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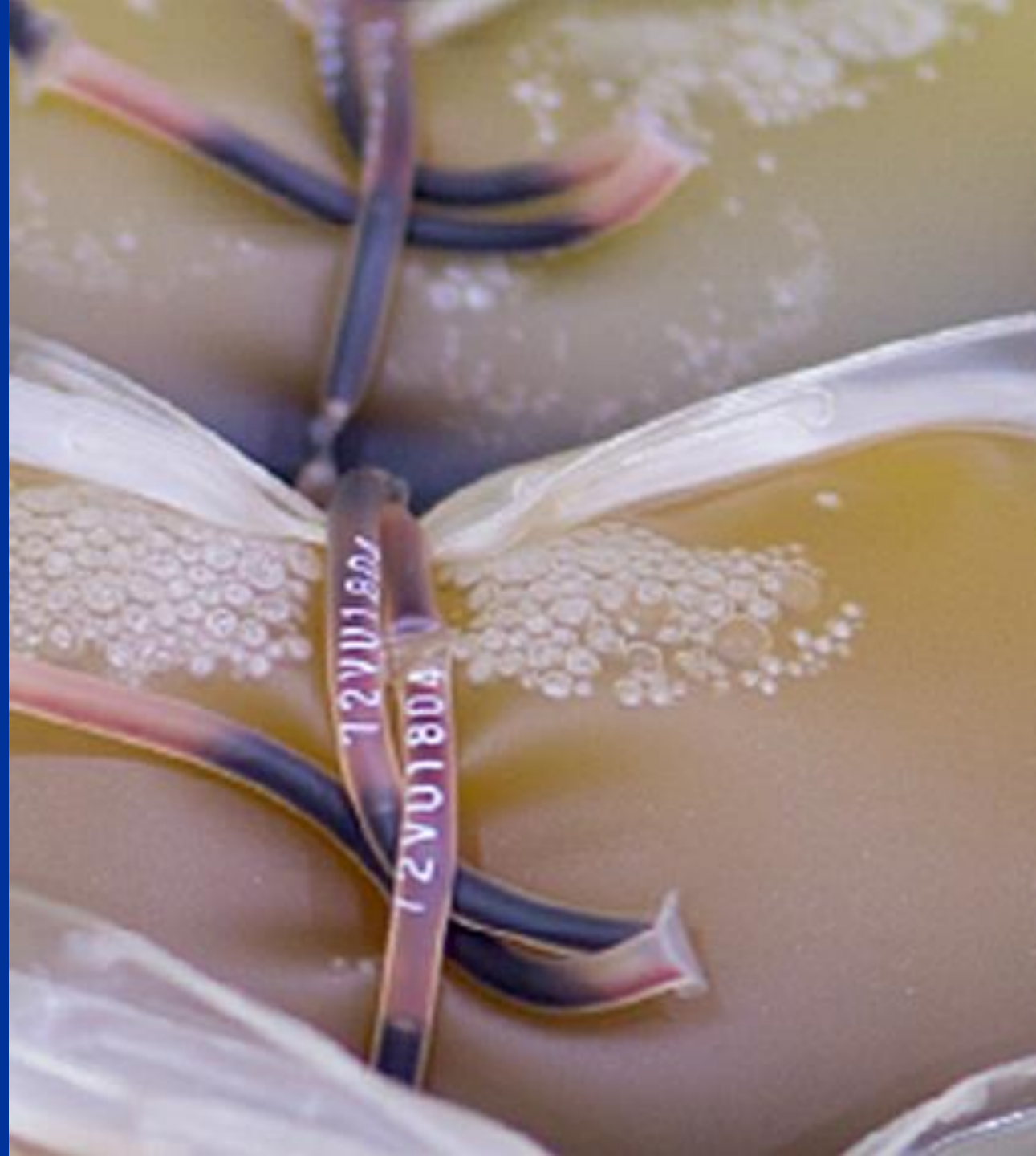
EDQM Stakeholder Event on Plasma Supply Continuity

26-27 March 2025, Council of Europe

Caroline Voltz-Girolt

Scientific secretary of the Haematology Working Party
Office of advanced therapies and haemato-oncology
European Medicines Agency



Disclaimer

The views expressed in this presentation are the personal views of the speaker and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties

EMA organisation and network

Management Board | **Executive Director** | **H-Div** | **V-Div**

CHMP | **PRAC** | **COMP** | **HMPC** | **PDCO** | **CAT** | **CVMP**

+ working parties

+ 8 scientific advisory groups

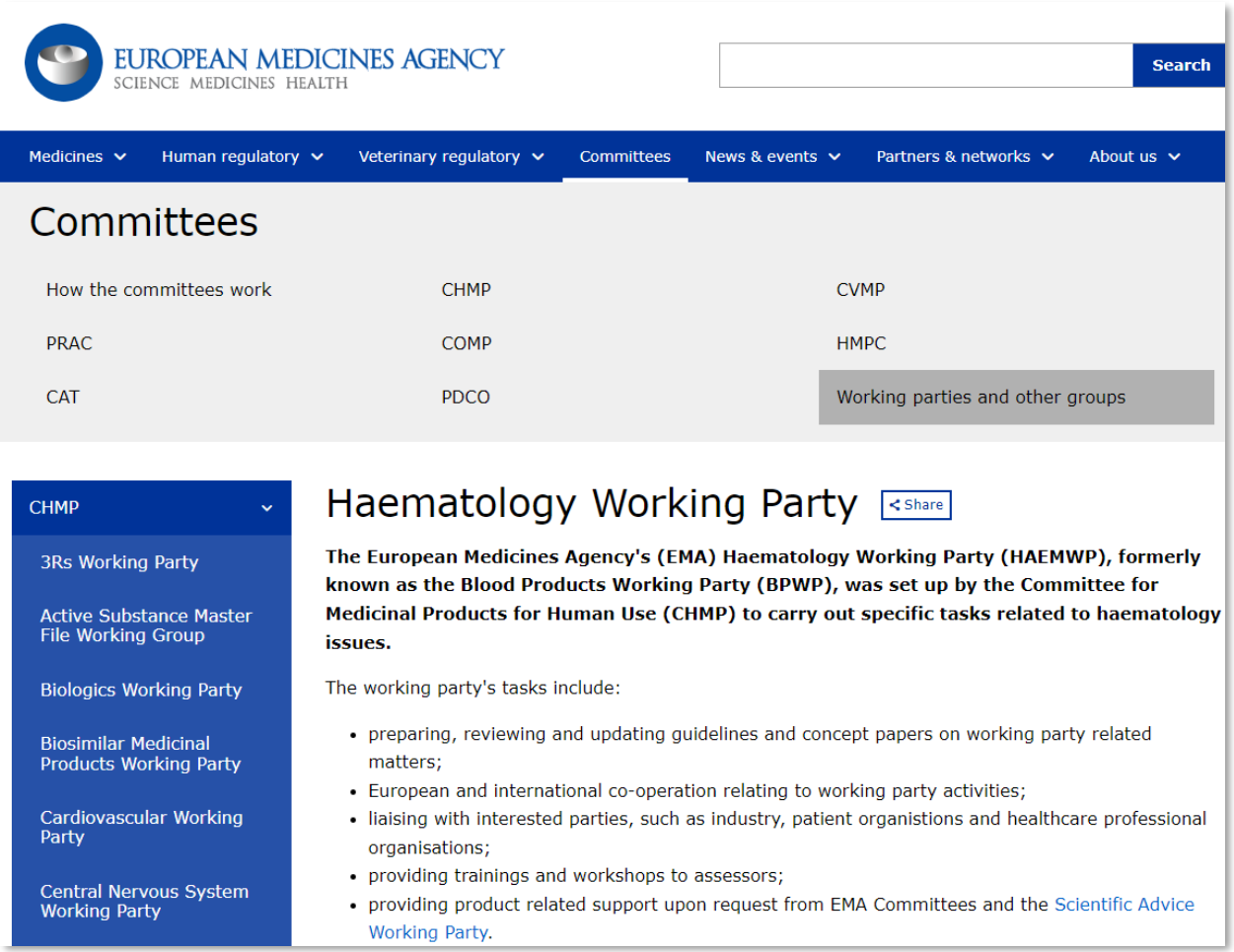
EU National Competent Authorities
~ 4000 European experts

EU institutions

~ 50 National regulatory authorities worldwide (ICH)

EMA

EMA Haematology working party and ESEC



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SCIENCE MEDICINES HEALTH

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Committees

How the committees work	CHMP	CVMP
PRAC	COMP	HMPC
CAT	PDCO	Working parties and other groups

CHMP

- 3Rs Working Party
- Active Substance Master File Working Group
- Biologics Working Party
- Biosimilar Medicinal Products Working Party
- Cardiovascular Working Party
- Central Nervous System Working Party

Haematology Working Party

Share

The European Medicines Agency's (EMA) Haematology Working Party (HAEMWP), formerly known as the Blood Products Working Party (BPWP), was set up by the Committee for Medicinal Products for Human Use (CHMP) to carry out specific tasks related to haematology issues.

