Proposal COM(2022) 338 of 14 July 2022 for a **Regulation** of the European Parliament and of the Council on **standards of quality and safety for substances of human origin intended for human application** and repealing Directives 2002/98/EC and 2004/23/EC.

SUBSTANCES OF HUMAN ORIGIN

cep**PolicyBrief** No 15/2022

LONG VERSION

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A. Key elements of the EU proposal

1 Context and Aim of the Proposal

- Substances of Human Origin (SoHOs) are any substance collected from the human body in whatever manner. These can contain living cells, non-living cells or no cells [Art. 3 (5)]. Examples of SoHOs are blood, plasma, reproductive cells (sperm and human eggs), stem cells in bone marrow and cord blood.
- SoHOs are applied to the human body with the aim of creating an interaction. This can be biological, mechanical or physiological [Art. 3 (6)].
- There are different types of SoHOs used for different purposes: for medical therapies, in medical devices and medicines and in research. For example, whole blood donations are used mostly for blood transfusions, plasma is used for the creation of medicines and reproductive cells are used to create life [see also the Final Report on a study of the European Commission supporting the Impact Assessment from 2022, p. 8].
- Collection, processing and supply of SoHOs is primarily carried out on a local small-scale by public services, hospitals and non-profit actors and they are made available by donation [p. 1]. Plasma and reproductive cells (sperm and human eggs) are mainly donated in for-profit centres. In the EU, there are around 1,400 blood establishments and more than 3,200 tissue and cell establishments. [see also the Final Report on a study of the European Commission supporting the Impact Assessment from 2022, p. 8]
- Currently, the quality and safety of SoHOs are regulated mainly by three separate directives on blood, tissues and cells and organs. This proposal will repeal the existing Blood Directive 2002/98/EC and Tissues and Cells Directive 2004/23/EC (the "BTC" legislation) two years after it comes into force [Art. 85]. Organs will still, however, be regulated by the Organs Directive 2010/53/EU. [pp. 1-2 and 13 and Recital 7]
- SoHO-based treatments provide large numbers of therapies in the EU every year: with 25 million units of blood transfused, 36,000 stem cell transplants, 940,000 cycles of in vitro fertilisation (IVF) (a technique whereby a human egg is fertilised by sperm to produce a baby), 14,500 cornea transplants (eye surgery to replace the damaged outer layer of the eye with donor tissue) and 2,000 skin transplants for burn wounds and other injuries [p.1, see also the Commission's accompanying "Factsheet"].
- There are 15 million blood donors, more than 39,000 human egg donors and 165,000 babies born from Medically Assisted Reproduction (MAR) each year [p. 1, see also the Commission's accompanying "Factsheet" and questions and answers on the proposal for new legislation on blood, tissues, and cells].
- With less than one serious reaction for every 12,000 applications, SoHOs have had good levels of quality and safety [p. 1]. However, the BTC legislation does not address current scientific and technical progress or recent epidemiological and societal developments (such as late motherhood) and therefore needs to be updated [p. 1, see also the "Briefing" of the European Parliamentary Research Service on the revision of the BTC legislation, p. 2].
- An evaluation by the Commission of the BTC legislation in 2019 showed the following main gaps and shortcomings [p. 1]:
  - patients lack full protection from avoidable risks due to rules being out of date;
  - donors and children born from medically assisted reproduction are exposed to avoidable risks;
  - divergent oversight by Member States hinders the cross-border exchange of blood, tissues and cells;
  - innovation is not being fostered; and
  - patients in the EU are at risk due to interruptions in the supply of blood, tissues and cells.
- The proposal aims to adapt the BTC legislation in order to accommodate new technologies and new risks, such as changing disease threats (e.g. COVID-19) [pp. 2 and 5]. The main aim of this proposal is to ensure patient safety and access to safe blood, tissues and cells for EU citizens [p. 2].
- The shortcomings in the BTC legislation are addressed in the proposal by providing measures to [p. 6]:
  - ensure safety and quality for patients treated with SoHO therapies and fully protect them from avoidable risks;
  - ensure safety and quality for SoHO donors and for children born from medically assisted reproduction;
  - improve harmonisation across the Member States;
  - facilitate innovation of SoHO therapies; and
  - mitigate risk of shortages.

