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COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

RISK OF COMMODIFICATION OF SUBSTANCES OF HUMAN ORIGIN

A POSITION STATEMENT OF THE EUROPEAN COMMITTEE ON ORGAN TRANSPLANTATION OF THE COUNCIL OF EUROPE (CD-P-TO)*

Adopted by the European Committee on Organ Transplantation (CD-P-TO) on 18 November 2022 following its 28th plenary meeting in Warsaw, Poland.

- The development of new therapeutic options based on substances of human origin (SoHO) brings unquestionable benefits to patients. However, their commercialisation, without appropriate limits on the financial benefits that they may generate, might jeopardise the altruistic donation of SoHO, essential for the treatment and survival of thousands of patients.
- The introduction of requirements for the development and production of SoHO-based therapies when not proportional to the potential risks, as well as the pursuit of disproportionate profits for manufacturers, marketers and intermediaries, may also pose a considerable threat to the sustainability of healthcare systems and threaten the equitable access to these therapies by patients.
- The aim of this position paper is to identify these risks and propose solutions that would help reconcile the fundamental ethical principles of voluntary and unpaid donation of SoHO and the prohibition of financial gain from the human body or its parts, with the development of new treatment opportunities for European citizens.

Background

Substances of human origin (SoHO) have the potential to save patients' lives or substantially improve their quality of life. Rapid advances in biological and medical research have led to these substances being increasingly used in new ways, such as in some types of innovative drugs. In addition, pharmaceutical companies have started requiring access to SoHO for research and product testing. Nevertheless, SoHO can only be obtained from the human body and the availability of donated allogeneic SoHO is currently limited, hence their use should be based on robust ethical principles.

* The present statement focuses on human tissue, cell and blood-derived products. However, the same considerations would be applicable to the field of organ transplantation. In the context of this document, the umbrella term "transplantation" should also be considered applicable in relation to medically assisted reproduction treatments.
As a rapidly evolving topic, the CD-P-TO may perform updates to this position statement in the future.

Some SoHO are used practically unaltered from the condition in which they were removed from the donor. Others, however, are processed into products that are almost unrecognisable as bodily material or are used in innovative applications that are regulated under frameworks other than those governing transplantation[1] and transfusion medicine,[2] e.g. advanced therapy medicinal products (ATMPs)[3] and medical devices.[4] Whether a blood, tissue or cell-based product is considered a medicinal product or a medical device instead of a blood component or a human tissue or cell transplant has important implications,[5] especially in the way these products are made accessible to patients, i.e. marketable products versus healthcare service. When SoHO-derived therapies are regulated under the transplantation or transfusion frameworks, they are provided as a therapeutic procedure after their quality and safety have been appropriately assessed. Conversely, human derivates regulated as ATMPs or medical devices are considered manufactured goods, which are typically made accessible to patients once their quality, safety and efficacy have been demonstrated, through their commercialisation by companies that generate a financial benefit.

Inevitably, this situation has created a market where procurement organisations, commercial tissue and blood banks, pharmaceutical companies and numerous brokers and distributors can charge fees for their services, with far-reaching consequences for the allocation of SoHO, the access to treatment by patients and the sustainability of public healthcare systems funding them. What constitutes a "reasonable fee" for the services provided has never been clearly defined, and this loophole can be exploited to turn altruistic donations into disproportionate profits. This situation creates tension between the altruistic principles of tissue and cell donation and industry's profit motivations. There is a risk that the interests of industry take precedence over the interests of patients and research. All these aspects around the commodification of altruistically donated human tissues and cells should be carefully and transparently considered with a view to guaranteeing the respect for fundamental ethical principles, safeguarding public trust, ensuring fairness and equity in patient access to treatment and supporting the sustainability of national healthcare systems, which are ultimately responsible for funding such therapies. In this sense, the choice of regulatory frameworks governing the use of these novel therapies involving SoHO may have far-reaching consequences and should be carefully considered through balancing evidence-based risks and potential benefits.

Despite their legal definitions, the lines between ATMPs, medical devices, transfusion medicine and tissue or cell transplants are blurred and this generates concerns regarding product classification. For example, in the European Union (EU):

- A product derived from human tissues or cells is considered an ATMP either when the tissues or cells have been subject to substantial manipulation, or when they are not intended to be used for the same essential function or functions in the recipient as in the donor.[3] However, these criteria are subject to interpretation.[6,7] Importantly, in the 15 years since the ATMP regulation was issued, no product classified as an ATMP based on the non-homologous use criterion has been granted a marketing authorisation in the EU.

- Products that are manufactured using derivatives of human tissues or cells that are rendered non-viable may be considered medical devices based on the ancillary function of the non-viable SoHO part.[4] Notably, the concept of ancillary function is not defined, and its interpretation is also controversial.

Importantly, the use of umbrella definitions (such as "substantial manipulation", "essential function" or "industrial manufacturing") may lead to the establishment of sometimes disproportionate requirements that are soundly based on potential risks from a scientific point of view. A clear example is represented by the bone marrow mononuclear cell fraction, which is rich in haematopoietic stem cells and stem cells of different types, including endothelial stem cells involved in neo-vasculogenesis in the adult.[8] It does not seem reasonable that the same product, obtained through a procedure considered a non-substantial manipulation, is processed in tissue establishments under transplantation standards for its allogenic use – administered by central venous route – into high-risk immunosuppressed patients diagnosed with haematological diseases, but must be processed under GMP for ATMPs when used autologously –

through a lower risk route of administration – to immunocompetent patients diagnosed with ischemic syndromes, because it has been considered that the cells are used for a non-essential function. The latter involves applying pharmaceutical quality standards, such as performing a sterility test based on the European Pharmacopoeia instead of a standard microbiological culture, among others, without a justifiable scientific basis, leading to unnecessary cost increases.