The working party's tasks include:

- preparing, reviewing and updating guidelines and concept papers on working party related matters;
- European and international co-operation relating to working party activities;
- liaising with interested parties, such as industry, patient organistions and healthcare professional organisations;
- providing trainings and workshops to assessors;
- providing product related support upon request from EMA Committees and the Scientific Advice Working Party.

Haematology European Specialised Expert Community

Share

The Haematology European Specialised Expert Community (ESEC) is a platform for information-sharing among European experts on scientific and regulatory topics related to haematology (non-malignant).

It operates under the Haematology Working Party (HWP) and Committee for Medicinal Products for Human Use (CHMP).

The Heamatology ESEC provides a platform for information-sharing about:

- emerging regulatory actions and guidelines from the European Medicines Agency's (EMA) scientific committees;
- completed assessments of product-related procedures and guidelines;
- ongoing EU activities in the field of haematology (non-malignant);
- international regulators' input;
- important scientific developments outside the European medicines regulatory network, such as new treatment guidelines.

The Haematology ESEC's tasks include:

- mapping competences across the European network of experts;
- providing training and up-skilling to the European medicines regulatory network;
- connecting experts from multidisciplinary teams and across topics of expertise.

The ESEC as a group does not contribute to any regulatory procedures or actions related to product-related activities and guidelines. This means it does not give advice or take decisions.

Individual ESEC experts can contribute to EMA's scientific work as members of scientific committees, working parties or drafting groups.

EMA Haematology working party: area of expertise

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Human regulatory

Overview | Research and development | Marketing authorisation

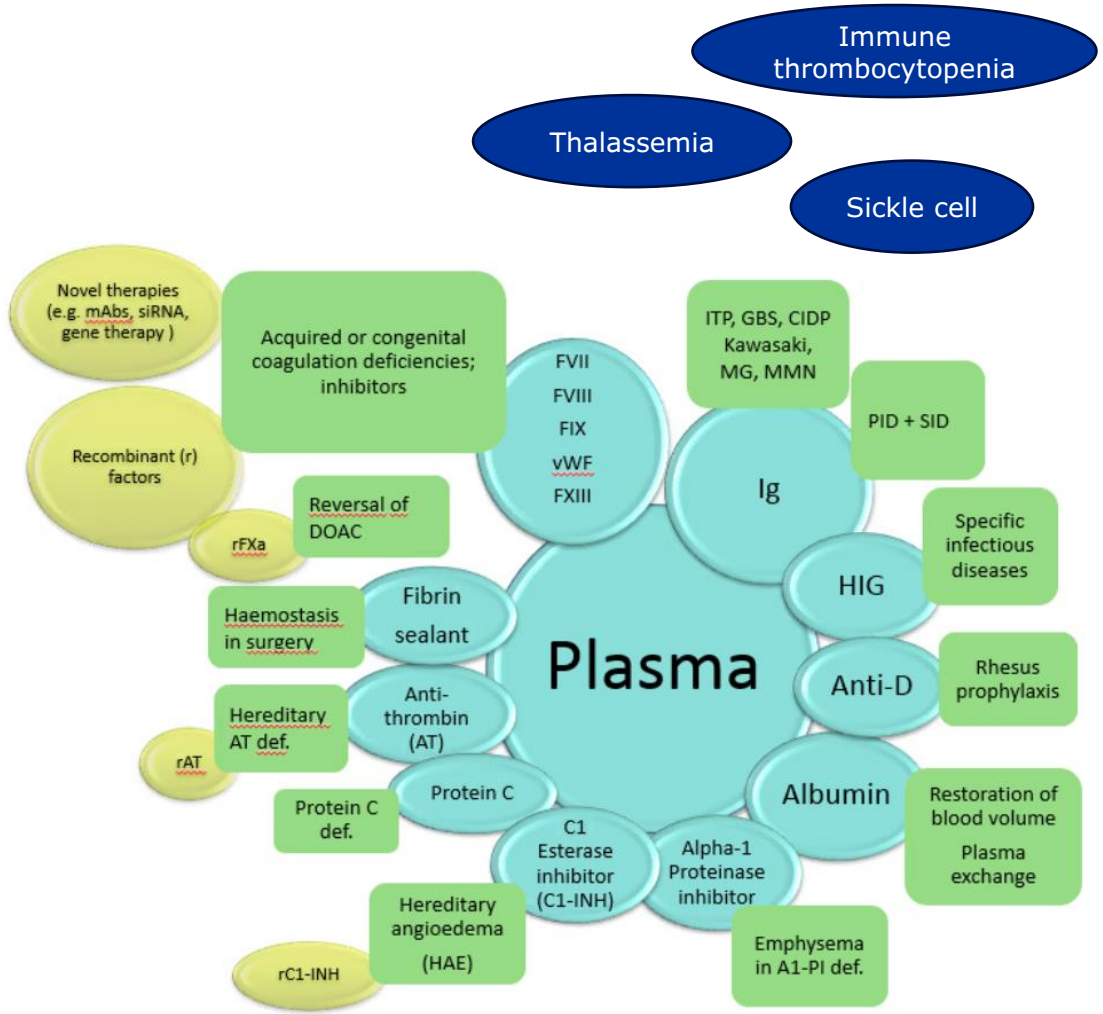
Post-authorisation | Herbal products

- Adaptive pathways
- Advanced therapies
- Clinical trials
- Compassionate use
- Compliance
- Data on medicines (ISO IDMP standards)
- Ethical use of animals
- Innovation in medicines

Clinical efficacy and safety: haematology and blood products (including biotech alternatives)

Share

Table of contents

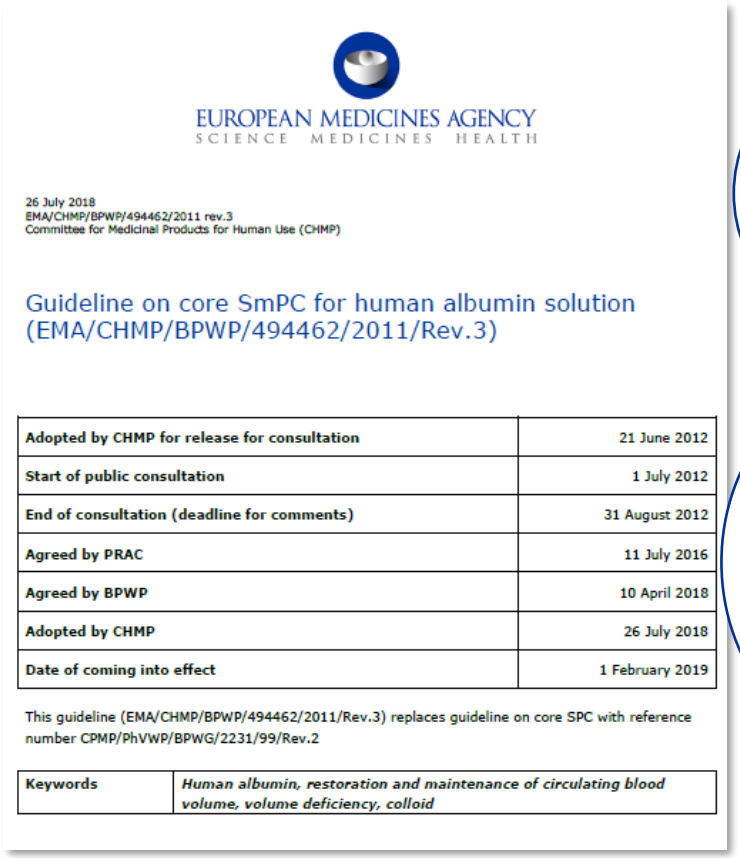


EMA

Plasma derived medicines

- Human albumin
- Normal immunoglobulins and specific immunoglobulins (anti-D, Hepatitis B, tetanus, rabies, tick-borne encephalitis)
- Plasma-derived FVIII or FIX medicines
- Other coagulation factors: plasma-derived FVII, fibrinogen, plasma derived Von Willebrand factor (VWF), prothrombin complex products
- Antithrombin
- Fibrin sealant

Human albumin



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SCIENCE MEDICINES HEALTH

26 July 2018
EMA/CHMP/BPWP/494462/2011 rev.3
Committee for Medicinal Products for Human Use (CHMP)

Guideline on core SmPC for human albumin solution (EMA/CHMP/BPWP/494462/2011/Rev.3)

Adopted by CHMP for release for consultation	21 June 2012
Start of public consultation	1 July 2012
End of consultation (deadline for comments)	31 August 2012
Agreed by PRAC	11 July 2016
Agreed by BPWP	10 April 2018
Adopted by CHMP	26 July 2018
Date of coming into effect	1 February 2019

This guideline (EMA/CHMP/BPWP/494462/2011/Rev.3) replaces guideline on core SPC with reference number CPMP/PhVWP/BPWG/2231/99/Rev.2

Keywords	*Human albumin, restoration and maintenance of circulating blood volume, volume deficiency, colloid*

Indication: Restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated, and use of a colloid is appropriate (core SmPC).

