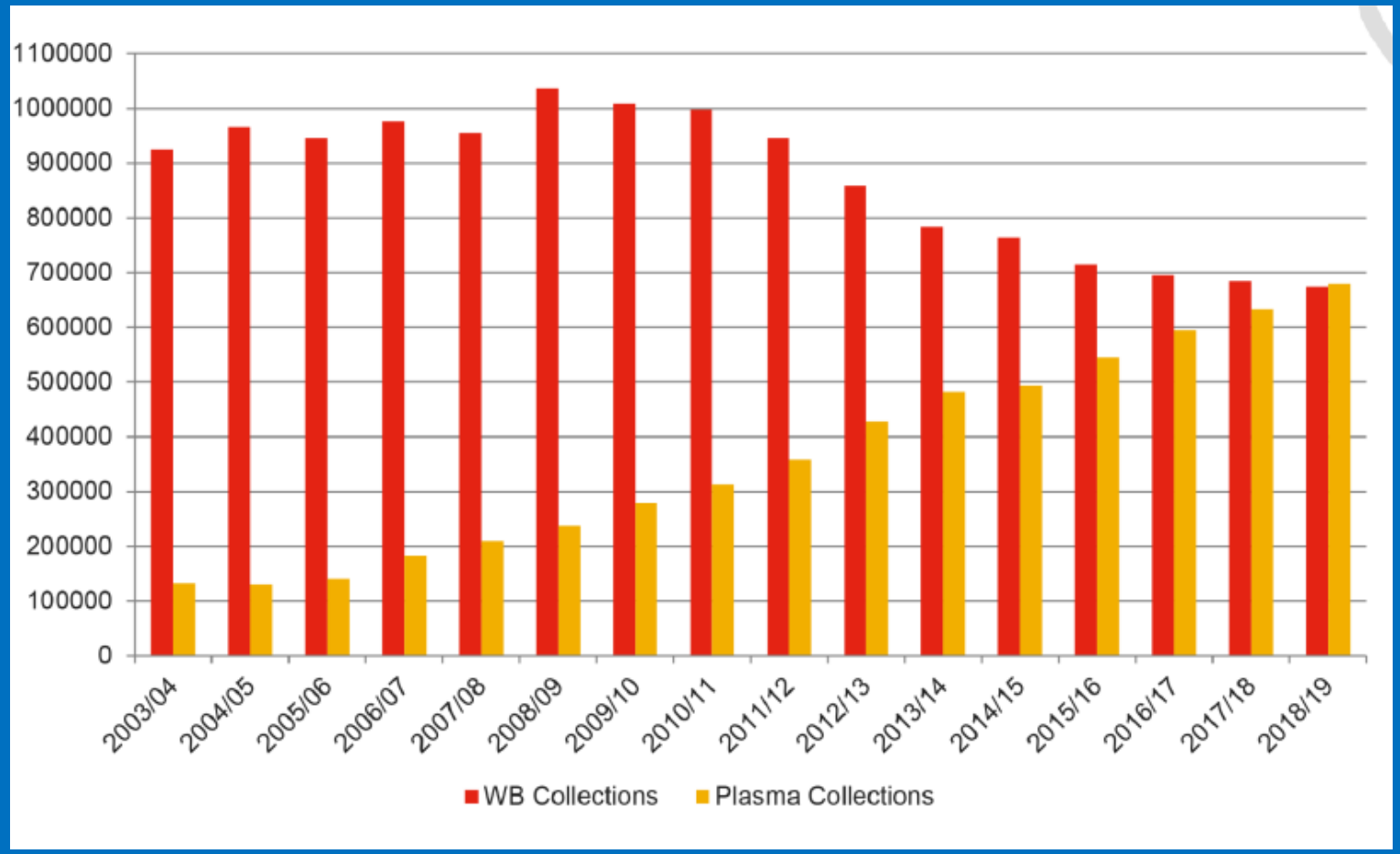
- European Commission introduced funding of Covid Convalsecent Plasma collections

- EBA with other organisations submitted for EU funding the SUPPLY project on EU plasma collection.

- However, more European plasma for manufacturing alone is not enough

- European plasma might not be used for PDMPs for European patients. Companies will aim for markets with the highest margin.

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

Conclusion

- Global PDMP demand will increase significantly. Europe will face the effects.

- Plasma value chain = donors - plasma collection centres - fractionation facilities - hospitals - physicians – patients - authorities. Each stakeholder is important for the care for the patients.

- Europe: aim for Strategic Independence !

- Clinical guidelines of IVIG.

  Put efforts in : **the Knowledge - Quality Cycle**

  Focus not on development but on implementation (education and training) and on evaluation (audits and feed back).

Thank you for your attention