2 Fundamentals of the Proposal

2.1 Background and general aspects

- The Commission suggests that the COVID-19 pandemic showed the need for proper donor protection [p. 101]. It bases this standpoint inter alia on the fact that there was no legal obligation to follow the guidelines of the European Centre for Disease Prevention and Control (ECDC) on donor selection and COVID-19 testing [see the Final Report on a European Commission study supporting the Impact Assessment of 2022, p. 6].
- The current BTC legislation mainly provides protection for SoHO recipients but only limited protection for donors and children born from medically assisted reproduction (from donated human eggs or sperm). This applies in particular to the reporting of adverse reactions of donors. [p. 5]
- For example, under current BTC legislation, the reporting of serious reactions in human egg donors is not required at EU level although these donors can have serious side effects from the hormonal treatments which they receive [see the "Briefing" of the European Parliamentary Research Service on the revision of the BTC legislation, p. 4].
- According to the Commission, increasing demand for donors in the commercial sector, for example plasma collectors and egg banks, increases the need for protection of donors [p. 5]. Safety standards will therefore be extended to donors of SoHOs [Recital 3 and p. 97, see also Commission questions and answers on the proposal for new legislation on blood, tissues, and cells].
- The proposal is based on Art. 168 (4) (a) Treaty on the Functioning of the European Union (TFEU) which allows Member States to introduce and maintain stricter protective measures on SoHOs. Member States can also set their own rules regarding ethical aspects, for example which SoHO can be donated and who has access to certain SoHO therapies, such as fertilisation therapies. [p. 3 and Recital 2]

2.2 Definitions

- A "SoHO National Authority" is designated by each Member State. It is responsible for coordinating exchanges with the Commission and with SoHO National Authorities in other Member States. [Art. 5 (4)]
- A SoHO entity carries out at least one SoHO "activity" such as donor recruitment, collection of SoHOs from donors or patients and human application of SoHOs. An example of a SoHO entity is a donor registry. [Recital 31 and Art. 2 (1) (a), (d) and (l) and Art. 3 (24)].
- A SoHO for which a lack of supply results in serious harm or risk of harm to patients, is defined as a "critical SoHO" [Art. 3 (41)].
- If a SoHO entity performs activities in connection with critical SoHOs such that a failure in performance could not be compensated by the activities of other entities, or no alternative substance or product is available to patients, this entity is defined as a "critical SoHO entity" [Art. 3 (42)].
- A "SoHO preparation" is a type of SoHO that: [Art. 3 (12) in connection with Art. 2 (1) (d)]
  - has been subject to at least one SoHO activity such as collection from a donor or patient;
  - meets a pre-defined specification; and
  - is intended for a clinical indication of a recipient such as treatment of a disease, or for distribution for the manufacture of a product regulated by other EU legislation (such as a medicinal product or a medical device) or as the starting and raw material of that product such as plasma used in medicines.
- Before a SoHO preparation can be applied to a patient, it needs to be approved by the competent authority in the Member State [Art. 5 (1) and Art. 40 (1)]. This is called a "SoHO preparation authorisation" [Art. 3 (25)].
- A "SoHO rapid alert" is a communication regarding a "serious adverse occurrence" (SAO) [Art. 3 (28)], a communicable disease outbreak or other information which might have an impact on the safety and quality of SoHOs across Member States. It aims to inform national competent authorities and the Commission quickly to enable rapid mitigation measures [Art. 3 (29)].

2.3 Scope of the Proposal

- The proposed Regulation covers blood including blood components such as red cells, white cells and plasma. It also covers tissues and cells, including reproductive cells (human eggs and sperm) and bone-marrow stem cells. It does not apply to organs [p. 2, Recital 6 and Art. 2 (1), Art. 3 (5)].
- The Commission suggests that the use of SoHOs other than blood, tissues and cells is increasingly common and donors as well as recipients require more protection. The scope of this Regulation therefore goes beyond the traditional substances of blood, tissue and cells, so that the same quality and safety standards apply to all SoHOs. [pp. 5 and 97 and Recital 6, see also the Commission's "questions and answers" on the proposal for a new legislation on blood, tissues, and cells]
- An example of this is human breast milk, which can be used to feed preterm infants where a mother is unable to breastfeed, or intestinal microbiota (human faeces), which can be used for the treatment of life-threatening diseases. These substances so far remain unregulated or are regulated in different ways in the Member States, even though similar risks exist as with blood, tissues and cells. [pp. 5 and 97, see also the Commission's "questions and answers" on the proposal for a new legislation on blood, tissues, and cells and the Final Report on a European Commission study supporting the Impact Assessment of 2022, pp. 294-295 and 307-308]
- SoHOs are handled in a variety of ways before being applied to the patient. Therefore, the proposed Regulation applies to all SoHO activities, from SoHO donor recruitment through to SoHO clinical outcome monitoring [Recital 9 and Art. 2 (1)].
- SoHO recipients, SoHO donors, and offspring (fetuses and children) from medically assisted reproduction, will fall within the scope of this Regulation [Art. 1, Art. 2 (1) and Art. 3 (11)].
- SoHOs intended for human application, SoHO preparations, and products manufactured from SoHOs and intended for human application, fall within the scope of this Regulation [Art. 2 (1)].
- SoHOs are also used to manufacture medicinal products, medical devices or food, or as the starting and raw material thereof. In these situations, the proposed Regulation applies to activities ranging from donor recruitment to human application and outcome monitoring. [Recitals 9 and 11 and Art. 2 (3)]
- The proposed Regulation also applies to the release, distribution, import and export of SoHOs until they are transferred to operators that are subject to different rules, such as those on medicines covered by Regulation (EC) No 726/2004 and Directive 2001/83/EC and medical devices covered by Regulation (EU) 2017/745 [Recital 11 and Art. 2 (3)].

