Safety profile of plasma for fractionation donated in the United Kingdom, with respect to variant Creutzfeldt-Jakob Disease

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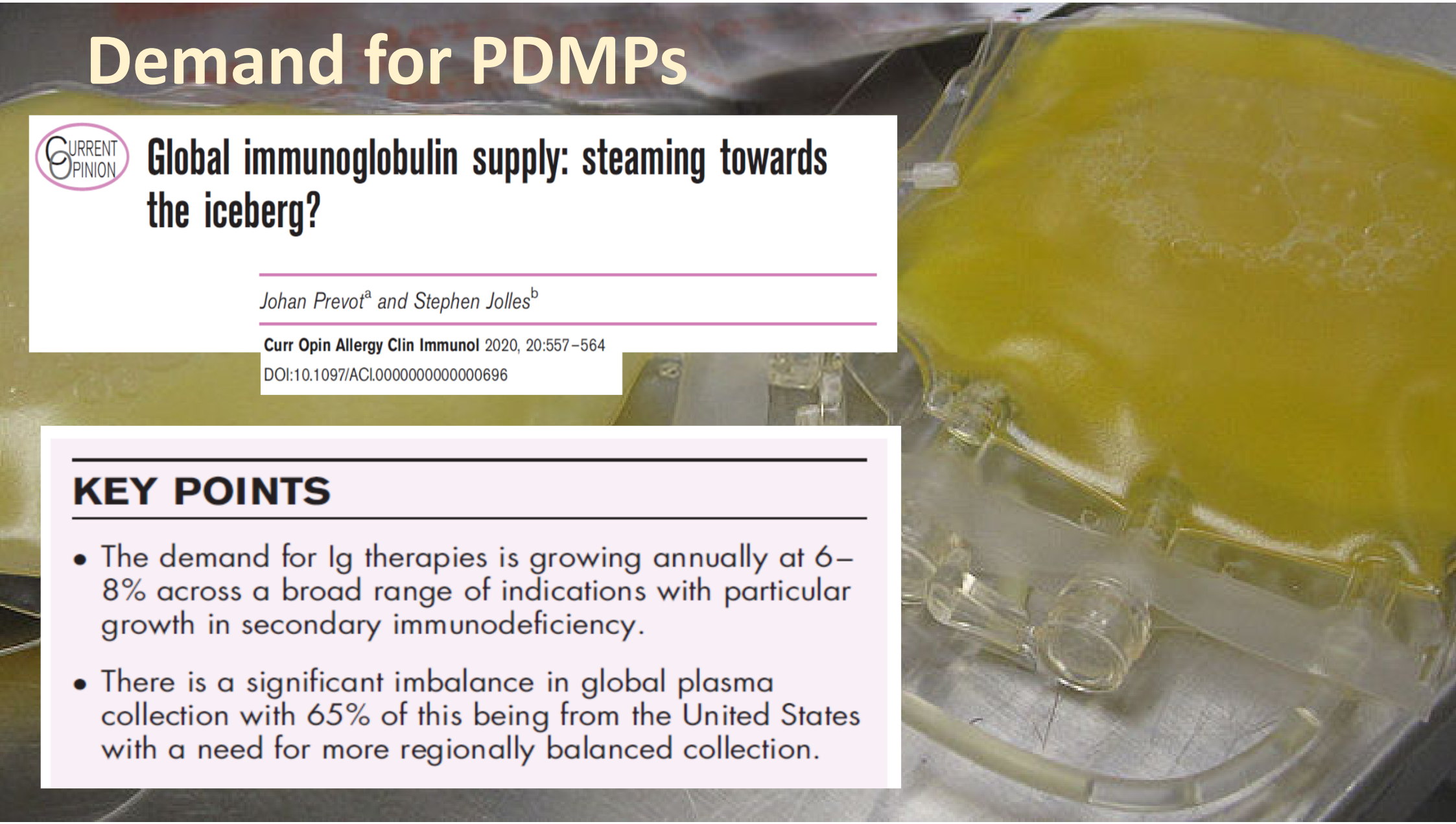
Declarations of interest

- Nothing to declare
- Authors are employees of:
  - UK Blood Services
  - UK Government
  - Academic institutions
  - Patient organisations
  - Trade organisations
  - Commercial fractionators

Demand for PDMPs



CURRENT OPINION

Global immunoglobulin supply: steaming towards the iceberg?

