Ref. Ares(2024)4531693 - 24/06/2024

European Commission

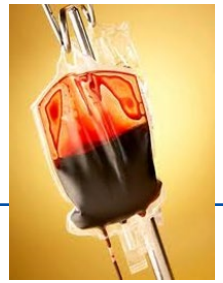
A new EU Regulation on standards of quality and safety for substances of human origin intended for human application

MDCG meeting

May 13 2024

Health

Current EU legislation on safety and quality of substances of human origin



Transfusion

Medicines

Bone marrow transplant

MAR

Tissue transplantation

BLOOD & PLASMA

TISSUES & CELLS

EU legislation since 2002
(4 Directives)

EU legislation since 2004
(4 Directives)

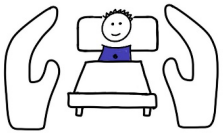
ORGANS

EU legislation since 2010
(2 Directives)

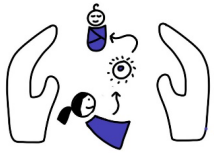
European Commission

Evaluation of the Blood, Tissue and Cell legislation - published in 2019

Overall – the legislation led to increased safety and quality of BTC but gaps and shortcomings were identified



1. Patients are not fully protected from avoidable risks because some rules are out of date



2. Legislation does not mitigate risks for BTC donors and for children born from donated eggs, sperm or embryos

3. Member States have divergent approaches to oversight

4. Full potential of innovative therapies is not reached for patients

5. Patients are vulnerable to interruptions in EU supply of some BTC

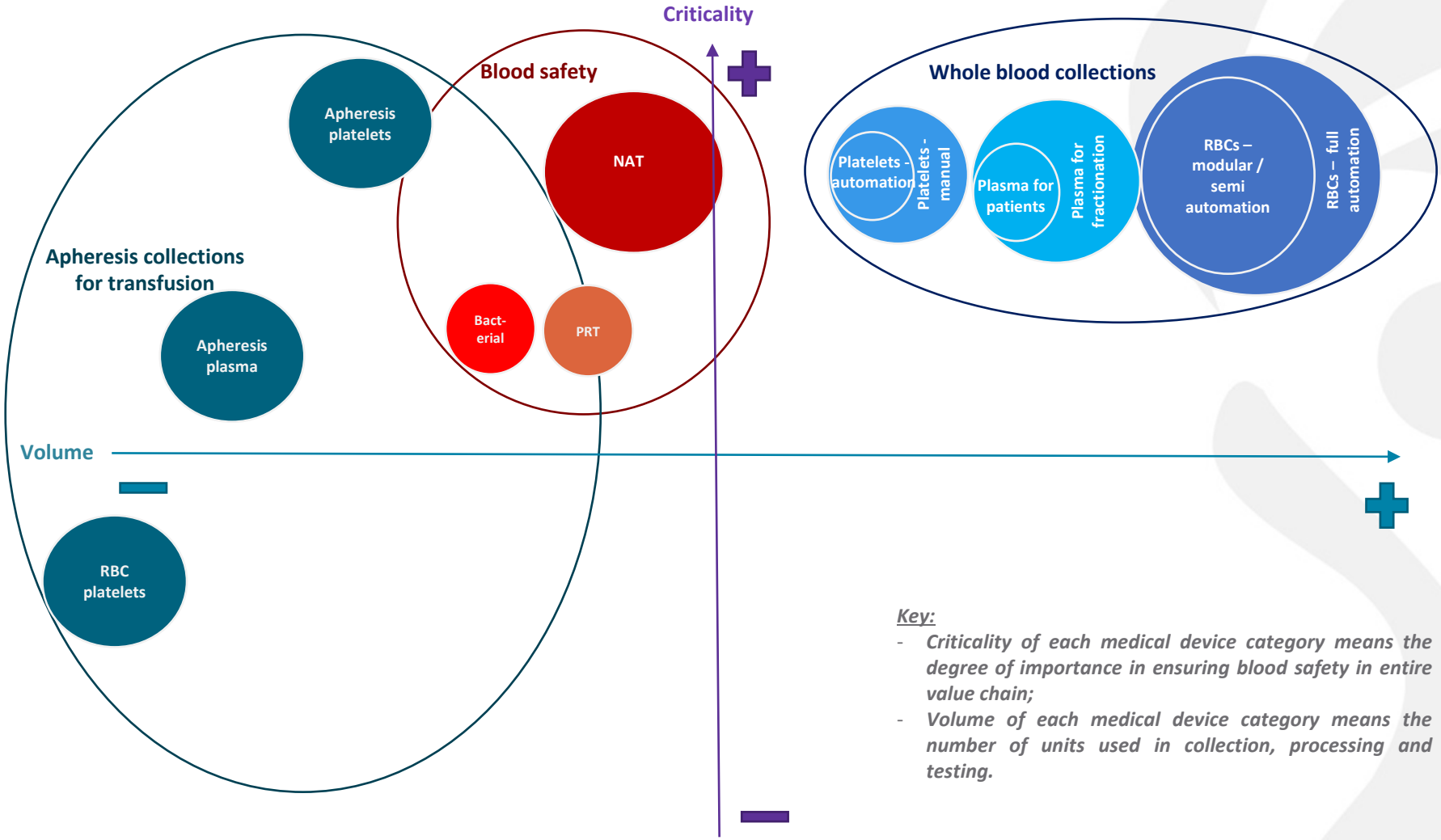
CoVID confirmed problems

European Commission

MD/IVD specific concerns

- Overall **dependency** SoHO sector on devices and diagnostics
- **Legal clarity** for combination products SoHO/MD and for SoHO starting materials for MD (e.g., collagen fillers)
- Need for **ad-hoc interactions** between vigilance systems in case of safety/quality alerts (e.g., Cryostor medium)
- Impact of EU legislation on **availability** MD/IVD that are essential for SoHO
  - blood bags – classification under new legislation + transition to DEHP-free bags
  - position paper EDQM working group views on IVD availability
  - Overall market failures and supply (collection kits bone marrow for paediatrics)
- Increasing **automation**, requires MD inputs for validation/authorisation SoHO authorities

What are the most critical MD for the blood supply



Key:

- *Criticality of each medical device category means the degree of importance in ensuring blood safety in entire value chain;*
- *Volume of each medical device category means the number of units used in collection, processing and testing.*