Posology: Haemodynamic performance should be monitored (blood pressure, pulse rate, central venous pressure, pulmonary artery wedge pressure, urine output, electrolyte, haematocrit/haemoglobin)

Warnings: used with caution in conditions where hypervolaemia (ddecompensated cardiac insufficiency, hypertension, oesophageal varices, pulmonary oedema, haemorrhagic diathesis, severe anaemia, renal and post-renal anuria).

Overdose: Hypervolaemia may occur if the dosage and rate of infusion are too high

- Used in the manufacture of medicines/vaccines/ATMPs as **raw materials / reagents** or in specific formulation (e.g Abraxane (paclitaxel))
- Human serum Albumin use in research (culture media)
- Serum albumin levels **can affect the half-life of drugs:** competition between drugs for albumin binding sites which can **affect potency** (Albumin–drug interaction and its clinical implication, Keishi Yamasaki *et al*)

EMA

Human normal immunoglobulins

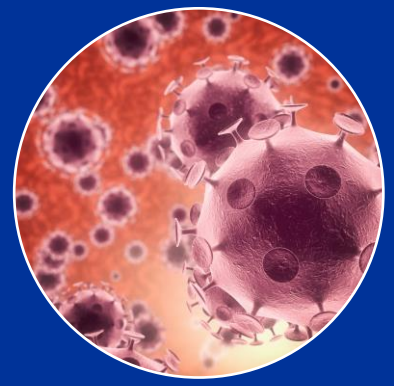
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 December 2021
EMA/CHMP/BPWP/94033/2007 rev. 4
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg)

Draft agreed by Blood Products Working Party	November 2016
Adoption by CHMP for release for consultation	15 December 2016
Start of public consultation	1 January 2017
End of consultation (deadline for comments)	31 March 2017
Agreed by Blood Products Working Party	14 June 2018
Adoption by CHMP	28 June 2018
Date of coming into effect	1 January 2019
Draft agreed by Blood Products Working Party	8 June 2020
Adopted by CHMP for release for consultation	17 September 2020
Start of public consultation	13 October 2020
End of consultation (deadline for comments)	13 January 2020
Revised draft agreed by the Blood Products Working Party	29 October 2021
Adopted by CHMP for release for consultation	16 December 2021
Date of coming into effect	1st January 2022

This guideline replaces Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg) (EMA/CHMP/BPWP/94033/2007 rev. 3)



Replacement therapy:

- **Primary immunodeficiency syndromes**
- **Secondary immunodeficiencies** patients with severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure) (e.g. oncology)

Immunomodulation:

- Primary **immune thrombocytopenia** (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count

Mainly CNS indication:

- **Guillain Barré syndrome**
- **Kawasaki disease**
- **Chronic inflammatory demyelinating polyradiculoneuropathy**(CIDP)
- **Multifocal motor neuropathy**

<**Measles pre-/post exposure prophylaxis** for susceptible adults, children and adolescents (0-18 years) in whom active immunisation **is contraindicated or not advised.**

Use of IVIG (IV use)

Human normal immunoglobulins

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 December 2024
EMA/CHMP/BPWP/496692/2023 rev 2
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg)

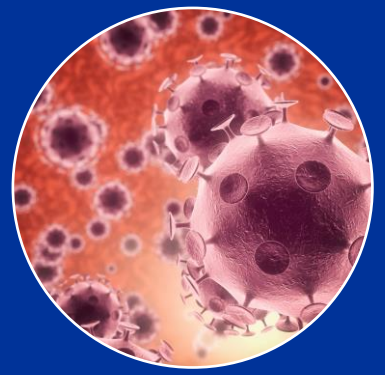
Draft

Revised draft agreed by Haematology Working Party	25 October 2024
Adopted by CHMP for release for consultation	2 December 2024
Start of public consultation	5 December 2024
End of consultation (deadline for comments)	31 May 2025

This guideline replaces Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg) (EMA/CHMP/BPWP/410415/2011 rev 1).

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

Keywords	***SCIg, IMIg, human normal immunoglobulin, primary and secondary immunodeficiency syndromes, hepatitis A prophylaxis, immunomodulation, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).***

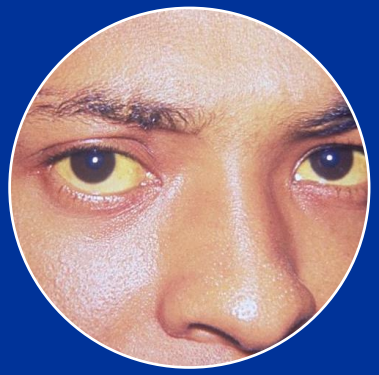


Replacement therapy (SC use):

- **Primary immunodeficiency syndromes**
- **Secondary immunodeficiencies** (patients with severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure)

Immunomodulation (SC use):

- ***Chronic inflammatory demyelinating polyradiculoneuropathy*** *(CIDP) as maintenance therapy after stabilisation with IVIg (under consideration)*



Hepatitis A prophylaxis (IM use):

EDQM monograph for Human normal immunoglobulin (0338)

Use of SCIG and IMIG use

Clinical data required IVIG

Primary immunodeficiencies (PID)

- **Open label, single-arm study** of 1 year duration in at least **40 patients with PID from** the PK study (approximately half children and adolescents)
- **Primary endpoint:** rate of acute serious bacterial infections is less than 1.0 per person per year
- **Secondary endpoints:** PK parameters, e.g. IgG trough levels, all other infections, antibiotic treatment, days lost from school/work, hospitalisations and fever episodes.
- The efficacy results from this study would apply to **all types of PIDs due to deficiency of functional IgG.**

Secondary immunodeficiencies (SID)

- If efficacy is proven in PIDs, indication granted for SIDs (extrapolation)

Immune thrombocytopenia

- **Open-label single arm study** of approximately 4 weeks duration in around 30 chronic (> 12 months duration) adult ITP patients with a baseline platelet count of <30 x 10*9/l.
- **Endpoint:** Number and % of patients with response (R), complete response (CR), and loss of response as well as time to response and duration of response and non-responders.

CNS indications

- If efficacy in PID and in ITP is established, then an extrapolation to GBS, Kawasaki's disease, MMN and CIDP might be possible

Clinical data required SCIG and IMIG for maintenance therapy

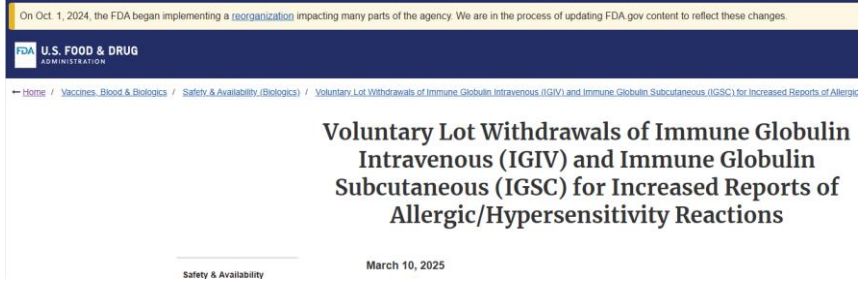
Primary immunodeficiencies (PID)

- **Open label, single-arm clinical trial** of one-year duration in at least **40 patients with PID from** the PK study (approximately half children and adolescents)
- **Primary endpoint:** rate of acute serious bacterial infections is less than 1.0 per person per year
- **Secondary endpoints:** PK parameters, e.g. IgG trough levels, all other infections, antibiotic treatment, days lost from school/work, hospitalisations and fever episodes.
- The efficacy results from this study would apply to **all types of PIDs due to deficiency of functional IgG.**

Secondary immunodeficiencies (SID)

- If efficacy is proven in PIDs, indication granted for SIDs (extrapolation) and CIDP?

Human normal immunoglobulins


On Oct. 1, 2024, the FDA began implementing a reorganization impacting many parts of the agency. We are in the process of updating FDA.gov content to reflect these changes.

U.S. FOOD & DRUG ADMINISTRATION

Home / Vaccines, Blood & Biologics / Safety & Availability (Biologics) / Voluntary Lot Withdrawals of Immune Globulin Intravenous (IGIV) and Immune Globulin Subcutaneous (IGSC) for Increased Reports of Allergic

Voluntary Lot Withdrawals of Immune Globulin Intravenous (IGIV) and Immune Globulin Subcutaneous (IGSC) for Increased Reports of Allergic/Hypersensitivity Reactions

Safety & Availability

March 10, 2025

Contraindications:

- Hypersensitivity to the active substance (human immunoglobulin) or to any of the excipients
- Patients with selective IgA deficiency who developed antibodies to IgA, as administering an IgA-containing product can result in anaphylaxis (IV)
- It must also not be administered IM in case of severe thrombocytopenia and in other disorders of haemostasis.