Johan Prevot[a] *and Stephen Jolles*[b]

Curr Opin Allergy Clin Immunol 2020, 20:557–564
DOI:10.1097/ACI.0000000000000696

KEY POINTS

- The demand for Ig therapies is growing annually at 6–8% across a broad range of indications with particular growth in secondary immunodeficiency.
- There is a significant imbalance in global plasma collection with 65% of this being from the United States with a need for more regionally balanced collection.

Supply risk to European patient care

Dependency on importation, primarily from the USA

USA has recently designated plasma as a *strategic resource:* exports may be restricted

Europe (inc UK) requires 64 tons of immunoglobulin per annum

~350,000 patients and demand is rising <6% per year

- European Blood Alliance: "Increasing plasma collection by not-for-profit blood establishments in Europe is a priority… to safeguard the supply of safe PDMPs …for patients in Europe while preserving donor health'
- Patient and trade organisations (IPOPI, EPODIN, IPFA, PPTA) concur that a regular and continuous supply of plasma is required as the health independence of Europe is a concern

However…

Geographic deferral of ex-UK donors and of UK plasma for fractionation

EU Regulatory Position #1 EMA

EMA/CHMP/BWP CJD position statement (3rd edition 2018):

'… donors who have spent a cumulative period of 1 year or more in the UK between the beginning of 1980 and the end of 1996 are excluded from donating blood/plasma for fractionation'

➤ Note that only 185 of 233 cases lived in the UK >6 months

However…

EU Regulatory Position #2 ECDC

Geographic deferral of donors and of UK plasma for fractionation

ECDC risk assessment (Aug 2021):

'…EU/EEA countries may consider **assessing their endogenous risks,** evaluating **product-specific data packages** (including the prion-reduction capacities of applied fractionation procedures), and balancing the assessed threat with the **supply need for PDMPs and source plasma** in their country.