2.4 Donor protection

- This proposal includes principles and technical rules for monitoring and protecting donors before, during and after donation, proportionate to the varying risk involved – including high risk, e.g., according to the Commission, the donation of human eggs or bone marrow [Recital 13 and Art. 52 (2)]. One example of a donor protection measure is the health evaluation which needs to be conducted prior to donation [Art. 53 (1) (f)].
- SoHO entities need to provide information to a central registry on donors who are (1) subject to a surgical procedure, such as in the case of bone marrow donation, (2) are treated with hormones or (3) who donate on a frequent and repeated basis. This especially allows for checks to ensure that donors do not donate too frequently. [Art. 53 (1) (j) and (3)]
- SoHO entities are required to detect, investigate and record information on adverse reactions – including those of donors [Art. 47 (1)]. If a "serious adverse occurrence" (SAO) [Art. 3 (28)] is detected, then SoHO entities must notify the competent authorities and communicate with other SoHO entities that are affected, especially if they handle SoHOs from the same donor [Art. 47 (2) and (6)].
- Examples of SAOs are: [Art. 3 (28)]
  - death;
  - life threatening, disabling or incapacitating conditions;
  - transmission of a genetic condition to offspring from medically assisted reproduction;
  - hospitalisation or prolongation of hospitalisation;

  - loss of quantity of SoHOs resulting in the cancellation or postponement of SoHO applications;
  - loss of highly matched or autologous SoHOs;
  - a mix-up of reproductive cells; and
  - prolonged sub-optimal health of a donor.

- Donations should be voluntary and unpaid. The reasoning here is that excluding financial gain will protect the health of donors by discouraging them from donating too frequently. It also aims to protect recipients from donors who are dishonest about their medical history. [p. 3, Recital 18 and Art. 54 (1)]

- However, Member States are allowed to set national rules on compensating donors by way of fixed rate allowances for losses arising from the donation [p. 3, Recital 18 and Art. 54 (2)].

2.5 Offspring of medically assisted reproduction

- The Commission suggests that current requirements for testing human egg and sperm donors for genetic conditions are out of date given the technology available. Monitoring and protection measures for children born from medically assisted reproduction (MAR) are also limited. [p. 5] Therefore, safety standards will be extended to about 165,000 children born yearly from MAR [see the Commission's questions and answers on the proposal for a new legislation on blood, tissues, and cells; and the Commission's accompanying "Factsheet"].

- Thus, "offspring from medically assisted reproduction", i.e., fetuses and children born following MAR, are also covered by the proposed Regulation [Art. 3 (11) and Art. 57 et seq.].

- SoHO entities should ensure that genetic conditions are not transmitted to offspring from MAR [Art. 58 (1)]. This will take place by means of genetic testing of donors and recipients [Art. 58 (3) (b) (i) and (ii)].

- SoHO entities must not apply SoHO preparations to recipients of MAR without proven benefit nor apply SoHO preparations unnecessarily to these recipients [Art. 58 10 (a) and (b)].

- Parents of children born from third party donation must be encouraged by SoHO entities to communicate any genetic conditions that emerge. The SoHO entity where the treatment took place must then communicate this information to the SoHO entity that distributed or applied the reproductive cells. This is to ensure that the implicated donor does not distribute more SoHOs. [Art. 47 (2)]

2.6 SoHO Coordination Board and the "EU SoHO Platform"

- Member States will be supported by the SoHO Coordination Board (SCB) [Art. 67 (1)]. The SCB will provide support with regard to the implementation of the proposed Regulation and will also have a role in decisions on the regulatory status of a product as well as joint inspections and SoHO preparation authorisations involving more than one Member State [Art. 68 (1) (a) and (f)].

- The Commission will establish a common IT platform, the "EU SoHO Platform", for the submission and exchange of data, within the EU, among SoHO entities, competent authorities, Member States and the Commission [Recital 41, Art. 73 (1), Art . 74 (1) and Art. 3 (31)].

- This includes information exchange between competent authorities and the Commission on "serious adverse occurrences" (SAOs) and a "SoHO rapid alert" [Art. 74 (2), Art. 36 (2) and Art. 3 (29)].

- According to the Commission, the EU SoHO Platform will lead to cost savings of more than 2 million euros by reducing duplication, i.e., since applications for authorisations will be introduced and assessed in parallel across the EU. Furthermore, it will lead to more efficient administrative processes – even though the Commission cannot quantify the cost savings at this time. [p. 10 et seq.]

3 Applicable legal regime

- The Commission's stakeholder consultations have shown that it is not always clear which of the following legal frameworks applies to a substance:

  - medicinal products legislation (Regulation (EC) No 726/2004 and Directive 2001/83/EC);

  - the Medical Devices Regulation (EU) 2017/745, and the
  - Advanced Therapy Medicinal Product Regulation (ATMP) (EC) No 1394/2007).