Warnings:

- Accidentally administered into a blood vessel, patients could develop **shock**. The recommended infusion rate must be closely followed.
- Hypersensitivity
- Thromboembolism (Arterial and venous thromboembolic events)
- Aseptic meningitis syndrome (AMS) (SC use)
- Interference with serological testing

Transmissible agents (Parvovirus B19)

- Invade red blood cell precursors in the bone marrow.
- Immunocompromised patients (organ transplant, HIV etc.) are prone to complications that affect the nerves, joints or bloodstream
- **Fifth disease**
- **Anemia**

Important aspects for plasma derived medicinal products

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2011
EMA/CHMP/BWP/706271/2010
Committee for medicinal products for human use (CHMP)

Guideline on plasma-derived medicinal products

Draft Agreed by Biologics Working Party	February 2009
Adoption by CHMP for release for consultation	19 March 2009
End of consultation (deadline for comments)	30 September 2009
Agreed by Biologics Working Party	June 2011
Adoption by CHMP	21 July 2011
Date for coming into effect	1 February 2012

This guideline replaces Note for Guidance on Plasma-Derived Medicinal Products CPMP/BWP/269/95, rev.3 dated 25 January 2001 (Doc. Ref. CPMP/BWP/269/95).

Keywords	*Plasma-derived medicinal products, collection and control of starting materials (plasma master file), manufacture, quality control, process validation, virus safety and stability*

- Use of detergent to remove enveloped viruses (HIV, HepB, HepC, etc..): Triton X
- Possibility of toxic residues from chemicals used in the process
- Non-removal of some non-enveloped viruses (parvovirus B19)

2-[4-(2,4,4-trimethylpentan-2-yl)phenoxy]ethanol (Triton X)

Regulatory process names 1 IUPAC names 28 Trade names 1 Other names 4 Other identifiers 19 ↓Groups:

Substance identity

EC / List no.: 618-344-0

CAS no.: 9002-93-1

Mol. formula:

Hazard classification & labelling

Danger! According to the classification provided by companies to ECHA in **CLP notifications** this substance is very toxic to aquatic life with long lasting effects, is very toxic to aquatic life, causes serious eye damage, is harmful if swallowed and causes skin irritation.

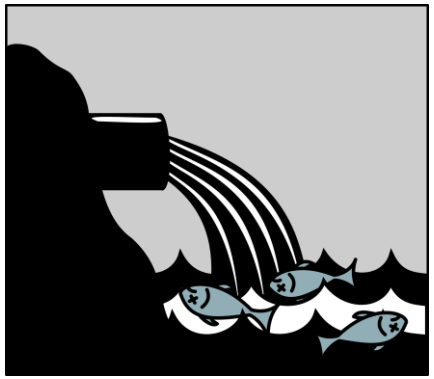
Properties of concern

ED Endocrine Disrupting

Important to know

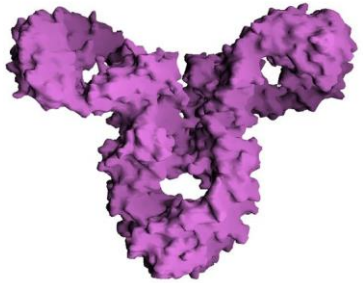
- Substance of very high concern (SVHC) and included in the candidate list for authorisation.
- Substance of very high concern requiring authorisation before it is used (Annex XIV of REACH).

Is further increasing the plasma supply the solution?



Manufactured using detergent (such as Triton X – endocrine disruptor)

Immunoglobulins usually given to treat side effects of medicines/vaccines



Evangeline Gallagher, special to ProPublica

Pharmaceutical Companies Are Luring Mexicans Across the U.S. Border to Donate Blood Plasma

Around 40 % of plasma imported from the US

Off label use of immunoglobulins?

EMA

EMA workshop on immunoglobulins 5 March 2025

The aims of the workshop were:

- To present the current regulatory requirements for the clinical development of immunoglobulins in support of a marketing authorisation application.
- To present the **clinicians' / healthcare professionals' perspective on the use of immunoglobulins** and their view on established and new indications.
- To present perspectives from **industry and Health Technology Assessment bodies** on the use of immunoglobulins.
- Presentations published
- Video recording and meeting report will follow

Updated guideline release for public consultation

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Home > Clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg) - Scientific guideline

Clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg) - Scientific guideline

Share

This guideline describes the information to be included when a marketing authorisation application for SCIg/IMIg is made. It addresses biological data, pharmacokinetics, clinical trials and patient follow-up.

Human | Scientific guidelines

Page contents

- Current effective version - under revision
- Revision 2
- Revision 1
- First version
- Related content

Keywords: SCIg, IMIg, human normal immunoglobulin, primary and secondary immunodeficiency syndromes, hepatitis A prophylaxis, immunomodulation, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Current effective version - under revision

Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg) - Revision 1

Adopted
Reference Number: EMA/CHMP/BPWP/410415/2011 rev 1
Legal effective date: 01/02/2015

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 12 December 2024
2 EMA/CHMP/BPWP/496692/2023 rev 2
3 Committee for Medicinal Products for Human Use (CHMP)

4 Guideline on the clinical investigation of human normal
5 immunoglobulin for subcutaneous and/or intramuscular
6 administration (SCIg/IMIg)
7 Draft

Revised draft agreed by Haematology Working Party	25 October 2024
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8
9 This guideline replaces Guideline on the clinical investigation of human normal immunoglobulin for
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11 1).
12

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

13

Keywords	***SCIg, IMIg, human normal immunoglobulin, primary and secondary immunodeficiency syndromes, hepatitis A prophylaxis, immunomodulation, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).***

Provide comments to the GL by 31st May: EUSurvey
Provide comments to the CoreSmPC by 31st May: EUSurvey

Thank you

Caroline.voltz@ema.europa.eu

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Acknowledgment: Haematology working party - special thanks to Daniela Philadelphy

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Monitoring and mitigating shortages of medicines and management of public health emergencies/major events

EDQM STAKEHOLDER EVENT - PLASMA SUPPLY CONTINUITY

Increasing and improving plasma collection in Europe

Klaus Kruttwig

Medicines and Medical Devices Shortages Specialist

Shortages management in the EU

Improving the availability of medicines authorised in the EU is a key priority for the **European Medicines Regulatory Network** (EMRN)

Regulatory authorities - within and outside Europe - are increasingly **working together** to prevent shortages and to limit their impact whenever they occur

EMA extended mandate: Monitoring and mitigating shortages of critical medicines

The EMA's role in **crisis preparedness and management** in reference to availability of medicinal products has increased significantly following the outbreak of the Covid-19 pandemic. **Regulation 2022/123** formalises the structures and processes established during the pandemic.

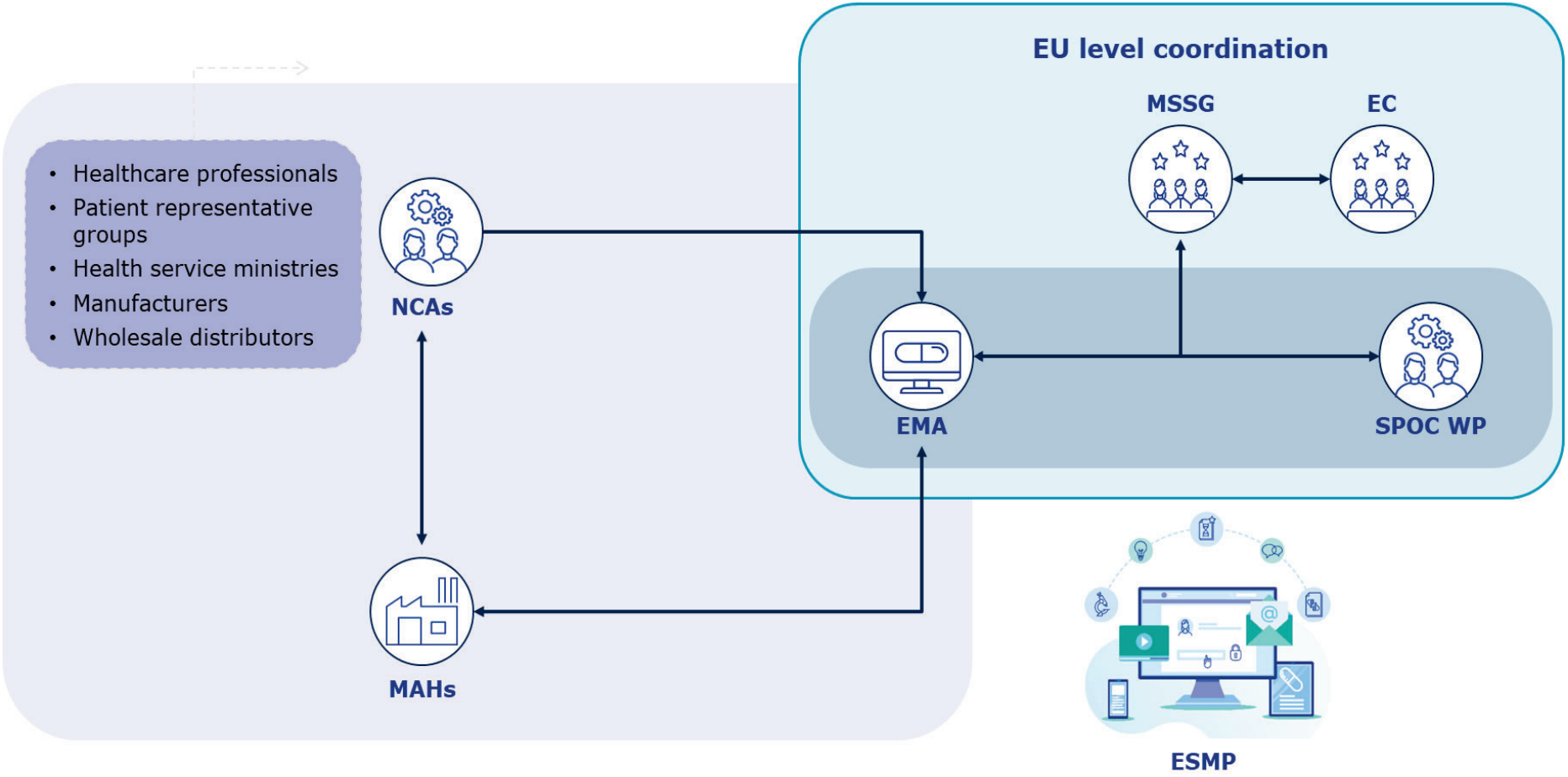
Provides a framework for activities established by the European Medicines Agency to monitor and **mitigate potential and actual shortages of medicines**