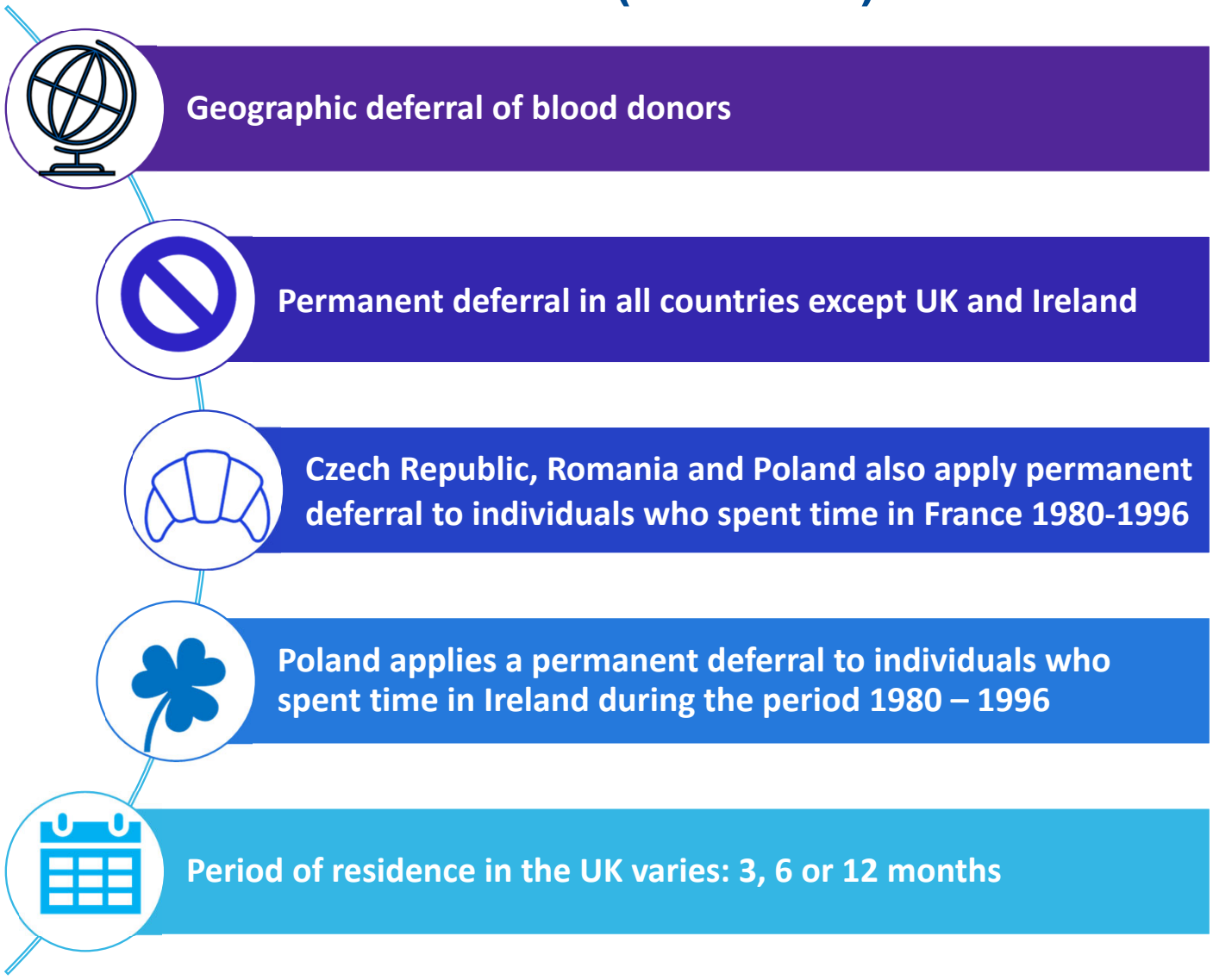
Until such data are available, EU/EEA countries may consider, as a precautionary measure, **preventing** the use of immunoglobulins and other PDMPs derived from UK plasma, as well as **the fractionation of UK plasma** in EU/EEA facilities'

ECDC technical report (Jan 2023):

"To determine whether current restrictions … residency or visits to the UK are still justified, **countries may consider** assessing the proportion of **blood donors deferred** and … comparing with the results of the Australian model... with the premise that a similar, or lower proportion of donors meeting this criterion could correspond to a similar or lower risk of transmission."

European Committee on Blood Transfusion (CD-P-TS) Nov 2022

What specific deferral policies does your blood service adopt related to vCJD risk?



European Committee on Blood Transfusion (CD-P-TS) Nov 2022

Moldova, Poland, Slovenia and Turkiye are considering change, others appear to have low motivation for change and many are awaiting central approval:

Czech Republic: "While permanent deferral is considered no longer necessary due to the extremely low risk, any change in the Czech regulations would **have little impact if not accompanied with a change of European Medicines Agency (EMA) and plasma fractionator requirements**".

Slovak Republic "No change being considered at the moment. Awaiting to see the policy changes in other EU countries."

Lithuania "**awaiting ECDC guidelines**"

Finland "hope (and encourage) **European level** activity for updated criteria"

Denmark "**Awaiting EU/EMA** to officially announce relaxations"

Norway "**awaiting the EU and EMA** to remove this requirement"

Greece "It is worth noting that, until now, no case of vCJD has ever been reported or recorded in the general population in Greece, thus permanent deferral of donors who had lived in the UK between 1980 and 1996 seems to have been unnecessary indeed, **it had a serious effect in the actual number of potential donors**."

What about vCJD?