  [p. 7, see also the "Briefing" of the European Parliamentary Research Service on the revision of the BTC legislation, p. 6, and the Final Report on a European Commission study supporting the Impact Assessment of 2022, p. 6].

- Stakeholders raised the point that SoHO-based therapies are not coherently interpreted and handled in the different Member States [p. 7]. As a result, substances and SoHO-based therapies have been classified differently by the Member States leading to different legal regimes being applied [p. 7, see also see also the "Briefing" of the European Parliamentary Research Service on the revision of the BTC legislation, p. 6].
- This Proposal does not change the distinguishing criteria which determine whether a product is regulated as a medicinal product or medical device, as defined in the Medical Devices Regulation (EU) 2017/745, Directive on Medicinal Products 2001/83/EC and the Regulation on Advanced Therapy Medicinal Products (EC) No 1394/2007) [p. 9].
- If there is a lack of clarity about the regulatory status of a substance, product or activity, Member States are responsible for deciding on this issue on a case-by-case basis. As part of this, the competent authorities have the obligation to consult and cooperate with authorities of other regulatory sectors, namely medicines, medical devices, organs and food. Competent authorities have the option to ask the SCB for its opinion on the applicable legal regime and it must be informed of the final decision. [Recital 24 and Art. 14 (1) (2) and (3)]
- Generally, the Commission can also decide on the applicable legal regime in order to ensure EU wide consistency. It may do so at the duly substantiated request of a Member State or on its own initiative via implementing acts. These decisions are then legally binding. [Recital 24 and Art. 14 (4)]

4 Improvement of safety and quality of SoHOs

4.1 Common standards for safety and quality

- According to the Commission, high standards for the quality and safety of SoHOs for all EU citizens can best be achieved through the introduction of common technical rules and guidance on safety and quality [pp. 3-4].
- This requires compliance with a "hierarchy" of safety and quality standards set out in [Recital 33, Art. 56 (4) (a) and (b), Art. 59 (4) (a) and (b)]
  - the guidelines of the European Centre for Disease Prevention and Control (ECDC) and the European Directorate for the Quality of Medicines & HealthCare (EDQM), or
  - other guidelines accepted by national competent authorities if these provide an equal level of quality, safety and efficacy, or if neither exist with regard to a particular issue, then
  - other international guidelines and scientific evidence in peer-reviewed publications.
- The Commission regards this hierarchy as preferable, especially since the guidelines of the ECDC and the EDQM can be adapted to disease threats and scientific progress relatively swiftly [p. 4, Recital 33, see also the Commission's questions and answers on the proposal for a new legislation on blood, tissues, and cells].
- According to the Commission, this approach does not interfere with the right of Member States to maintain and introduce more stringent measures [Article 168 (4) TFEU]. In fact, it increases the level of safety and quality to be achieved in all Member States and thereby reduces the need in most cases for more stringent measures that can create barriers to cross-border exchange and patient access. [p. 4]
- Currently though, also according to the Commission, guidance from the ECDC on protecting donors and patients from communicable diseases, transmitted by SoHOs, is already widely applied in the sector. This is also the case for guidance from the EDQM on risks to the quality and safety of blood, tissues and cells [Recitals 35 and 36, see also the Commission's questions and answers on the proposal for a new legislation on blood, tissues, and cells].

4.2 Authorisation of new SoHO preparations

- Current authorisation procedures do not require a risk assessment. The proposed Regulation envisages a risk assessment carried out by the applicant for an authorisation for SoHOs processed or used in new ways. [pp. 10 and 97, Recitals 27 and 28 and Art. 41 (2) (b)]
- The risk assessment needs to evaluate the risk involved and needs to include a plan for clinical outcome monitoring in case there is a risk to the SoHO preparation [pp. 10 and 97, Recitals 27 and 28 and Art. 41 (2) (b) and (c)]. This plan should demonstrate safety, quality and efficacy (benefits) and be aligned with the level of risk [Art. 41 (2) (c) and (3)].
- Competent authorities should share information and evidence on new SoHO preparations via the EU SoHO Platform. This will allow national competent authorities to accept authorisations of SoHOs which were previously authorized in another Member State [Recital 30 and p. 98].
- SoHO preparation authorisations are, by default, valid in the entire EU. However, the Member States remain in control since a national competent authority may suspend or withdraw the authorisation. [Art. 20 (3), Art. 21 (6) (7) and (8)]
- Additionally, Member States can generally set stricter rules [Art. 4]. Therefore, an authorisation of a SoHO preparation from another Member State may be rejected by that Member State until it has been proven that these stricter rules have been met [Art. 20 (3)].
- In case of a health emergency and in the interests of public health, it is possible to distribute and apply SoHO preparations without authorisation in a Member State. A corresponding request needs to be approved by the national competent authority [Art. 64 (1)]. The latter must communicate the decision to the SoHO National Authority, which then informs the Commission and the other Member States [Art. 64 (2)].