Sets **processes/tools for shortages reporting** and coordinates **responses** of EU countries to shortages of critical medicines during crisis and for monitoring of events which might lead to a crisis situation.

Established the "**Medicines Shortages Steering Group**" (MSSG) supported by the **SPOC Working Party** and a Network of contact points from pharmaceutical companies (MAH i-SPOCs)

Establishment of the **European Shortages Monitoring Platform** (ESMP) in January 2025

National and EU level coordination



Mitigating the impact of medicines shortages

International cooperation

Global Regulatory Working Group on Drug Shortages

- Meets every quarter and share information about relevant drug supply issues (exchange of information and support each other)
- International cooperation on Drug Shortage Reporting, Signal Detection and Signal Assessment
- International cooperation and alignment on shortage mitigation and prevention strategies

Bilateral exchanges with e.g. FDA, HC, TGA, etc.

- Shortages of concern to both regions
- Exchanges of best practices to mitigate and prevent shortages

MSSG Solidarity Mechanism

The VSM is used as a **last resort** to **temporarily alleviate critical shortages** in a Member State.

VSM allows a MS to **request assistance** from other Member States in obtaining stocks of a medicine during **critical shortages.**

7 VSM procedures concluded in 2024, all successfully

Conditions:

1. EMA already notified of the shortage (SPOC WP)
2. No or insufficient therapeutic alternatives available
3. Insufficient quantifies to treat critical indications
4. No or insufficient relief from short-term measures
5. Urgency (e.g., < 1 month supply)

MSSG Solidarity mechanism process (europa.eu)

MSSG Toolkit

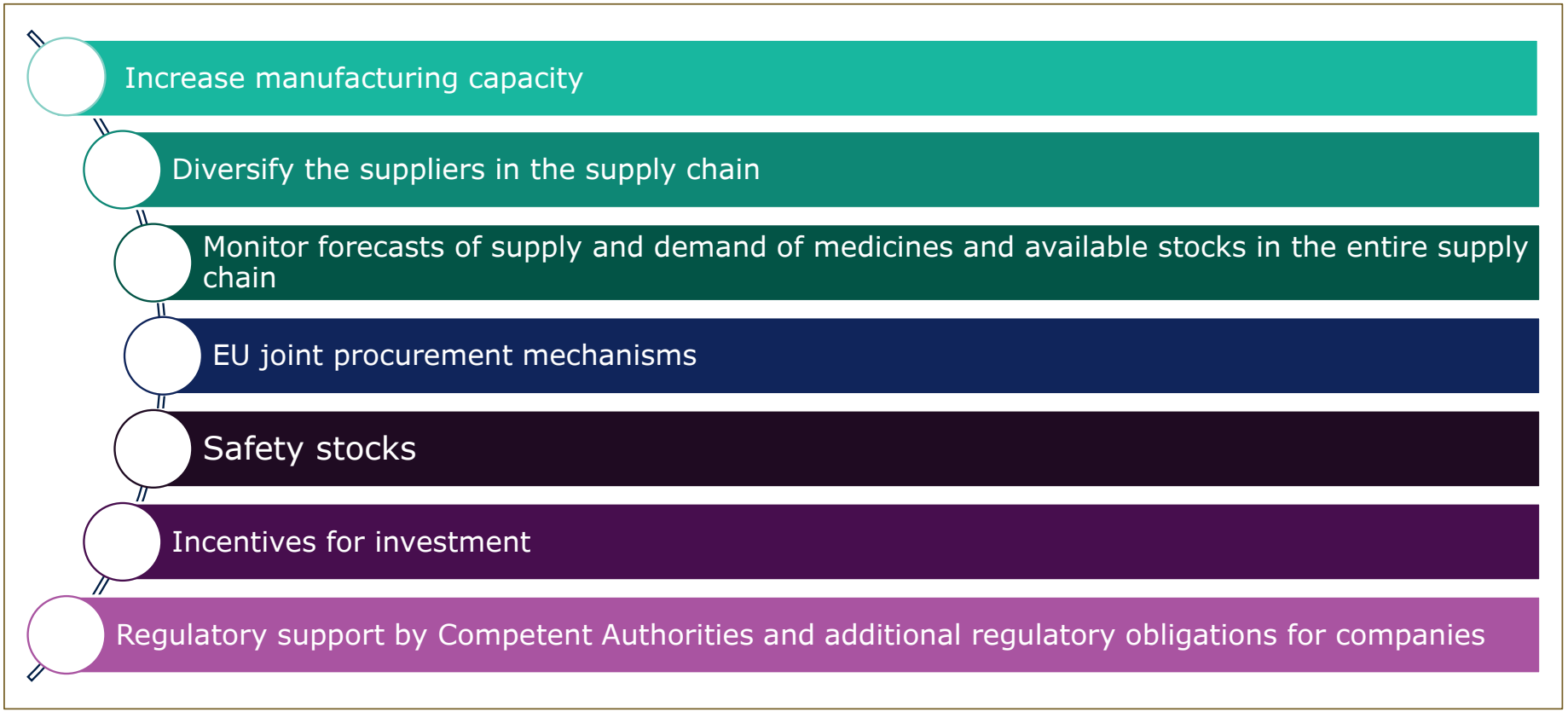
Regulatory flexibilities

- Labelling exemptions
- Extension of shelf life
- Accelerating supply-critical variations
- Liaison with EDQM (CEP acceleration

MSSG recommendations toolkit (europa.eu)

Prevention of medicines shortages

Recommendations to strengthen supply chains of critical medicinal products



Union list of critical medicine

1. Ensuring medicines considered to be most **critical for health systems** are available at all times.

2. Critical medicines may be subject to coordinated Union level actions to **improve security of supply**.

3. Provide **industrial capacity/ support** where medicines' supply chain vulnerabilities and dependencies are identified.

4. **Recommendations to Industry** on *"diversification of suppliers and inventory management"*