The vCJD outbreak was smaller than had been feared: 178 cases in the UK, 233 worldwide

The first cases were in 1995, the peak was in 2000, the most recent case in 2016

Agricultural and food chain interventions were effective

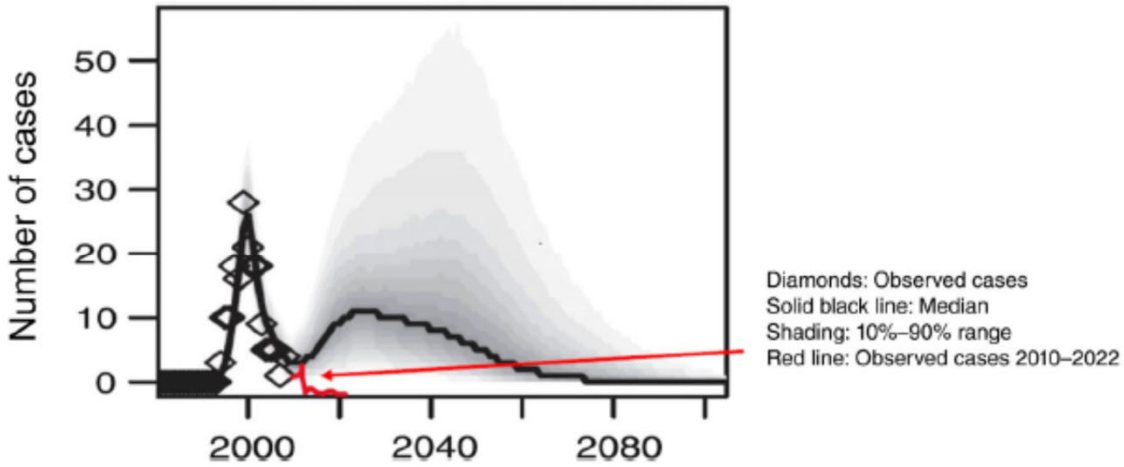
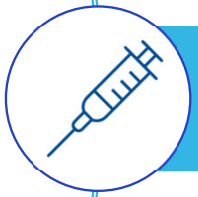


FIGURE 1 Modelling from 2010 predicting a significant second peak of infections. The actual number of cases has been much smaller (adapted from [26]).

Transfusion Transmission

Four instances of probable TT-vCJD - three clinical cases and one asymptomatic infection with post-mortem confirmation

One haemophiliac found to have abnormal prion in his spleen at post-mortem after he died from an unrelated cause in 2008



He had been treated with 8Y (intermediate-purity Factor VIII), two batches of which included a donation from a single donor who subsequently died of vCJD in 1997

8Y considered the probable cause of infection; this remains the only case implicating Factor VIII; causal connection is unproven and no identified cases related to any other PDMP

Precautionary measures were taken in the UK, including cessation of fractionation and implementation of leucodepletion in 1999

- there have been no transmissions since (>58 million transfusions)

Changes in other jurisdictions

- UK approval to manufacture IgG and Albumin from UK Plasma for UK patients
- US removed deferral of former UK residents and recipients of transfusion in the UK
- Australia, Ireland and Israel removed deferral of former UK residents
- Hong Kong removed deferral of former residents of UK, France and Ireland
- In all cases, the benefits to blood and plasma supply were considered to outweigh the negligible risk from vCJD

Modelling of risk

vCJD

- Prevalence x infectivity x susceptibility etc

PRF

- Prion Reduction Factor of PDMP process is >4 log
- 7000 fold lower risk than FFP transfusion

Risk

- Less than one death for every 36.4 billion units of UK plasma
- One possible death from vCJD every 33,000 years

Benefit from ex-UK donors in Europe and fractionation of UK plasma

UK migration data

1.8 million potential donors in the EU are deferred based on previous residence in the UK

×

Australian experience

In the 6 months following removal of deferral, 5% of newly eligible donors registered and 32K donors made 68K donations