5 Access to SoHOs

5.1 Strengthening of oversight

- Based on the 2019 evaluation of the BTC legislation, differences in oversight between Member States have a negative impact on the cross-border exchange and availability of blood, tissues and cells [p. 5].
- Strengthening common oversight by national competent authorities, for example, by way of joint inspections, is likely to increase trust between Member States and should thus help to increase cross-border exchange and thereby EU-wide patient access [p. 10].

5.2 Mitigation of shortages

- The exchange of SoHOs between Member States is essential to safeguard supply and ensure patient access, especially when a specific match is required between a recipient and a donor. This exchange is particularly important in the event of local crises or shortages. [Recital 47]
- Currently, there is a lack of monitoring measures both at EU and Member State level, which makes it difficult to predict the future EU supply of SoHOs and take the appropriate mitigating measures [p. 6].
- Also, the EU has no mandate for direct intervention in supply management. Reliable monitoring and notification of shortages, however, would help Member States to take action to mitigate shortages. One particularly important example is blood plasma, as the EU is dependent on supplies from the United States for the manufacture of plasma-derived medicines. [p.6]
- To mitigate the risk of shortages, Member States must establish a national SoHO emergency plan and make reasonable efforts to promote SoHO donation [Art. 62 (1) and (2)].
- Critical SoHO entities must send a “supply alert” to their competent authority in case of the unavailability of SoHOs which could lead to cancellation or postponement of the application of critical SoHOs and therefore represents a serious risk to health [Art. 63 (1)]. This is then communicated to the SoHO National Authority [Art. 63 (2) (a)].
- The SoHO National Authorities may submit the supply alert to the EU SoHO Platform if it effects other Member States or if cooperation between Member States is needed to address the issue [Art. 63 (3)].

B. Legal and political context

1 Status of legislative procedure

14.07.22 Adoption by the Commission

Open Adoption by the European Parliament and the Council, publication in the Official Journal of the European Union, entry into force

2 Options for exerting political influence

Directorates General:	DG Health & Food Safety
Committees of the European Parliament:	Environment, Public Health and Food Safety, Rapporteur: Nathalie Colin-Oesterlé (EPP, FR)
Federal Ministries:	Health
Committees of the German Bundestag:	Health
Decision-making mode in the Council:	Qualified majority (acceptance by 55% of Member States which make up 65% of the EU population)

3 Formalities

Basis for legislative competence:	Art. 168 (4) (a)TFEU
Form of legislative competence:	Shared competence (Art. 4 (2) TFEU)
Procedure:	Art. 294 TFEU (ordinary legislative procedure)

C. Assessment

1 Economic Impact Assessment

Protecting patients, donors, and children born from medically assisted reproduction, as well as supporting equal access to safe SoHOs, are desirable objectives to be achieved at EU level. The fact that Member States will generally have to accept SoHO authorisations from other Member States supports these objectives and also benefits the internal market. There are, however, a number of measures which may not have their intended impact and could run counter to the Commission's aims.

1.1 Protection of donors

ECDC guidelines on donor selection and testing were presumably not always followed during the COVID-19 pandemic and that may have put donors and staff at risk.[1] The provisions envisaged by the proposal will ensure that donors are generally better protected.

For example, SoHO entities will be required to register donors, who donate "frequently" or on a "repeated basis", in a donor registry. Registration of these donors is, in principle, a good idea, as it may protect the donor from overexploitation by donating too much and too frequently. However, the proposed Regulation does not indicate what is meant by "frequently" and "repeated basis" which could result in divergent approaches in the interpretation of these terms. A more detailed definition is required – with at least a range of values and consideration for the fact that a separate definition is required for each SoHO.

[1] ECDC (2020) "Technical Report on Coronavirus disease 2019 (Covid-19) and supply of substances of human origin in the EU/EEA, second update" , p. 7 and European Commission (2022), "Study supporting the Impact Assessment of the Revision of Directive 2002/98/EC on safety and quality of human blood and blood components and of Directive 2004/23/EC on safety and quality of human tissues and cells", p. 6 . All references last checked: 09.11.2022.

The obligation to report adverse reactions will also help to protect the health of donors as this information allows for action to be taken, such as using another method of donation, changing the procedure for the donation, or limiting the group of people who can donate.[2] Obligatory reporting of adverse reactions will increase access to valuable data which may help to formulate mitigating measures where necessary.

In principle, donors should be allowed to receive compensation for any losses resulting from the donation. In this regard, Member States can set fixed rate allowances based on their national context. This will give them broad scope to set the upper limit for the allowance which may take the form of financial compensation. However, as national contexts vary widely across the EU, Member States will set different upper limits which may result in certain countries being more attractive to donors than others and give rise to a surplus of donations in one country and a shortage in others. It could also put donor health at risk because donors may be able to make a financial gain from donating in a Member State with a higher fixed rate. One solution, therefore, may be to introduce SoHO-specific caps, adjustable to inflation, at EU level to prevent significant disparities.