Increasing automation of SoHO activities, with MD

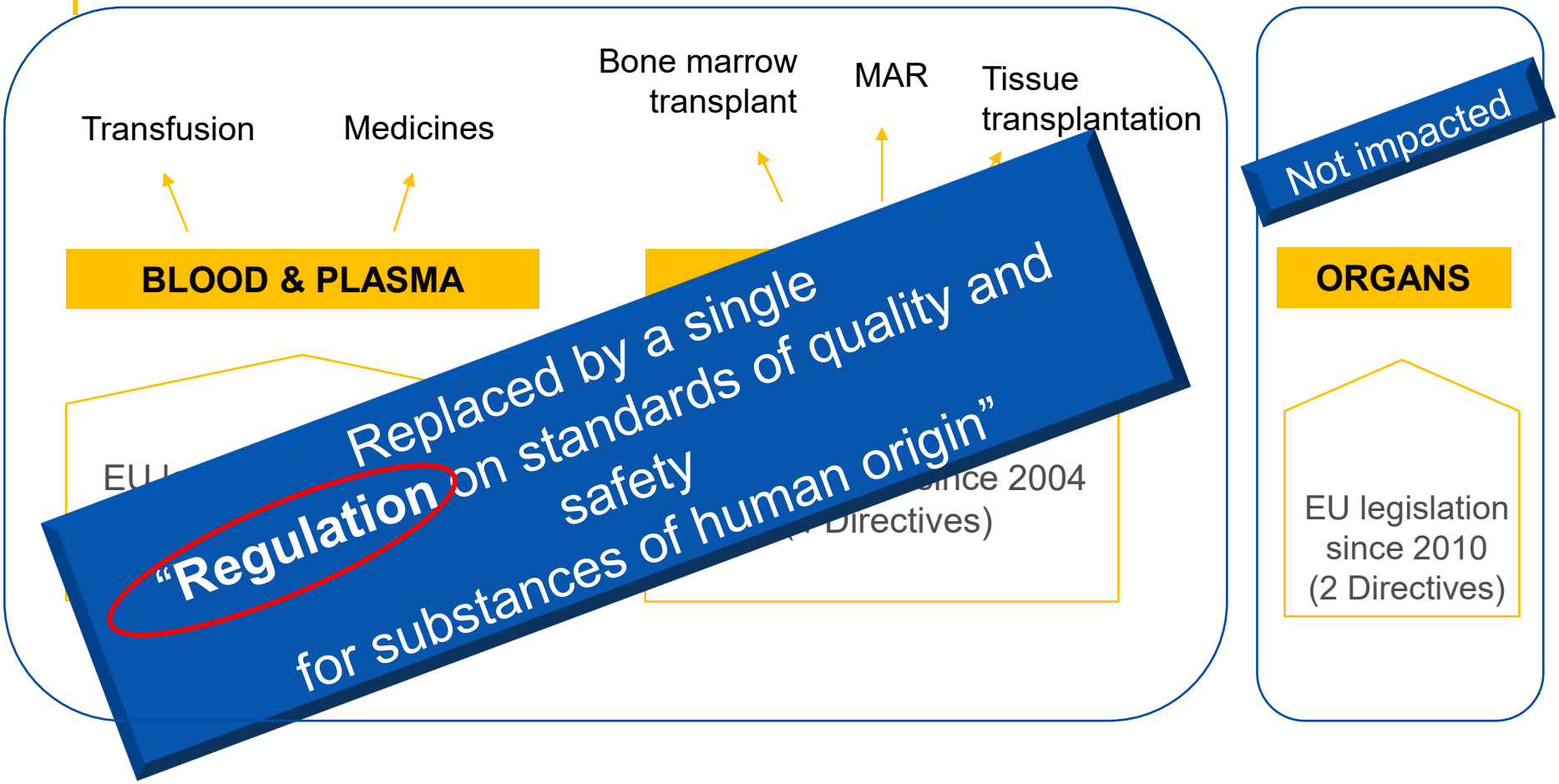
SoHO

Stem cell transplant

(CAR-T)

Figure 3 Advances in automated devices for stem cell differentiation improve standardisation, cost reduction and high-throughput capabilities. The CliniMACS Prodigy Platform from Miltenyi Biotec is a fully-automated, closed-system approach to generating differentiated cells