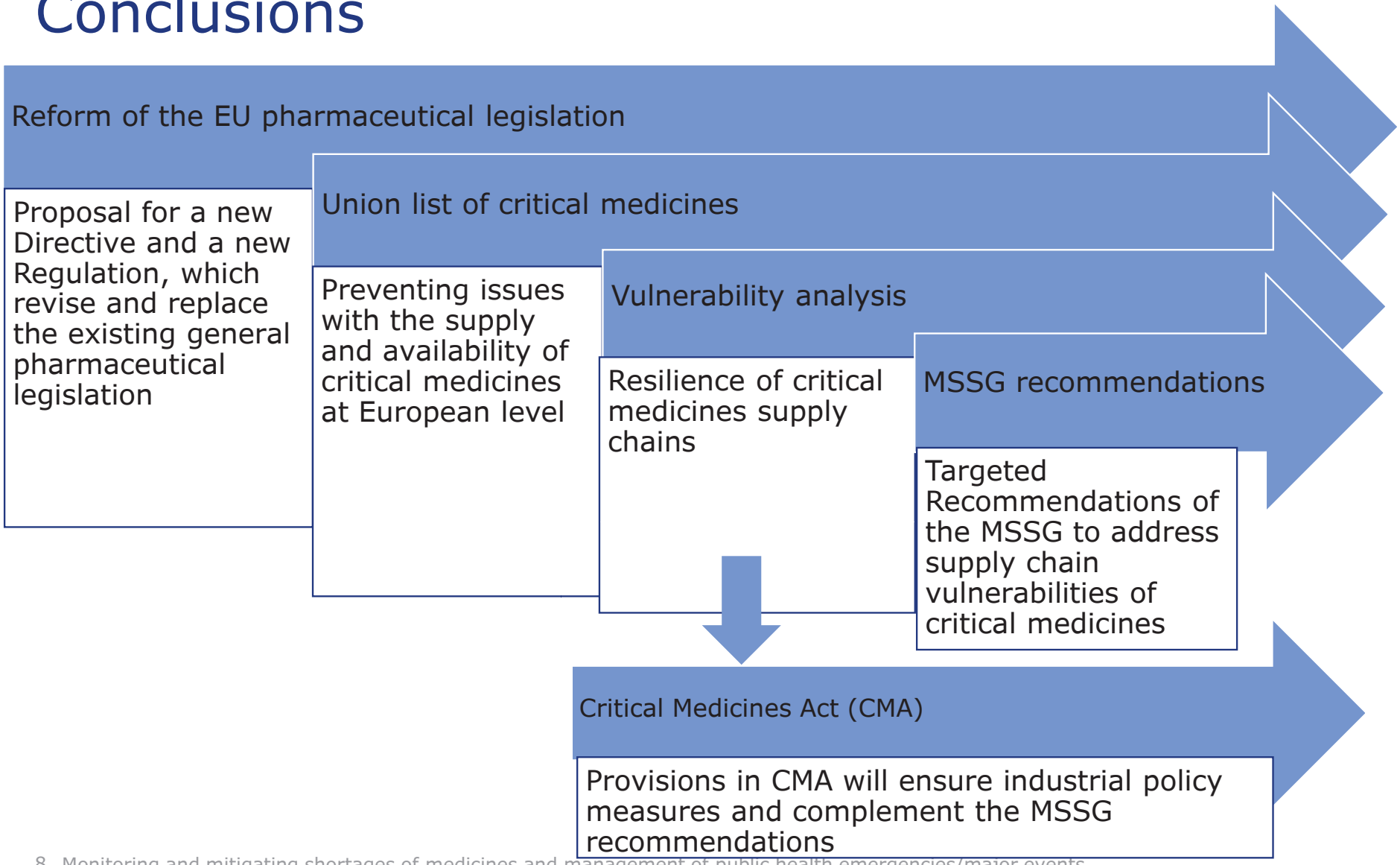
[Union list of critical medicines]

EMA/536385/2024
16 December 2024

Union list of critical medicines - version 2

ATC level 5	ATC description The Anatomical Therapeutic Chemical code	Date of inclusion
J06BA01	HUMAN NORMAL IMMUNOGLOBULIN	1 December 2023
J06BA02	HUMAN NORMAL IMMUNOGLOBULIN	1 December 2023
J06BB01	HUMAN ANTI-D IMMUNOGLOBULIN	1 December 2023
J06BB02	HUMAN TETANUS IMMUNOGLOBULIN	1 December 2023
J06BB04	HUMAN HEPATITIS B IMMUNOGLOBULIN	16 December 2024
J06BB05	HUMAN RABIES IMMUNOGLOBULIN	1 December 2023

Conclusions



Conclusions

- The MSSG, supported by the SPOC WP, continues to ensure a robust response to medicine supply issues under **preparedness activities and during a major events/public-health emergencies**. It coordinates urgent actions within the European Union (EU) to manage medicine supply issues.
- **Shift** from a reactive (**management**) approach to a proactive (**prevention**) approach to ensure supply of medicines.
- **New EU pharmaceutical legislation** proposal currently under negotiation, together with the initiatives foreseen in the **European Commission Communication on tackling medicine shortages in the EU, including the Critical Medicines Act** will further reinforce security of supply for critical medicines and prevention of shortages.
- EMA continues to monitor critical shortages of immunoglobulins, including through the SPOC WP and the dedicated subgroup.
- The MSSG is finalising a set of recommendations addressing the supply and vulnerability constraints.

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Thank you

klaus.kruttwig@ema.europa.eu

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Collection of anti-D plasma in Europe

EBA/EDQM joint survey

Dragoslav Domanović, MD, PhD,

EBA Medical Director

Safe blood for Europe

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BLOOD
ALLIANCE

- Declaration of Interest

I have no conflict of interest to declare

EUROPEAN BLOOD ALLIANCE

Introduction

- **Reported shortages in the USA**
- A multifactorial situation affecting supply and including the shortage of an active ingredient and some manufacturing issues experienced at the manufacturing site.
  - FDA - CBER-Regulated Products: Current Shortages, December 2024 and February 2025
  - American Society of Health-System Pharmacists Drug Shortages (ASHP) in July 2024 and February 2025
- **Reactions in the USA**
  - Recommendations on the appropriate use of prenatal prophylaxis and use of IgG anti-D in situations of shortages
  - AABB: Paper
- **Plasma for the production of IgG anti-D is predominantly collected in the USA**
- **No clinically effective monoclonal or recombinant products**
- **Geopolitical situation**

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EBA/EDQM joint survey

Purpose

EBA/EDQM launched a short joint survey to gain insights into the current state of anti-D plasma collection as well as the possibilities for initiating anti-D plasma collection in Europe

Survey

The questionnaire was distributed to EBA and EDQM members. Survey period 30 October 2024 – 6 December 2024

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Responses received

1	Belgium	Service du sang croix rouge francophone de Belgique
2	Croatia	Croatian Institute of Transfusion Medicine
3	Czech Republic	Ministery of Health
4	Denmark	Department of Clinical Immunology, Capital Region, University Hospital, Copenhagen, DK
5	Denmark	Organisation of Transfusions Centres in Denmark (OTCD)
6	Estonia	North Estonia Medical Center
7	Finland	Finnish Red Cross Blood Service
8	France	EFS
9	Hungary	Hungarian National Blood Transfusion Service
10	Ireland	Irish Blood Transfusion Service
11	Italy	Italian National Blood Centre
12	Italy	Italian NAtional Blood Centre - National Institute of Health
13	Latvia	State Blood donor center of the Republic of Latvia
14	Luxembourg	Croix-Rouge luxembourgeoise
15	Netherlands	Sanquin
16	Northern Ireland	Northern Ireland Blood Transfusion Service
17	Norway	Norwegian Medical Products Agency
18	Poland	National Blood Centre of Poland
19	Slovenia	Slovenian Institute for Transfusion Medicine
20	Switzerland	Trnsfusion Swiss Red Cross
21	Türkiye	Health Science University Diskapı Yildirim Beyazit Training and Research Hospital
22	United Kingdom	Joint Professional Advisory Committee (JPAC, for UK Blood Services)
23	Wales	Welsh Blood Service

23 responses from 19 countries

- **2 responses from Denmark**
- **2 responses from Italy**
- **For UK**
  - **JPAC for UK blood services**
  - **Northern Ireland**
  - **Wales**

EU- 16/27 (59%)
EU/EEA – 16/30 (53%)
CoEU – 19/39 (49%

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Q 1. Is there a program for anti-D-specific plasma collection in your country?

None of the countries surveyed has a program for anti-D-specific plasma collection