1.2 Protection of children born from medially assisted reproduction

Measures put in place to protect the health of children born from medically assisted reproduction as well as the recipients, will have a positive impact on the health of these two groups. The obligation for SoHO entities to share information regarding a genetic condition in children born from medically assisted reproduction will protect future recipients from using reproductive cells from that same donor. The use of modern techniques for the genetic testing of donors of reproductive cells and recipients may be beneficial for both the children born from medically assisted reproduction and the recipients, as it will be more likely that a genetic condition will be detected at an early stage.

1.3 Applicable legal regime

The procedure envisaged by the proposal for deciding which legal regime is applicable to a substance, for example following activities which are part of the SoHO-Regulation – e.g., pharmaceutical or medical devices law – and the uncertainty that comes with it, may delay the approval of new SoHO substances, products or activities and subsequently their use on patients. The required consultation between different competent authorities and, if needed, the SCB may take time, especially if more than one other competent authority needs to be consulted. It is not clear from the proposal whether national competent authorities are only supposed to cooperate with other national competent authorities in their own Member State or can also cooperate with those in other Member States or at EU level, such as the European Medicines Agency (EMA). This is only clear for SoHOs used in the manufacture of medicines or their raw materials.

It is unclear whether Member State decisions on the applicable legal regime are binding for other Member States. This needs to be clarified. The same uncertainty exists with regard to the SCB opinion. This may result in different legal rules being applied to the same substance or product in the EU. Only implementing acts by the Commission would allow for certainty to this regard as these are legally binding for all Member States. Yet, these are framed as exceptions to the rule. This creates significant uncertainty in cases where it is unclear whether e.g. medical devices law or pharmaceutical law applies. This is a hinderance to a functioning internal market.

1.4 EU-SoHO Platform

The EU SoHO Platform will play an important role in the collection and exchange of data, such as assessment of new authorisations, the reporting of adverse reactions and the reporting of supply problems. The sharing of authorisations for new SoHO preparations, including data on evidence, between Member States via the EU SoHO Platform will reduce the administrative burden on both competent authorities and applicants. However, there are technical challenges in connection with the practical implementation of the platform. Not all SoHO entities or competent authorities may be connected on time as this requires every SoHO entity to have some form of digital infrastructure and knowledge of IT. There is also a risk of delay: for example, the introduction of an IT system (EUDAMED) as part of the Medical Devices Regulation (EU) 2017/745 has still not been implemented, is

[2] For example, by age group or Body Mass Index.

only partially finished and its use is not yet mandatory.[3] Also, the use of IT as part of the Commission Delegated Regulation (EU) 2016/161 supplementing the EU Falsified Medicines Directive 2011/62/EU caused IT issues, such as problems with software and databases not being up to date.[4] As a result, it is possible that digitalization will not reduce the costs of monitoring measures to the extent foreseen in the proposal.

1.5 (Cross-border) Reporting of a "serious adverse occurrence"

The sharing of SAOs between competent authorities and the Commission can be of vital importance to the protection of patients and donors. For example, if an SAO results in death or prolonged hospitalisation of the recipient of a SoHO treatment, Member States have the option to increase monitoring of recipients undergoing the same SoHO treatment or not to use SoHOs from a donor which might have caused the SAO in a recipient.

1.6 Application of common safety and quality standards

There is already a high degree of harmonisation regarding technical standards on safety and quality as the EDQM and ECDC Guidelines are already applied by those working with SoHOs throughout the sector. The proposal allows for other rules to be applied if they can demonstrate similar quality, safety and efficacy. This may lead to divergent levels of safety, quality and efficacy since standards may vary and the rules they contain may be subject to multiple interpretations. To fulfill the aim of harmonised rules in all EU Member States, it would be advisable to apply the EDQM and ECDC guidelines only where applicable to ensure a consistent approach to the quality, safety and efficacy of SoHOs across the EU.

The Commission states that the ECDC and the EDQM guidelines will be updated regularly based on new technology, innovation and disease threats. The lack of updated guidelines was, however, one of the shortcomings of the BTC legislation. Regular updating by the EDQM and ECDC is welcomed but the proposal must specify how and when this will be done.

1.7 Fundamental aspects regarding the authorisation procedure of new SoHO preparations

Proportionate risk assessment

The introduction of a proportionate risk assessment as part of the SoHO authorisation procedure will improve the safety, quality and efficacy of SoHOs. It could, for example, protect patients seeking fertility treatment who are offered so called add-on treatments that are not always effective.[5] These are treatments which claim to be effective at improving the chances of having a baby but evidence is lacking or unreliable.[6] One example of such treatment is "assisted hatching"[7].[8]

Clinical monitoring

The specific requirements of clinical monitoring are based on the results of the proportionate risk assessment. This does make sense in theory, as recipients of a high risk SoHO preparation require more monitoring than those receiving a low risk SoHO preparation. In practice though, it will be difficult for applicants to determine the risk involved as the different levels of risk, "low", "moderate" and "high" are not defined in the proposal. This may

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3 European Commission (2022), "Medical Devices - EUDAMED".