Commission proposal to revise the legislation



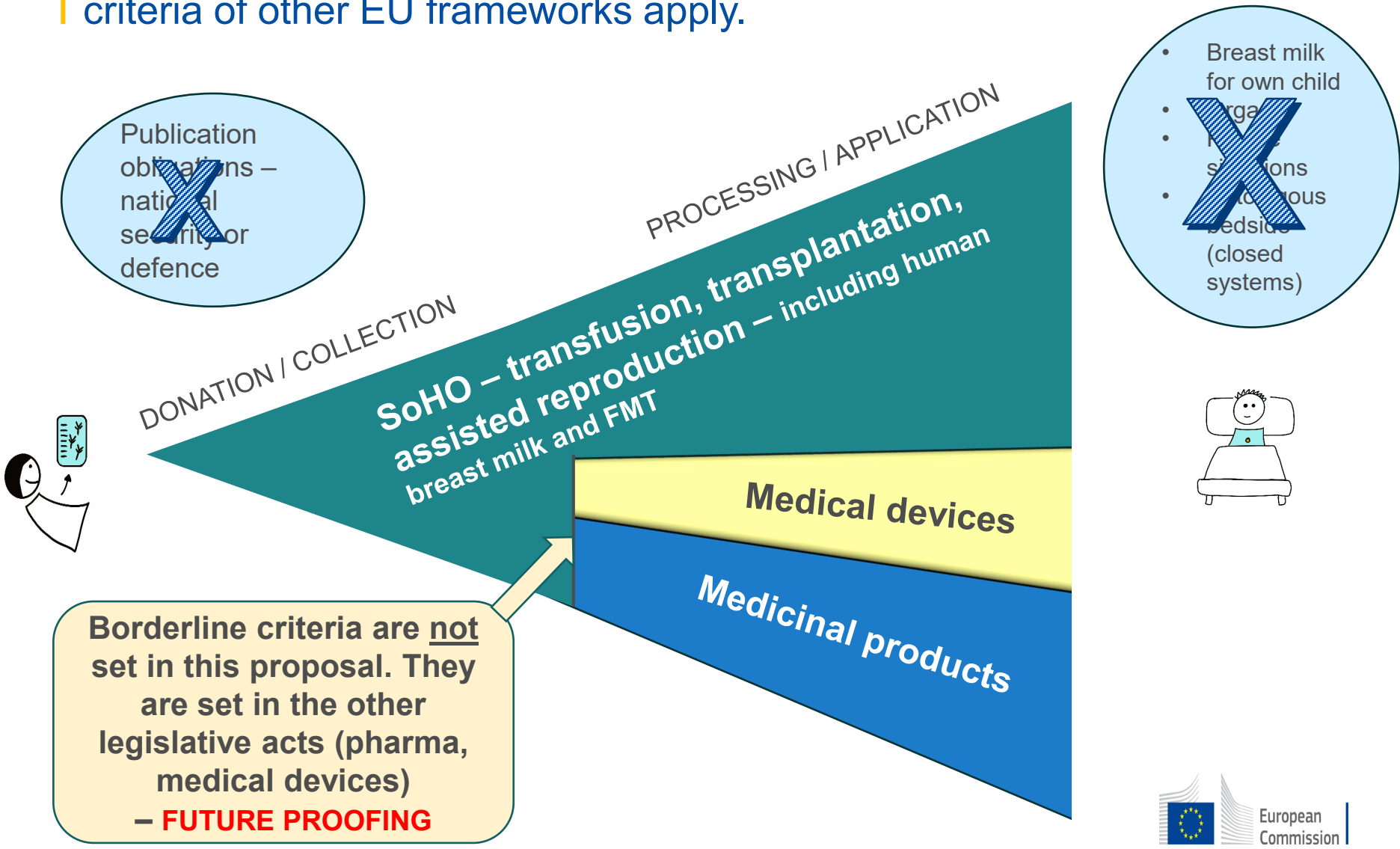
Key new and changed concepts

- **Scope and advice**
- **SoHO activities, entities and establishments**
- **SoHO Preparations and their authorisation**
- **Standards and hierarchy of technical guidelines**
- **Donor Protection and Voluntary Unpaid Donation**
- **Recipient and offspring protection**
- **Vigilance**
- **Supply continuity**
- **Digitalisation – the SoHO platform**

This presentation explains the concepts in the Regulation, as proposed by the Commission and amended during negotiations.

European Commission

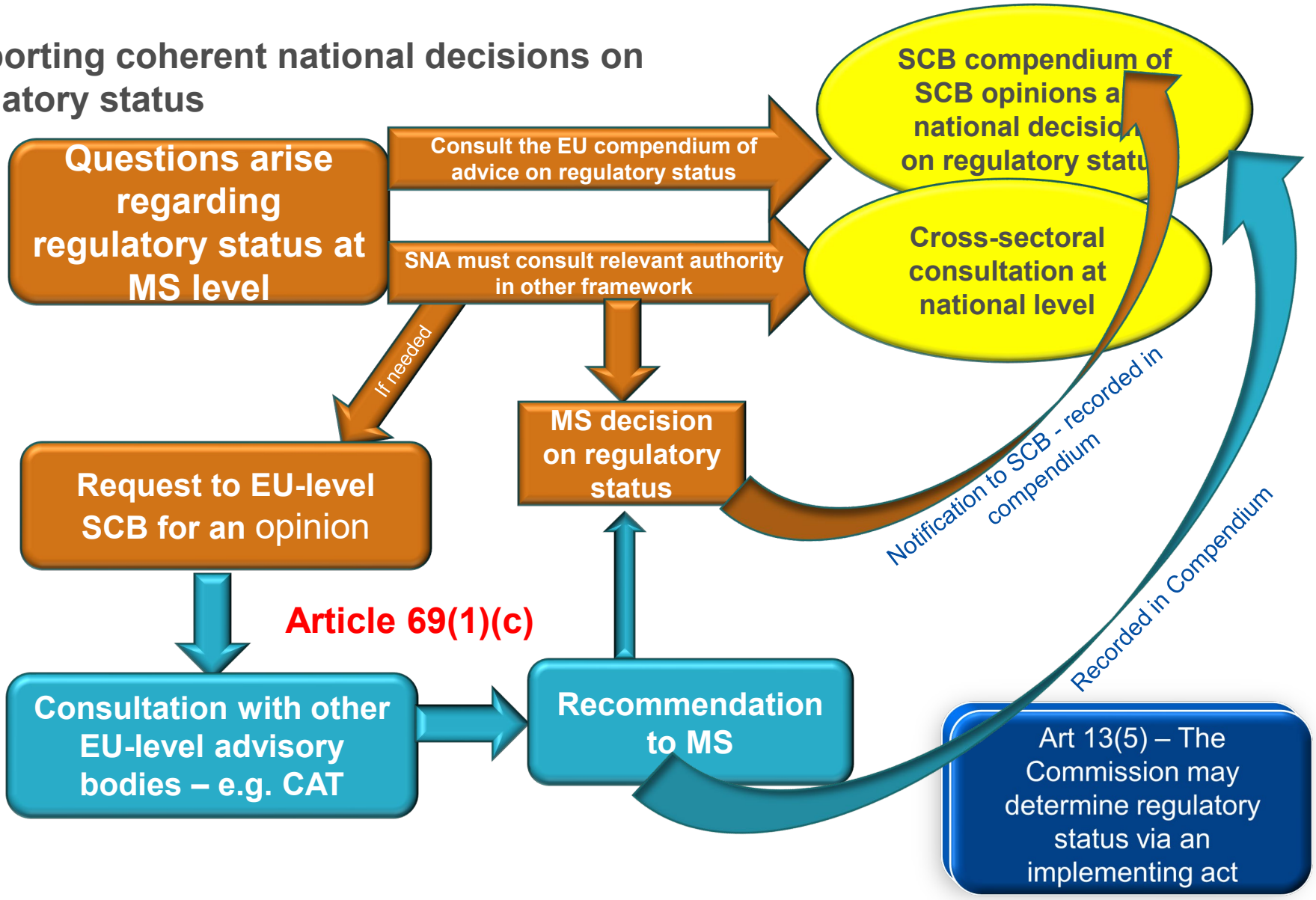
Scope: Regulation covers all steps for all substances originating from the human body for subsequent application to the human body (some limited provisions for autologous and 'in relationship' SoHO), unless scope criteria of other EU frameworks apply.