=

UK collections

Currently c340K litres/year of recovered plasma

+

If UK donors in EU are readmitted

@ 1.43 % donation rate

= 26 K litres/year

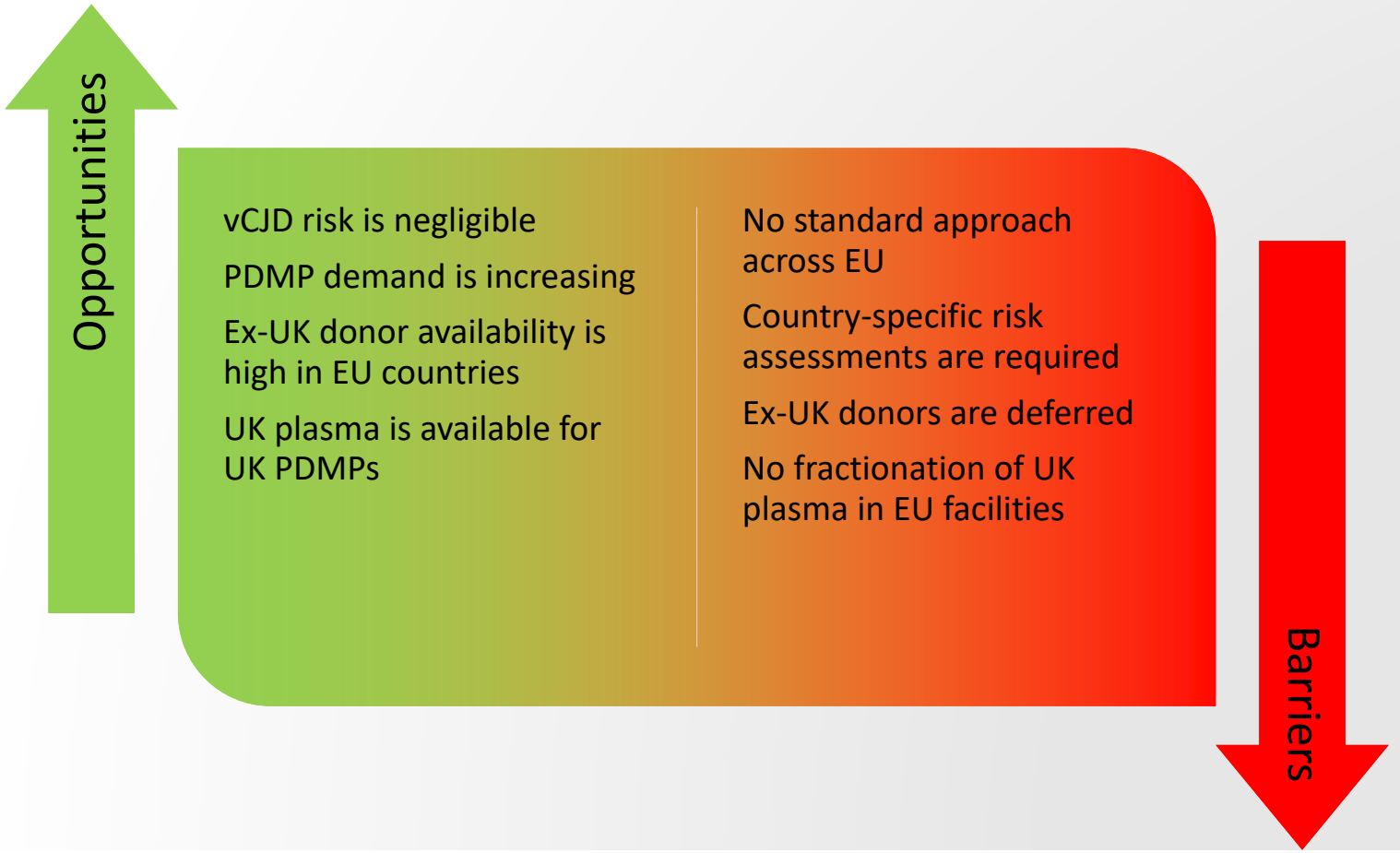
=

c365,000 litres/year of plasma available for manufacture of PDMPs for EU or return to the UK