4 K. Dalton, G. Connery, K.D. Murphy & D. O'Neill (2022), "Pharmacists' views on the impact of the Falsified Medicines Directive on community pharmacies: A cross sectional survey", p. 5, Table 4.

5 Human Fertilisation & Embryology Authority (2022), "Treatment add-ons with limited evidence" and J. Harper, E. Jackson & K. Sermon et al., (2017), "Adjuncts in the IVF Laboratory: where is the evidence for ´add-on´ interventions?", p. 485.

6 Human Fertilisation & Embryology Authority (2022), "Treatment add-ons with limited evidence"; P, David, D. F. Albertini, N. Gleicher & A. Caplan (2022), "The changing world of IVF: the pros and cons of new business models offering assisted reproductive technologies", p. 305 and J. Harper, E. Jackson & K. Sermon et al., (2017) "Adjuncts in the IVF Laboratory: where is the evidence for ´add-on´ interventions?", p. 485 et seq.

7 This is a method whereby acid, lasers or other tools are used to make a hole in the outer layer of the embryo which helps the embryo to break out of this outer layer so that it can implant in the womb. See Human Fertilisation & Embryology Authority (2022), "Assisted hatching".

8 Human Fertilisation & Embryology Authority (2022), "Treatment add-ons with limited evidence", "Assisted hatching", and J. Harper, E. Jackson, K. Sermon et al., (2017), "Adjuncts in the IVF Laboratory: where is the evidence for ´add-on´ interventions?", p. 487 et seq.

lead to divergent interpretations of the level of risk, and delay the authorisation of new SoHO preparations and products.

No proportionate risk assessment in case of a "health emergency"

The possibility, in case of a health emergency, of obtaining a SoHO authorisation without following the regular authorisation procedure (emergency authorisation), and thereby also skipping the proportionate risk assessment, could be beneficial for patients in times of crisis. However, the term "health emergency" is not defined in the proposal nor is there a reference to any other legislation or procedure for determining whether a health emergency exists. This makes it difficult to determine when a "health emergency" exists which in turn gives rise to a risk that competent authorities will have different approaches when it comes to defining a "health emergency". Both a clear definition and a procedure need to be part of the proposed Regulation. Additionally, with regard to communicating the decision to accept a "health emergency": the proposal contains clear rules on who communicates the decision to whom and in what order. However, the means of communication is unclear and also needs to be clearly defined in the proposed Regulation. A practical option would be to use the EU SoHO Platform for this.

1.8 Access to SoHOs

Mitigating risks of shortages

The Commission notes that the lack of monitoring provisions regarding supply at EU and national level makes it difficult to mitigate the risk of shortages. To ensure sufficiency of supply, Member States must have a national emergency plan and make reasonable efforts to promote donation. However, during the COVID-19 pandemic, for example, individual Member States proved that they were indeed capable of taking mitigating measures at national level to ensure sufficient SoHO supply. Thus, France and Italy successfully initiated media campaigns to increase blood donation.[9] And in the case of bone marrow, patients continued to be matched with the right donor despite the COVID-19 pandemic.[10] In France, urgent treatment with umbilical cord blood also continued without delays during the pandemic.[11]

With regard to measures at EU level, stakeholders raised the issue[12] that supply monitoring and crisis preparedness measures will require significant efforts without having a direct impact on the risk of shortages of critical SoHOs.[13] Measures to mitigate shortages of SoHOs now foreseen at EU level, such as the national monitoring plan and supply monitoring, will not reduce the risk of shortages as these measures are unlikely to sufficiently reduce de facto EU dependency on SoHOs from third countries. This is particularly true for plasma and – on an individual level – in cases where a specific match is needed between a donor and a recipient. It would therefore be advisable for the Commission to introduce additional measures to reduce this dependency on third countries, such as supporting Member States by facilitating information exchange on donor campaigns between Member States. Reducing dependency on third countries would also reduce the risks associated with the transportation of SoHOs and could ensure quicker patient access due to shorter transportation distances.

General exchange of SoHOs within the EU

It is doubtful that a harmonised set of rules on safety and quality is really needed for the purpose of increasing the exchange of SoHOs within the EU. For example, according to the Commission, an increase in trust between Member States as a result of harmonised standards on the safety and quality of SoHOs, and increased oversight, will increase the exchange of SoHOs. This view is based on an assumption and lacks sufficient proof of a causal connection. There is already significant exchange of SoHOs at EU level when needed, in particular reproductive cells, plasma, bone marrow stem cells and cord blood units.[14]

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9 Blood and Beyond (2021), "Blood use in Europe: learning from the impact of Covid-19: A Blood and Beyond policy briefing", pp. 4 -5.