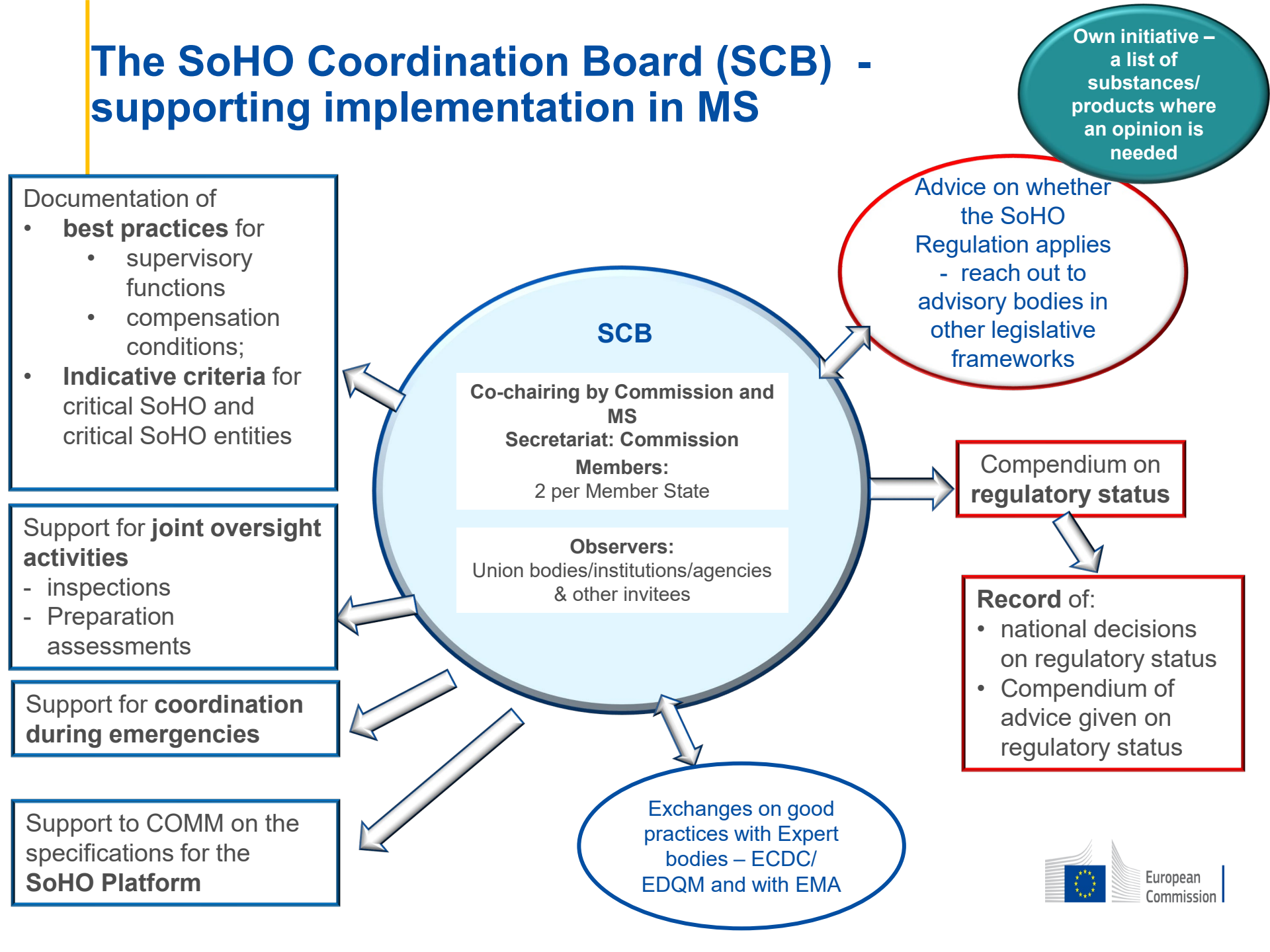
European Commission

Article 13: consultation and cooperation with authorities of other regulatory sectors

Supporting coherent national decisions on regulatory status



The SoHO Coordination Board (SCB) - supporting implementation in MS

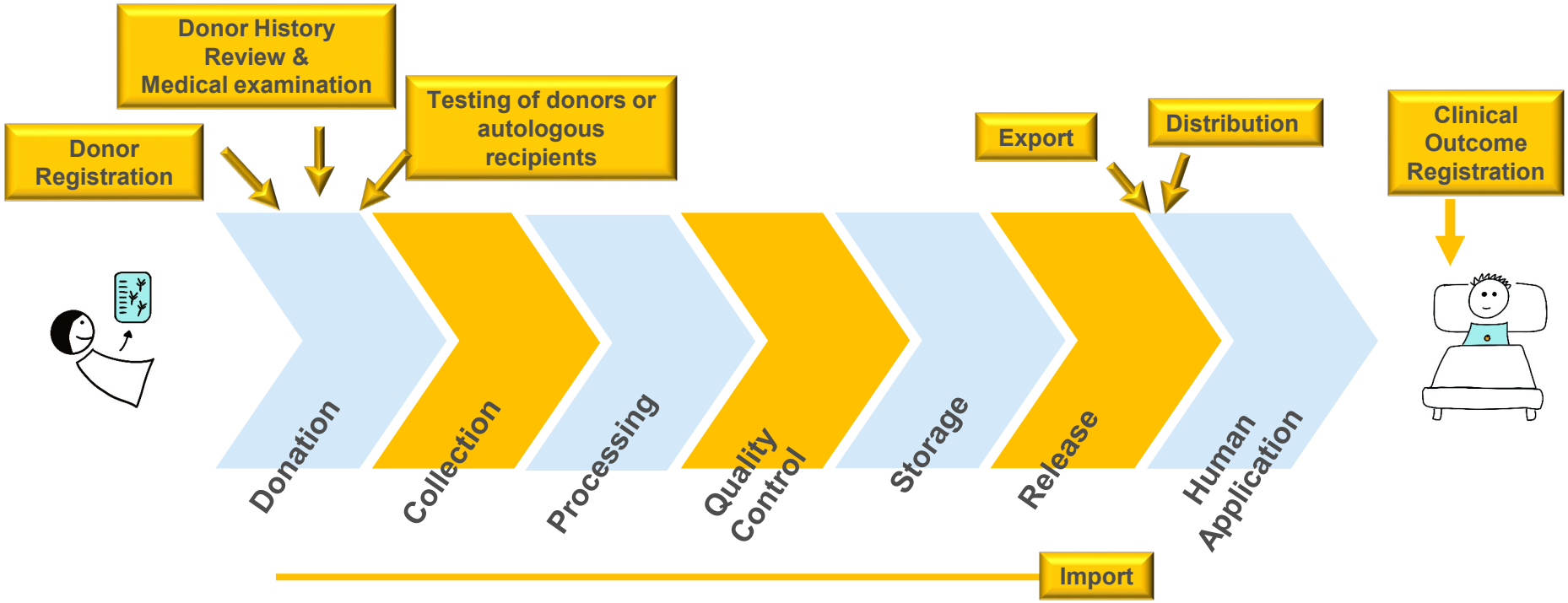


European Commission

Key new and changed concepts

- Scope and advice
- SoHO activities, entities and establishments
- SoHO Preparations and their authorisation
- Standards and hierarchy of technical guidelines
- Donor Protection and Voluntary Unpaid Donation
- Recipient and offspring protection
- Supply continuity
- Digitalisation – the SoHO platform

Supervision of all SoHO Activities that directly impact safety, quality or effectiveness



Any actor organising one or more SoHO activity/ies needs to register as SoHO entity with the Competent Authority