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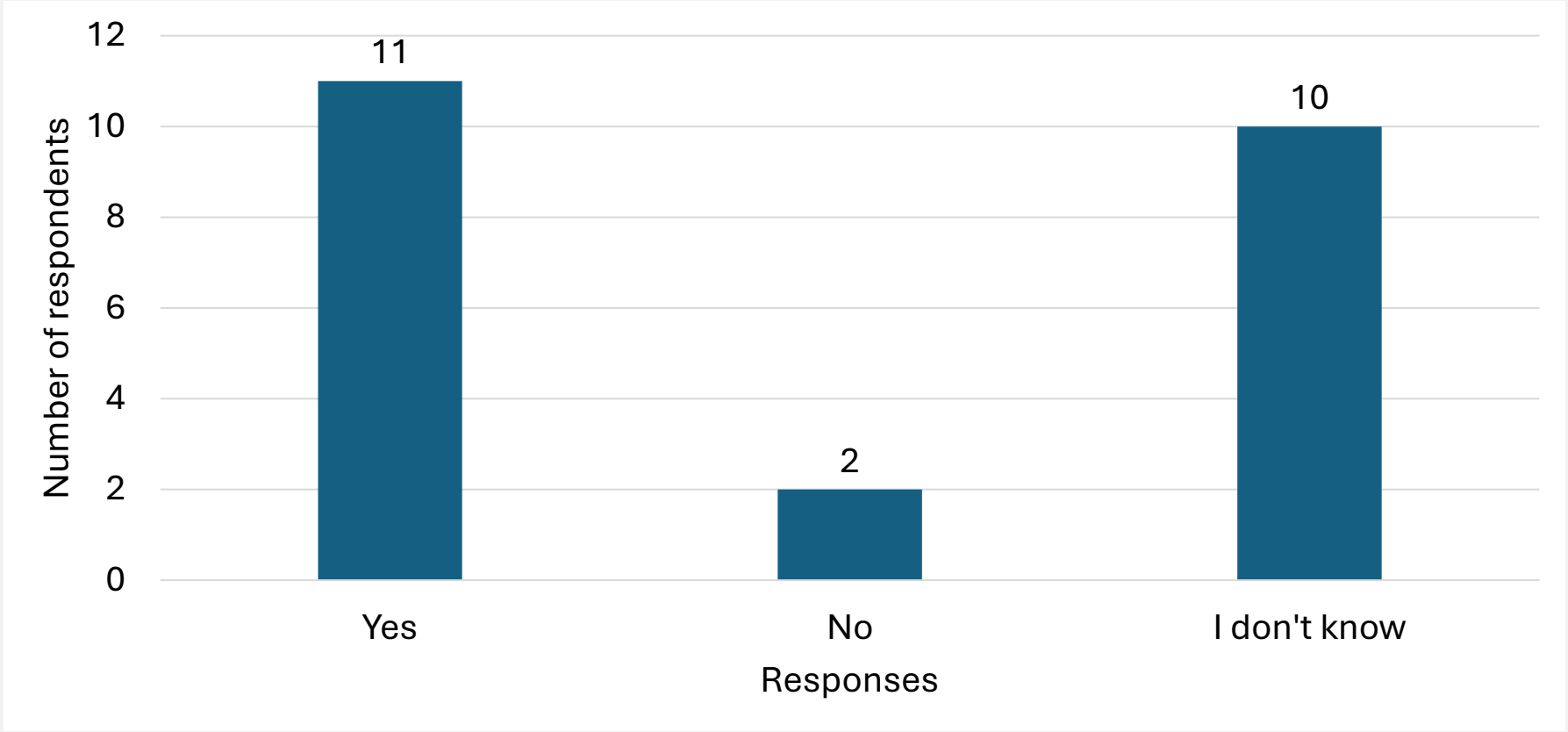
Q2. If NO, would you consider starting/restarting the program, which may contribute to a common European plasma pool in the future?



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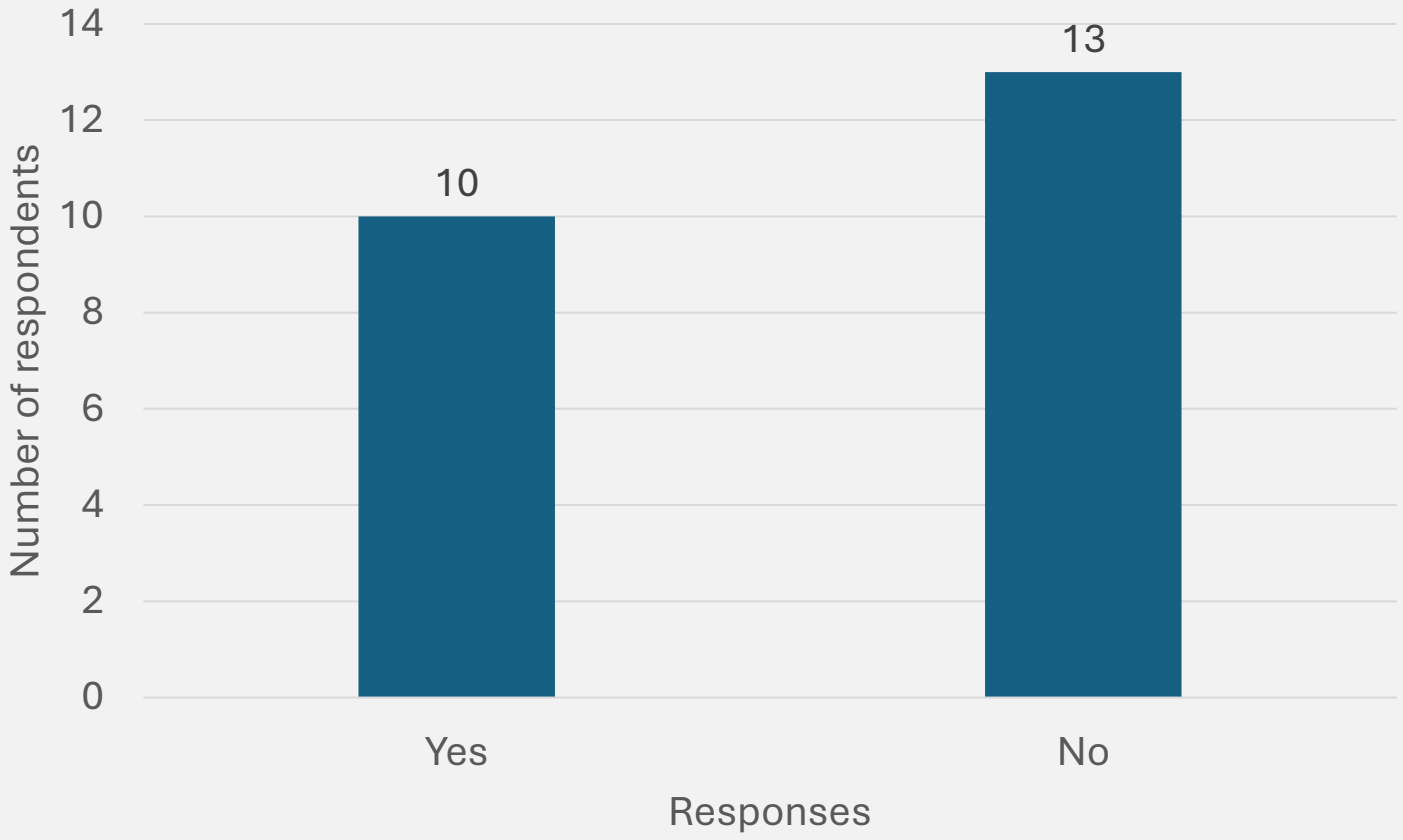
Q3. Has your Blood Establishment run an anti-D plasma collection in the past?



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Q4. If yes, could you please briefly describe it?

Regular program from 1960’ to 1990' (CZ, FI, NI, SI, UK, W)	6
Regular program from 1960'to 1982 (DK)	1
Regular program from 1960'to 2019 (NL)	1
Regular program terminated in 1990’ (F)	1
Experimental collection 1974 (EST)	1
Small local collections (500L planned for 2025) (PL)	1
Recombinant anti-D antibodies in development (DK)	1

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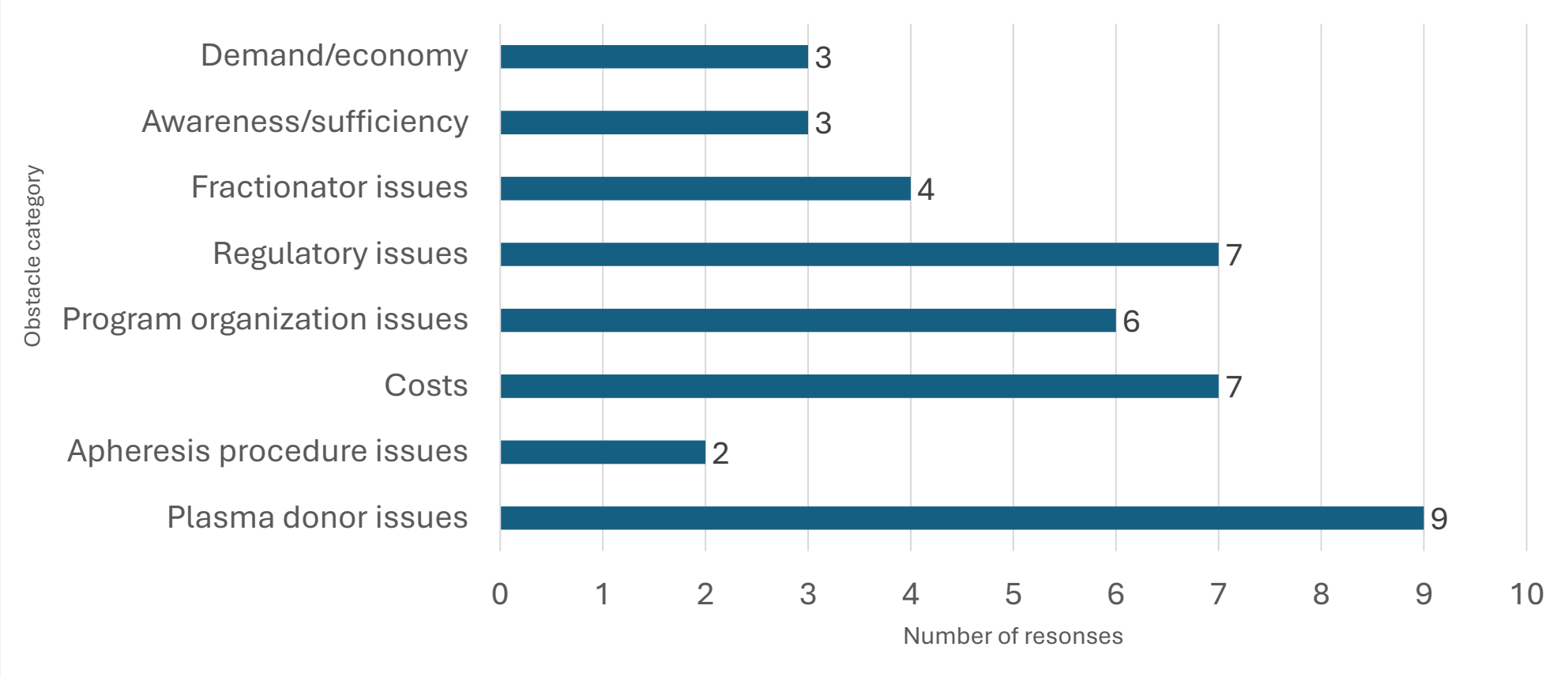
Q5. From your perspective, what are the main obstacles in developing/restarting such a program?