10 Euronews (2020) "How even the COVID-19 crisis could not stop bone narrow donations getting through".

11 H. Rafii, I. Ionescu, A. Ruggeri & F. Garnier et al. (2022) "Impact of COVID-19 pandemic on the use and release of cord blood units facilitated by the French Cord Blood Banks Network: on behalf of the Agency of Biomedicine, Eurocord and the French Society of Bone Marrow Transplant and Cell Therapy (SFGM-TC)", p. 126.

12 During the consultation prior to the publication of the proposal.

13 As foreseen in this proposal, see p. 7.

14 European Commission (2022), "Study supporting the Impact Assessment of the Revision of Directive 2002/98/EC on safety and quality of human blood and blood components and of Directive 2004/23/EC on safety and quality of human tissues and cells", Annex 15, pp. 403 and 405.

The exchange of reproductive cells and cross-border travel by patients for fertility treatment in the EU is mainly due to differences in national regulations on the donation of reproductive cells and fertility treatment.[15] This leads to differences in the supply of reproductive cells. For example, the primary countries for human egg donation are Spain, the Czech Republic and Belgium, with about half of all European human egg donations being carried out in Spain.[16] Yet, the proposal does not address these kinds of shortages at national level as they relate to ethical decisions on the use of reproductive cells in the individual Member States, some of which prohibit human egg donation.[17]

Supply alert at EU level

Competent authorities have the option to submit a supply alert to the EU SoHO Platform if this might have an effect on other Member States or if cooperation between Member States is needed to address that particular SoHO-supply issue. However, this could also in fact help with the monitoring of supply in the EU and provide the basis for informing recipients about potential delays or the cancellation of treatment and would therefore be an overall improvement in cooperation across Member States. In order for this to have a lasting impact, the submission of the supply alert to the EU SoHO Platform should be made obligatory.

2 Legal Assessment

2.1 Competence

Unproblematic. Art. 168 (4) (a) of the Treaty on the Functioning of the European Union (TFEU) allows the EU to set standards for quality and safety of SoHOs without limiting the right of Member States to set higher standards.

2.2 Subsidiarity and Proportionality vis à vis Member States

Unproblematic.

2.3 Compatibility with EU law in other respects

Unproblematic. Most notably, the proposal is in line with Article 3 (2) (c) of the EU Charter of Fundamental Rights which prohibits commercialization of the human body. The proposal does contain the principle of voluntary unpaid donation, but donors should not incur any financial disadvantage related to their donation. Thus, Member States are allowed to set compensation or reimbursement in the form of fixed rate allowances based on the national context.[18] It is advisable to ensure close monitoring of the implementation of compensation and reimbursement rules in Member States to ensure that they are in line with the aforementioned fundamental decision of the EU Charter.

D. Conclusion

The aims of the proposal – ensuring the protection of patients, donors and children born from MAR as well as equal access to SoHOs – are worthwhile. However, it is questionable whether all the measures introduced in the proposed Regulation are necessary and will be effective in achieving these objectives.

EU citizens will benefit from some of the measures. In particular, the obligations on data sharing between the Commission, Member States and different SoHO entities regarding adverse reactions, supply, donation frequency and new authorisations will protect EU citizens from avoidable risks to their health and generally ensure better access to safe SoHOs. The introduction of an EU SoHO Platform to facilitate data sharing is therefore appropriate. However, given the practical challenges, data sharing may not take place as intended or be as rapid as envisaged. This could then result in an increased administrative burden for professionals working with SoHOs without having a positive impact on health protection. Furthermore, definitions that are missing

[15] M. Salama, V. Isachenko & E. Isachenko et. al. (2018), "Cross border reproductive care (CBRC): a growing global phenomenon with multidimensional implications (a systematic and critical review)", pp. 1278-1279 and European Commission (2022), Study supporting the Impact Assessment of the Revision of Directive 2002/98/EC on safety and quality of human blood and blood components and of Directive 2004/23/EC on safety and quality of human tissues and cells, Annex 15, p.403 and 405.

[16] M. Salama, V. Isachenko & E. Isachenko et. al. (2018), "Cross border reproductive care (CBRC): a growing global phenomenon with multidimensional implications (a systematic and critical review)", pp. 1278-1279.

[17] This is the case, for example, in Germany; see also Leopoldina Nationale Akademie der Wissenschaften (2022), "Egg donation, Embryo Donation. Surrogacy".

[18] As foreseen in this proposal, see Recital 18 and Art. 54.

from the proposed Regulation need to be included to ensure consistent interpretation across the EU and especially to provide clarity for professionals working with SoHOs.

In addition, measures to ensure sufficient supply of SoHOs are well intended but may not have the planned impact and may not be necessary for the entire SoHO sector. Supply and demand for certain SoHOs such as blood can be sufficiently regulated by the Member States themselves, even during times of crisis. Instead, the introduction of measures to address dependency on SoHOs from third countries is recommended, as this would directly benefit access to safe SoHOs within the EU.