European Commission

….but risk-based oversight, ensuring efficient use of authority resources

A **SoHO entity** carries out **one or more SoHO activities**

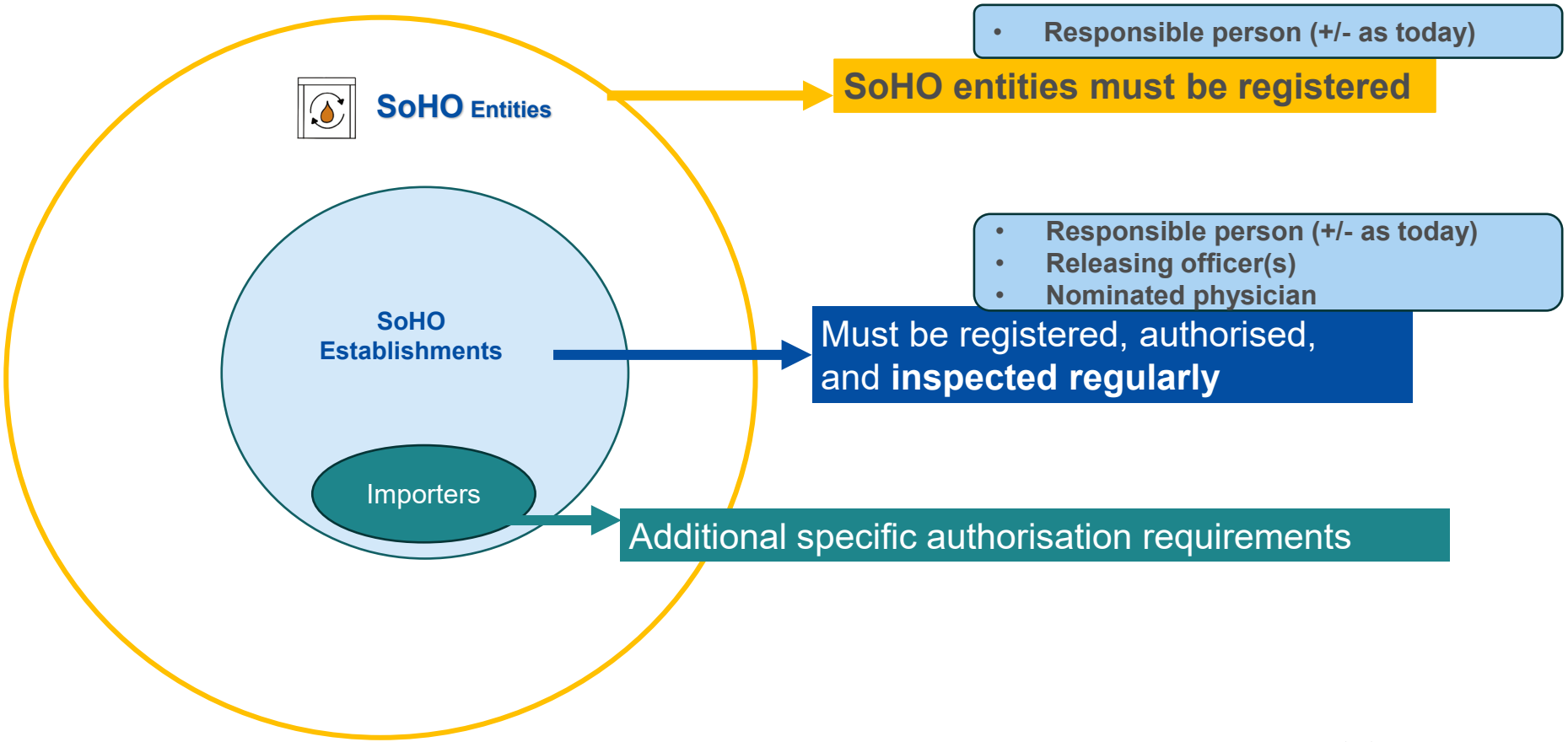
A **SoHO establishment is a SoHO entity that** carries out at least

- **Both processing and storage, or**
- **Release, or**
- **Import, or**
- **Export**

Note: ***CAs may regulate a SoHO entity as a SoHO establishment, even if it does not meet the criteria above, if it considers that the entity has a particularly important impact (e.g. a testing laboratory that tests donors for a whole region or country, a register that identifies and selects donors for one or more Member States).***

European Commission

The concept of **SoHO entities** and **SoHO establishments:** graded approach to oversight - high level of transparency



European Commission

Key new and changed concepts

- Scope and advice
- SoHO activities, entities and establishments
- SoHO Preparations and their authorisation
- Standards and hierarchy of technical guidelines
- Donor Protection and Voluntary Unpaid Donation
- Recipient and offspring protection
- Vigilance
- Supply continuity
- Digitalisation – the SoHO platform

SoHO Preparation Authorisation – robust evidence of safety and effectiveness

What is a 'SoHO Preparation'?

A particular SoHO that has been **subjected to processing,** and where relevant other SoHO activities, **has a specific clinical indication and is intended for immediate application to a recipient or for distribution.**

→ Must be **authorised**

EXAMPLE

SoHO	**SoHO Preparations**
Blood	Plasma
	Red blood cells
	Platelets

European Commission

What is meant by effectiveness?

For the field of SoHO, effectiveness reflects the 2 concepts embedded in the medicinal product and medical device legislative frameworks, depending on the substance

- a **measurable response** in the patient after human application ('efficacy')