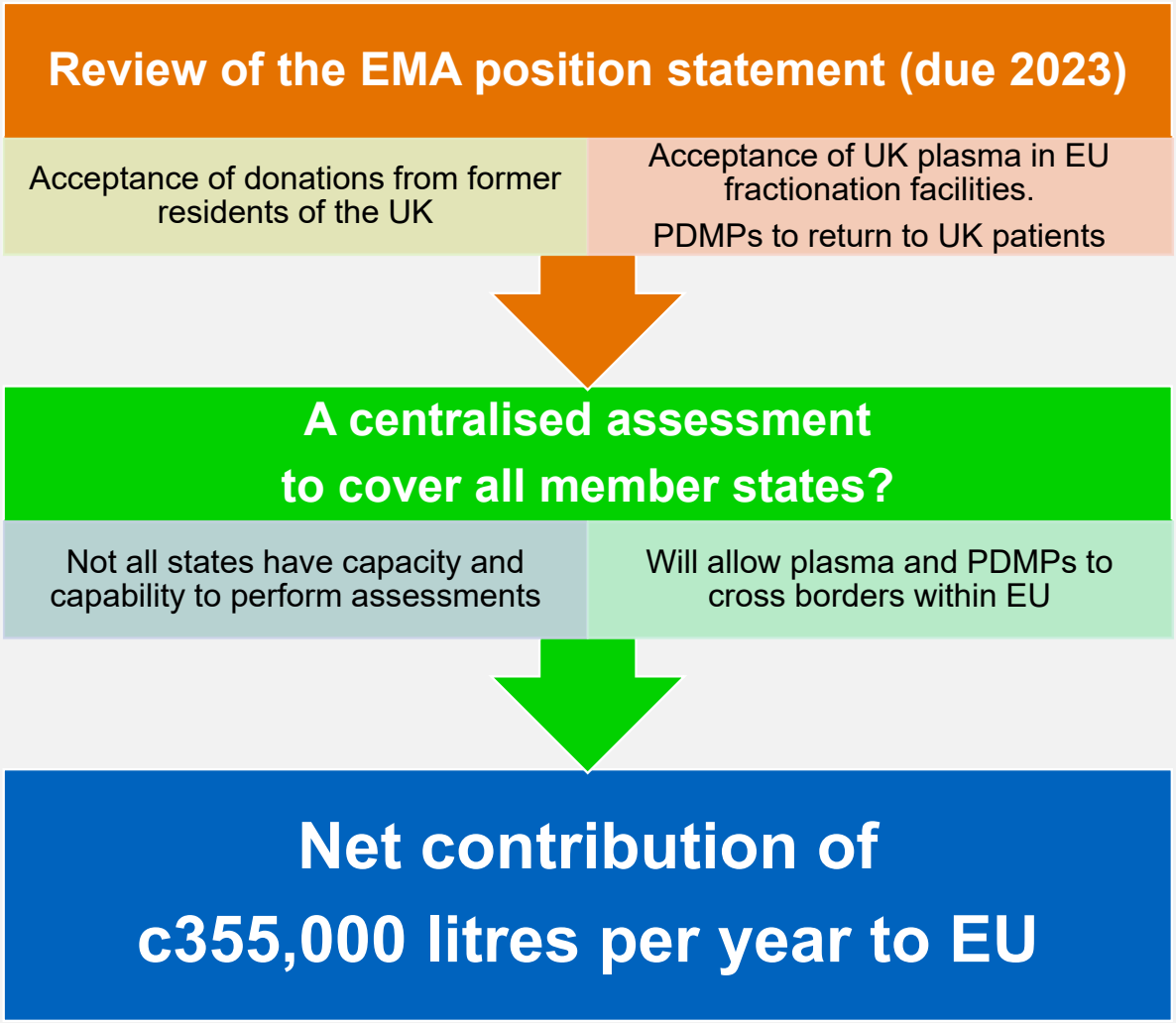
→

Immediate relief of a significant amount of pressure on the supply of PDMPs to patients in Europe

UK plasma and ex-UK donors could support EU plasma supply



What next?


Review of the EMA position statement (due 2023)
Acceptance of donations from former residents of the UK
Acceptance of UK plasma in EU fractionation facilities.
PDMPs to return to UK patients
A centralised assessment to cover all member states?
Not all states have capacity and capability to perform assessments
Will allow plasma and PDMPs to cross borders within EU
Net contribution of c355,000 litres per year to EU

Thank you for your attention

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REVIEW

Vox Sanguinis ISBT International Society of Blood Transfusion

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