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Q5. From your perspective, what are the main obstacles in developing/restarting such a program? Details - A

Plasma donor issues	
• Recruitment and selection and remuneration/compensation (CRO, EST,UK)	3
• Donor immunization (CRO,CZ,EST,SI,UK)	5
• Limited number of naturally immunized donors (FI,NO,PL)	3
• Donor management (I)	1
Apferesis issues	
• Absence ot apheresis program in the country (IR)	1
• Present only at the central institution (FI)	1
Costs	
• Allocation of resources and/or adequate financial support (DK, I, CH)	3
• Costs to run the program, (NL, NO,PL)	3
• Time and resources (NI)	1
Program organization issues	
• Lack of experience and know-how (EST, NO)	2
• Training issues for the personnel involved (I)	1
• Capacity to establish a new programme (UK,NI)	2
• Organization difficulties (CRO)	1

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Q5. From your perspective, what are the main obstacles in developing/restarting such a program? Details-B

Regulatory issues	
• Donors with Abs are not eligible to donate (EST)	1
• National legislative frameworks that prevent mixing plasma coming from other countries (I)	1
• Regulatory hurdles and governmental approval (CRO, CH,W)	3
• Donor immunisation program to be validated by Competent Authority (F, CH)	2
Fractionator issues	
• Small batches from national sources (CZ)	1
• Need for a new contract with the fractionator (EST)	1
• Willingness of the fractionator (F)	1
• Choice of the manufacturer and choice of the product type (NL)	1
Awareness/sufficiency	
• National and international awareness at the political, scientific and professional level (DK)	1
• Strategic adherence (CH)	1
• Self-sufficiency (TR)	1
Demand/economy	
• Bussiness model not so impressive (DK	1
• Reducing demand by foetal DNA screening (UK, NI)	2

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Q6. Other remarks.

Recruiting of small numbers of donors needed for national self-sufficiency seems to be possible (CZ)
Initiate a scientific-technical innovative collaboration in the context of EBA, EDQM or WHO, by • Sharing of quality assurance standards, programs, and thoroughly tested biological material for anti-D immunization that would reduce the time for implementation of real-world immunization activities and maximize safety for involved donors. • Scaling up RhD-immunization of voluntary D-negative donors, collecting anti-D-rich plasma from immunized donors, further processing, and clinical use of purified IgG anti-D immunoglobulin. • EU collaboration could pave the way for a common and standardized high-quality solution for all steps. • An EU scientific program in the context of EIC Pathfinder or the like should be considered, for solving the outstanding issues. A **possible way forward would be the two activities pursued in parallel: i) immediate production of a polyclonal human anti-D and ii) developing a monoclonal anti-D to replace the polyclonal preparation in due time. (DK)**
Collecting information for the introduction of an anti-D specific plasma collection program (H)
Defiine the best practices for use of anti-D. Low dose necessary to limit use early in pregnancy. Is it 1500 IU necessary; or 1000IU (NL)
Northern Ireland is due to implement in house fetal DNA screening to reduce demand on anti-D. (NI)
The supply of anti-D IG has always been low on the list of priorities, despite its importance and the reliance on importation. Establishing the plasma collection program was a priority so anti-D plasma remained relatively low on the radar. **Weakness and shortages in the supply chain for the non-invasive foetal RHD test kits** (e.g. shortage due to competing with the manufacturing of COVID-19 test kits during the pandemic) may cause a reduction in foetal D typing that would increase demand for anti-D in countries where such testing has been implemented. (UK –JPAC)

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Conclusions I

Currently, no surveyed countries have programs for collecting anti-D-specific plasma. This makes the supply of anti-D products vulnerable to possible shortages. However, several European countries are interested in starting or reviving these collections, while others remain undecided. The main challenges include donor-related issues, costs, and various organizational and regulatory hurdles.

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Possible paths forward

1. Establish anti-D plasma collections across Europe
   a. shared “blueprint” as to how best to proceed regarding donor recruitment and safe immunisation strategies
   b. Exploring the potential for a common “European” batch of anti-D plasma for fractionation
2. Support the development of monoclonal/recombinant anti-D products
3. Optimize prenatal screening and prophylaxis policies
   a. Foetal DNA screening and appropriate dosing of anti-D prophylaxis
4. Establish a common EU recommendation for using IgG anti-D during potential shortages

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List of nationally authorised products containing human anti-d immunoglobulin in the EU/EEA MS

Product Name	Producer	EU/EEA Member State
Rhophylac 300 µg	CSL BEHRING	AT, BE, CY, CZ, DE, ES, FR, GR, HU, IE, IS, IT, LU, MT, NL, PL, PT, RO, SI, SK, XI
Rhophylac 200 µg		BE, DE, FR, IS, IT, LU, NL, PT,
Rhophylac		DK
Rhesonativ 625 IU/ml	OCTAPHARMA	AT, BG, CY, CZ, EE, FI, FR, HR, HU, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK,
Rhesonativ 750 IU/ml		BG, HU, PL, PT, RO, SE, SI, SK,
Rhesonativ 300 µg		DE, LU
Rhesonativ		DK
RhoGAM Ultra-Filtered PLUS 50 µg	KEDRION	BE,
IMMUNORHO 300 µg		IT,
IMMUNORHO 200 µg		IT
RhoGAM Ultra-Filtered PLUS 300 µg		LU, RO
D-Gam 250 µg/ml	BIO PRODUCTS LABORATORY	CY, XI
D-Gam 50 µg/ml		XI

EMA. Human Medicines Division. List of nationally authorised medicinal products. Active substance(s): human anti-d immunoglobulin. Procedure No. PSUSA/00001614/202403. 31 October 2024

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Rh Immune Globulin Consumption in Europe (200 to 300 mcg Vials/Syringes x 000)

Total Europe	2005	2008	2014
Vials (000)	1,057.3	1,173.4	1,286.6
Population (MM) *	505.9	510.7	517.6
Vials/Syringes/Capita	2.1	2.3	2.5

MRB

To produce 1,286,600 vials of IgG anti-D, we need 128,660 plasma donations each year. This can be achieved with 32,165 donors, each donating 4 times annually.

Anti-D plasma: $675 per liter on average, compared to $725 in 2024, for a titer of 45-50 mcg/ml.

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Approximate need for anti-D IgGs and anti-D plasma in the European Union.

- To protect ~440,000 RhD-negative pregnant women carrying RhD-positive babies, the EU needs approximately 44,000 donations of anti-D plasma (~26,400 litres of plasma at 600 ml per donation). This amount is needed in the case of prenatal foetal RhD typing and can be collected from 11,000 donors donating four times a year or approximately ~25 donors per million population.

Assumptions

- Number of live births in the EU 2023*.....3,667,000
- Abortions per 1000 live births in the EU 2022.....199 (~ 20%= 729,335)
- Assessed number of pregnancies (A+B) 4,394,335
- Proportion of RhD-negative women carrying RhD- positive foetus = 10 % of all pregnancies**
- Approximate number of pregnancies requiring anti-D prophylaxis (C X D) = 439,433
- Number of anti-D doses from 1 plasma donation = 10 (One plasma donation => 10 vials of 300ug/1000 IU) ***
- Number of necessary plasma donations E/F = 43,943
- EU population in 2023 was 448.803.000
  - *Eurostat
  - **Chilcott, J., Lloyd Jones, M., Wight, J. et al. (4 more authors) (2003) *A review of the clinical effectiveness and cost-effectiveness of routine anti-D prophylaxis for pregnant women who are rhesus-negative*. Technical Report. Core Research, Alton.
  - *** Ellen van der Schoot
  - **** Eurostat https://ec.europa.eu/eurostat/web/interactive-publications/demography-2024#growing-population

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- Conclusion II

Ensuring a continuous and secure supply of IgG anti-D products is crucial for Europe. There are viable options for achieving this through collecting anti-D plasma across Europe and supporting the development of effective monoclonal or recombinant products. This will require collective action and commitment from all European stakeholders, including fractionators, as well as the allocation of financial resources and political support.