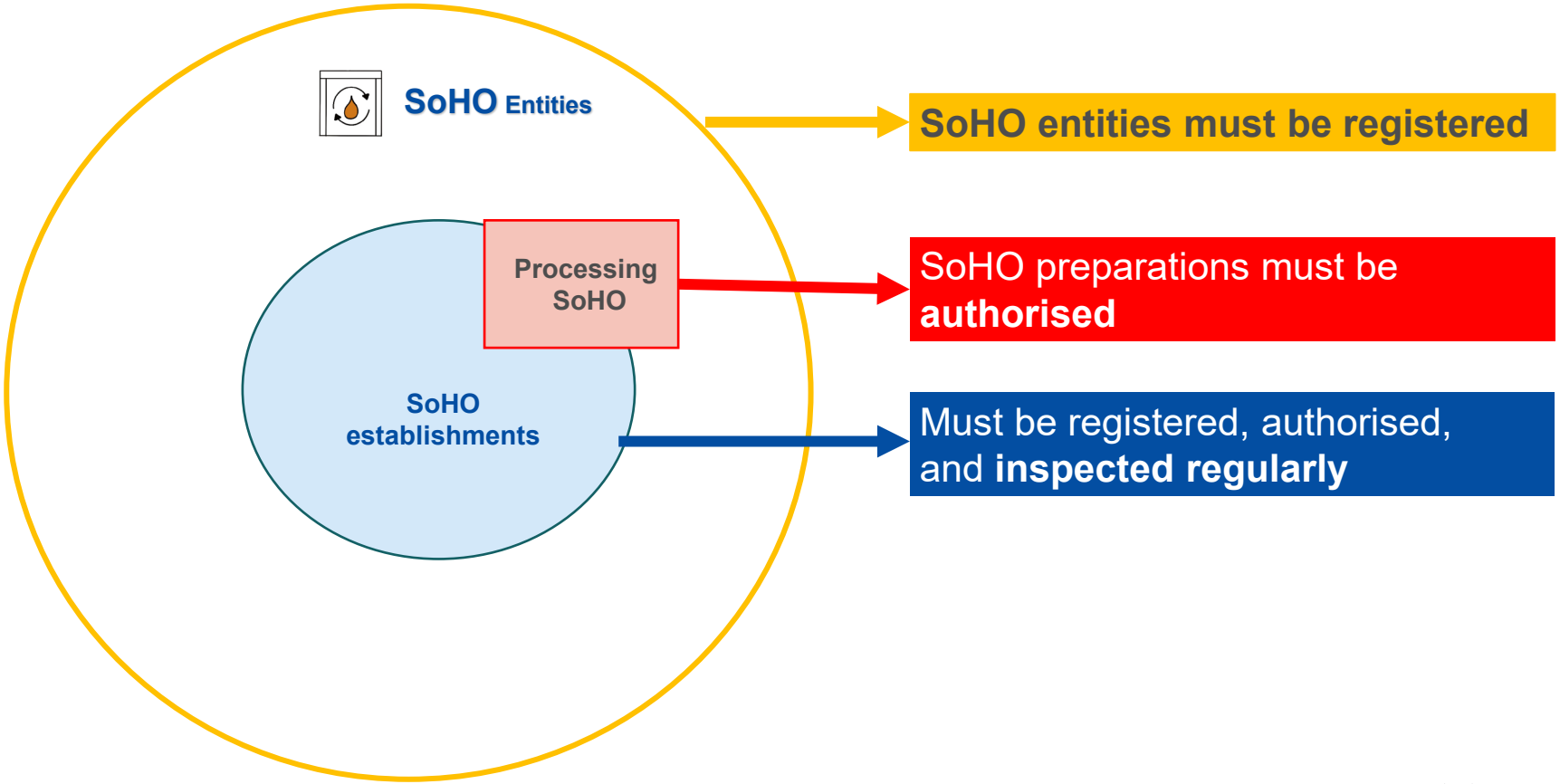
    e.g. bone marrow transplant

- **success or failure** of the SoHO after human application ('functionality')

    e.g. cornea transplant, live birth

European Commission

SoHO preparation authorisations will be held by SoHO establishments and by SoHO entities that process autologous SoHO next to the patient



European Commission

SoHO Preparation Authorisation

Taking into account any relevant EDQM monograph

1 Systematic Benefit:Risk Assessment to determine the evidence available on safety, quality and effectiveness

2 Submission of an application, including laboratory validation and other safety, quality and effectiveness data and, where relevant, a clinical outcome monitoring plan proportionate to risk

3 Assessment of the application by the competent authority

- Grant authorisation for the SoHO preparation
- **OR**
- Grant of an approval of the Clinical Outcome Monitoring plan
- **OR**
- Refuse authorisation

4 Assessment by the competent authority of evidence of safety, quality and effectiveness data gathered in clinical outcome monitoring

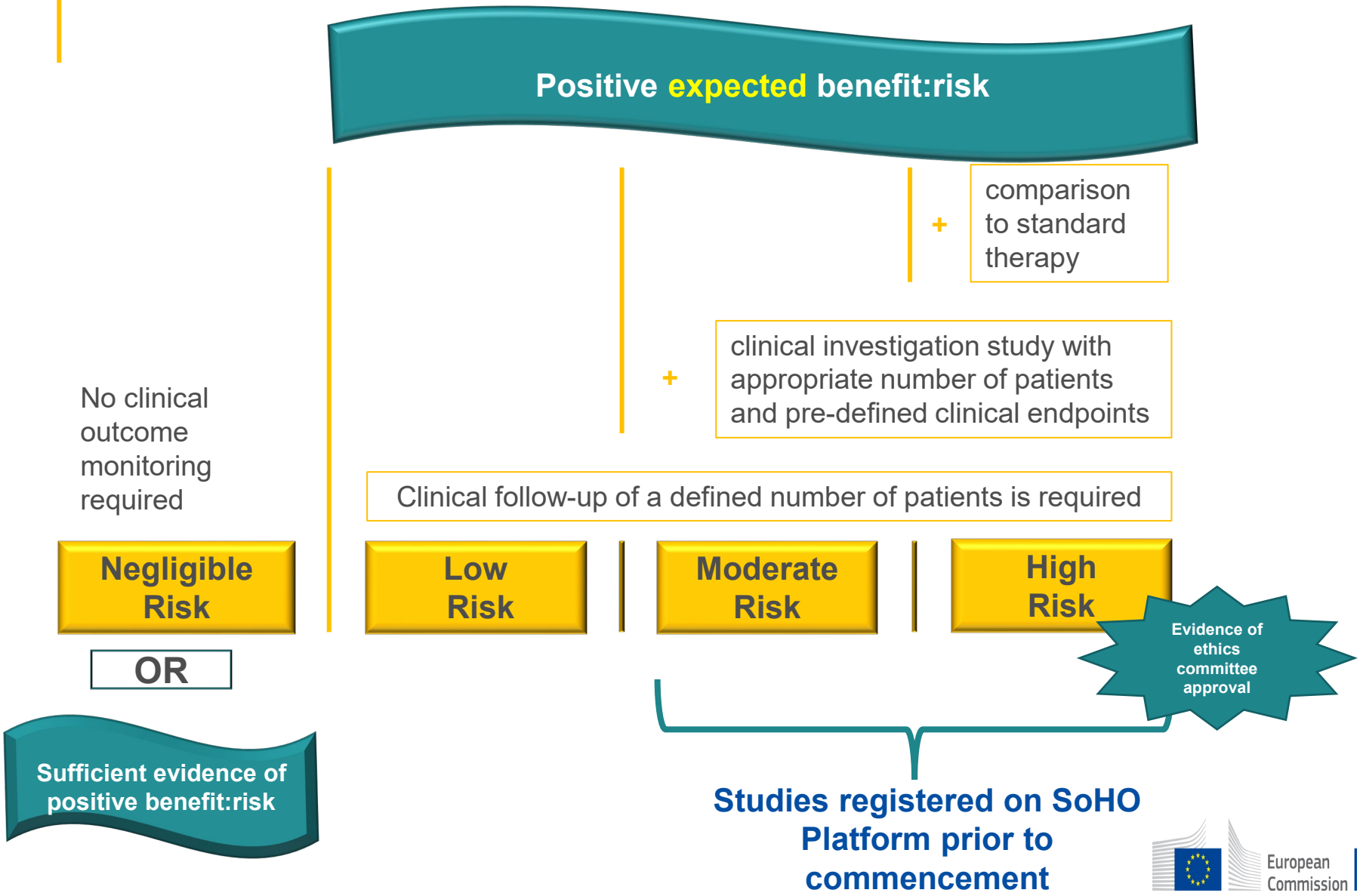
- Grant authorisation
- **OR**
- Refuse authorisation

Based on preparatory work done by GAPP Joint Action
(incl. stakeholders from 17 countries: 15 CAs & professional associations)

GAPP

European Commission

Clinical Outcome Monitoring Plans for gathering further evidence of safety and effectiveness in recipients



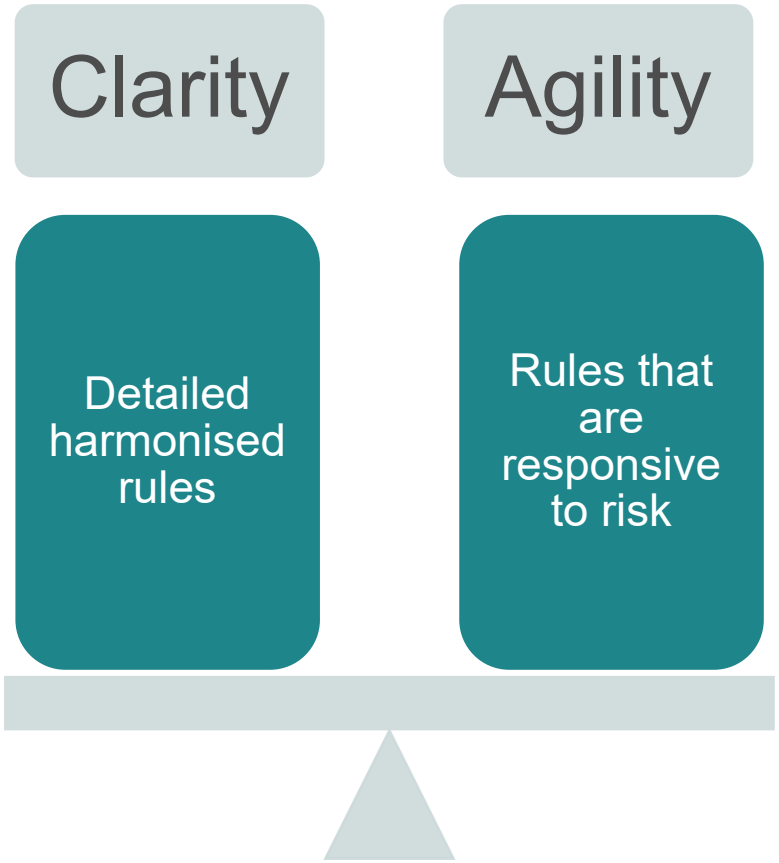
European Commission

Key new and changed concepts

- Scope and advice
- SoHO activities, entities and establishments
- SoHO Preparations and their authorisation
- Standards and hierarchy of technical guidelines
- Donor Protection and Voluntary Unpaid Donation
- Recipient and offspring protection
- Vigilance
- Supply continuity
- Digitalisation – the SoHO platform

European Commission

The challenge of setting technical rules



STANDARDS	
Defined in the Regulation	Generic

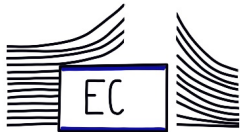
TECHNICAL GUIDELINES	
The way to comply with the standards – normally defined outside the Regulation	Detailed and including SoHO specific elements

European Commission

Implementation of high level standards through technical guidelines – staying up-to-date with the science in an agile way

SoHO entities shall follow the highest available levels of standards (Art. 56 & 59):

Commission Implementing Legislation → "where the Commission deems necessary"



If none:

Technical Guidance on the EU SoHO Platform → Published & updated by ECDC/EDQM

Inspectors shall deem the standards to be met

OR:

"Equivalent" Guidance → Deemed by CAs to achieve equivalent standards

MS shall demonstrate compliance with standards – **may do so** by demonstrating equivalence to ECDC and EDQM

OR:

Other guidelines or methods based on international standards or scientific evidence

Entities shall demonstrate equivalence to inspectors – **may do so** by demonstrating equivalence to ECDC and EDQM

European Commission

Key new and changed concepts

- Scope and advice
- SoHO activities, entities and establishments
- SoHO Preparations and their authorisation
- Standards and hierarchy of technical guidelines
- Donor Protection and Voluntary Unpaid Donation
- Recipient and offspring protection
- Vigilance
- Supply continuity
- Digitalisation – the SoHO platform

SoHO Donor Protection – significantly strengthened – generic standards

Protection of SoHO living donors before, during, and after the collection .

- Including for donations by relatives
- Information & consent
- Physical and mental integrity, non-discrimination, data protection & safeguarding of anonymity (with some exceptions e.g. ID of MAR parents when allowed or obliged in MS)
- Donor health evaluation
- Risk-proportionate approach to donor monitoring: registration of donors subjected to
    - surgical procedures,
    - medicinal product treatment,
    - frequent or repeated donations implying risk to health
- Required reporting of serious adverse reactions in donors

Protection of the dignity and integrity of SoHO deceased donors

- Information & consent by relatives, when applicable

European Commission

Voluntary & Unpaid Donation

Principle maintained
Based on Recommendations of the Council of Europe Committee on Bioethics

- **NO financial incentives or inducements** to donate
- **Compensation** of living donors for losses can be allowed in accordance with the principle of VUD and the CoE recommendations on Financial Neutrality
- When a Member State allows compensation – **upper limit to be set in national legislation** – transparent criteria based on best practices established by the SCB
- Compensation conditions set in MS to be **shared** with the other MS via the SCB
- Donation **promotion and publicity activities** must not refer to compensation (without prejudice to national laws on information provision)

Considerable elaboration of recitals (4) to explain provisions

European Commission

Key new and changed concepts

- Scope and advice
- SoHO activities, entities and establishments
- SoHO Preparations and their authorisation
- Standards and hierarchy of technical guidelines
- Donor Protection and Voluntary Unpaid Donation
- Recipient and offspring protection
- Vigilance
- Supply continuity
- Digitalisation – the SoHO platform

European Commission

Recipient and offspring protection

- Identification and mitigation of risks from **transmissible infectious, genetic, malignant diseases**
- Identification and mitigation of risks from **toxins, contaminants** from the environment, other donations, the personnel, the equipment, reagents etc.
- Identification and mitigation of risks of **detrimental effects on inherent properties of the SoHO concerned**
- Identification and mitigation of risks of **harmful immune reactions**
- Application of national rules regarding the **maximum numbers of offspring** from one SoHO donor
- **No application of SoHO unnecessarily** or in cases where there is no proven benefit
- No promotion of SoHO application based on **misleading information**
- No human application of SoHO without therapeutic or assisted reproduction objective (i.e. **no cosmetic or exclusively nutritional applications**)

Key new and changed concepts

- Scope and advice
- SoHO activities, entities and establishments
- SoHO Preparations and their authorisation
- Standards and hierarchy of technical guidelines
- Donor Protection and Voluntary Unpaid Donation
- Recipient and offspring protection
- Vigilance
- Supply continuity
- Digitalisation – the SoHO platform

European Commission

Vigilance overview – largely unchanged

No change to SAR/SAE definitions!

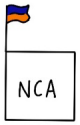
SoHO Entities

Send SAR/SAE notification & SAR/SAE investigation report to their CA

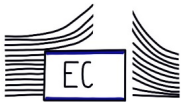
Competent Authorities

- Verify info of SAR/E notifications & investigation reports, assess the results of the investigation, inform the entity
- Send annual summary of SAR/E notifications & investigation reports received to their **SoHO National Authority**
- Launch **SoHO rapid alerts**

Communication with CAs from other frameworks



- Submits annual summary to the **EU SoHO Platform**
- Publishes aggregated summary for their MS



- Aggregate the summaries from the **SoHO National Authorities**
- publish annual SoHO vigilance report

European Commission

Vigilance enhancements

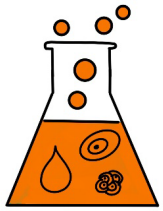
- Inclusion of SAR reporting requirement for SAR in **living SoHO donors**
- Clarification that **SAR/E detected during clinical outcome monitoring** must be reported
- Obligation for reasonable efforts to encourage recipients of MAR donations to communicate information on **genetic conditions in offspring** – when serious these are reportable as SAR
- **Role of ECDC** for SAR concerning infectious disease transmissions
- Formalisation of **communication** requirements with **CAs in other sectors**, when appropriate
- Clarification that **loss of SoHO** constitutes an SAE in defined situations
- CAs to provide **guidance and templates** to professionals and to **inform relevant SoHO entities of Rapid Alerts** received

Key new and changed concepts

- Scope and advice
- SoHO activities, entities and establishments
- SoHO Preparations and their authorisation
- Standards and hierarchy of technical guidelines
- Donor Protection and Voluntary Unpaid Donation
- Recipient and offspring protection
- Vigilance
- Supply continuity
- Digitalisation – the SoHO platform

European Commission

Resilience of Supply



Critical SoHO

'Critical SoHO' are SoHO that for which an insufficient supply will result in serious harm or risk of harm to patients or a serious interruption in manufacture of critical products regulated by other legislation.

A '**critical SoHO entity**' is a SoHO entity that carries out activities contributing to the supply of critical SoHOs and the scale of those activities is such that a failure to carry them out cannot be compensated by activities of other entities or alternative substances or products for recipients.

Supply of **critical SoHO** is protected by:

- **Obligations on Member States** to ensure a sufficient, adequate and resilient supply
  - Facilitate donation
  - Communication and education
  - Optimal use
- **Activity data collection** and monitoring
- Supply **alerts**
- National **SoHO emergency plans**
- SoHO Entity **emergency plans**
- **Derogations** and additional measures in emergency situations

New article!

European Commission

Key new and changed concepts

- Scope and advice
- SoHO activities, entities and establishments
- SoHO Preparations and their authorisation
- Standards and hierarchy of technical guidelines
- Donor Protection and Voluntary Unpaid Donation
- Recipient and offspring protection
- Vigilance
- Supply continuity
- Digitalisation – the SoHO platform

European Commission

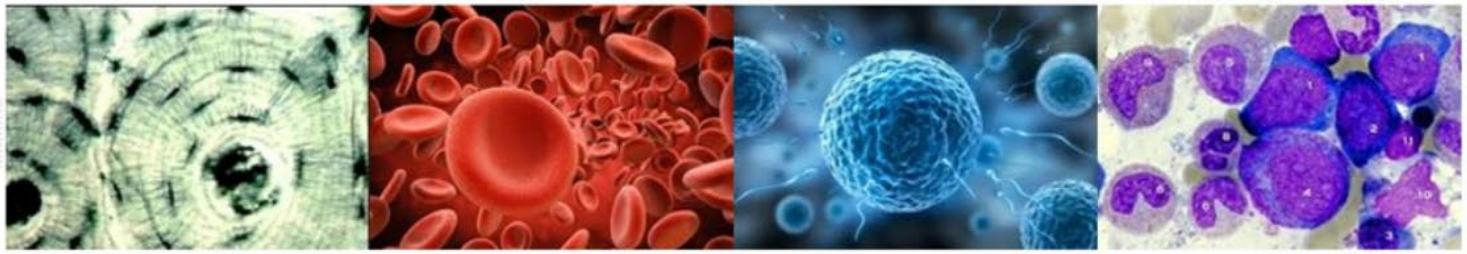
Digitalisation – efficiency, transparency, monitoring

European Commission

Next steps
Entry into Force and Date of Application

- Formal approval by the Council of the EU
- The Regulation will enter into force 20 days after its publication in the Official Journal of the European Union – during **2024** (~ before summer)
- 3 years before the provisions become applicable - **2027** (an additional year for some provisions)

Conference on the new Regulation on Substances of Human Origin



24 June 2024, BREYDEL Auditorium, Brussels

European Commission

Commission

Current & future EU4H actions SoHO

Support implementation
Focus on implementation

Project name (year)	Scope
1. SUPPLY (2021)	Shortages, supply continuity (plasma)
2. EGALITE (2021)	Availability, accreditation (Tissues)
3. BRAVEST (2021)	Crisis resilience (Organs)
4. EuroTRACTOR (2021)	Outcome registry (HSC)
5. EUMAR (2021)	Outcome registry (MAR
6. SIGHTSoHO (2021)	Training authorities (B,
7. Cooperation Agreement EDQM (2021)	Guidelines, vigilance, su
8. Readership (2022)	New obligations entities in ho ls (B, TC)
9. GAPP-Pro (2022)	New obligations process authorisation (B, TC)
10. New SoHO Breast Milk (2023)	Implementation new requirements for Breast milk banks
11. New SoHO FMT (call will be relaunched in 2024)	Implementation new requirements for FMT
11. Paired kidney exchange (2023)	Organs
12. Cooperation Agreement EDQM (2024)	Guidelines, y (B, TC, O)
13. SoHO-X ICT (2024)	SoHO digita
14. Support for Organisational by SoHO Authorities (call to be launched in 2024)	Support the nctions in the new SoHO reg
15. Regulatory Coherence (call to be launched in 2024)	Topics of concern across EU frameworks

Test streamlined autorisation/validation of new SoHO preparations including automation steps with CE devices

SoHO starting materials for MD, and combination products require cross-sector «handshakes» between developers and between authorities in 2 sectors

https://health.ec.europa.eu/blood-tissues-cells-and-organs/overview/proposal-regulation-substances-human-origin_en

Public Health

Home > Blood, tissues, cells and organs > Overview > New EU rules on substances of human origin

New EU rules on substances of human origin

PAGE CONTENTS

On 24 April 2024, the European Parliament has approved the new Regulation on standards of quality and safety for substances of human origin intended for human application.

- Press release
- Factsheet

The final text of the Regulation is available on the European Parliament website.

The Commission Proposal was tabled in July 2022.

Other interesting links

- SoHO framework: Blood, tissues, cells and organs - European Commission (europa.eu)
- Blood national competent authorities per Member State: 1b1a130e-d8dd-43e5-a96d-436d7a7bb64e_en (europa.eu)
- Tissue/cell national competent authorities per Member State: 3ed005e8-581a-4707-be71-99d1bb123536_en (europa.eu)

Thank you

European Commission