In addition to this complex reality, the lack of a homogenous approach to the regulation of research and evaluation of efficacy in the field of transplantation and transfusion medicine (because of the competences that have been conferred through Article 168 of the Treaty[9] on the Functioning of the EU) plays a role in over-classifying SoHO-based products as ATMPs. Aiming to ensure the protection of human health, Medicines Agencies in some countries may tend to over-classify certain SoHO-based products as medicines, even if they could be overtly considered transplants, given that mechanisms of oversight and evaluation may be inexistent or not sufficiently robust in the transplant setting. Nevertheless, regulatory requirements for novel therapies should be proportional to the potential risks and take into account the best available non-clinical and clinical evidence.

In July 2022, the European Commission adopted a proposal for a Regulation on standards of quality and safety for SoHO intended for human application[10] that, if adopted, will repeal the EU Directives on blood[2] and tissues and cells.[1] This proposed Regulation has entered the debate stage at the European Parliament and the Council of the EU. In parallel, the World Health Organization has drafted a proposal to foster the Regulatory Convergence of Cell and Gene Therapy Products.[11] Added to the many debates in this field that are taking place worldwide, both initiatives provide an opportunity to define a framework for collaboration between health authorities responsible for SoHO and the bio-technological and pharmaceutical industry, which will ultimately lead to the authorisation of therapies that are safe and accessible to all patients in need.

This document assesses the risks of commodification of SoHO under the current European setting and puts forward several proposals aimed at ensuring that the ethical principles of voluntary and unpaid SoHO donation and the non-commercialisation of the human body are respected, even in the context of innovative therapies that may, on occasion and based on risk-based assessments, need to be regulated under different regulatory frameworks.

Potential risks associated with the unrestrained commercialisation of SoHO-derived therapies

1. **Risk of violation of fundamental ethical principles.** The voluntary and unpaid donation of SoHO is firmly established by the Council of Europe,[12] the World Health Organization,[13] the EU,[1,2,14] the World Medical Association,[15] and the World Marrow Donor Association.[16] The Council of Europe Convention on Human Rights and Biomedicine[12] states that "*the human body and its parts shall not, as such, give rise to financial gain*" in order to protect human dignity and promote the altruistic donation of SoHO.[17] The manufacture of SoHO-derived ATMPs and medical devices involves the transformation of SoHO used as starting or raw material. Similarly, the preparation of some grafts for transplantation may also require complex processing steps. However, SoHO are donated under the principle of altruism and within a regulatory framework contrary to profit. ATMPs and medical devices are often marketed by companies that generate a profit, and this may also be the objective of commercial tissue establishments. Nonetheless, if not proportionate and appropriately disclosed to donors, this commercial goal is likely to undermine the altruistic and informed consent given by the donors and could even jeopardise the altruistic donation of the SoHO so desperately needed by patients whose survival or quality of life depend on them.

2. **Risk to the sustainability of healthcare systems.** The commercialisation of SoHO-derived ATMPs and medical devices is often associated with high costs derived from marketing activities, including fees for obtaining and holding patents and licenses for commercialisation, as well as the application of manufacturing standards[18] other than those under the transplantation regulatory framework[1,19] (although they may not always be necessary or justified based on scientifically sound risk-based assessments).[8] In fact, the prices of marketed ATMPs range

from several tens of thousands of euros to about 2 million euros per treatment, which can seriously strain the sustainability of healthcare systems.[20,21] These prices do not necessarily correspond to the costs and investments made by pharmaceutical companies for their development, manufacture and distribution.[22,23] Moreover, SoHO used as starting or raw materials for the manufacture of ATMPs are usually procured and undergo initial processing at public establishments funded by public healthcare systems.[15]

3. **Risk to patient access to SoHO-based therapies.** The high price of certain SoHO-derived ATMPs and medical devices can compromise their accessibility to patients because certain products may not be publicly funded, or public funding may be limited to a restricted number of patients.[24] This would largely restrict the access to those patients who are able to pay for them privately. On the other hand, patient access to these treatments may be compromised by a lack of supply when companies unilaterally decide to stop manufacturing certain products (e.g. for financial reasons).[25] It is important to emphasise that frequently SoHO result from the altruistic and sometimes complex act of donation,[26,27] which means that their availability may sometimes be limited. For this reason, patient access to treatment must be governed by the principle of equity[12,13,26] and not be subject to market rules.

Proposals to avoid the commodification of SoHO

1. To preserve and reaffirm the principle of non-commercialisation of SoHO, and to prohibit any remuneration of subjects who donate SoHO, whatever their final destination and future application may be, including the preparation of therapies that may be regulated under regulatory frameworks different than those governing transplantation. Mechanisms to guarantee transparency in donor recruitment strategies (including compensation schemes) and to regulate profits generated by SoHO-based therapies, including medicinal products and medical devices, should be developed. Moreover, a transparent pricing model that allows a proportionate profit and a possible economic return to contribute to the sustainability of donation programmes and the transformation of source materials could be sought. This approach would facilitate society's access to treatments that would not exist without their participation through the unpaid donation of SoHO as starting materials.

2. To establish mechanisms to guarantee transparency with regard to the final use of donated SoHO, including when seeking informed consent from donors. This consent should specify the destination of the donated biological material, whether for research or treatment purposes, and, where relevant, the possibility of subsequent profit for a third party.

3. To improve co-ordination between the various bodies and health authorities regulating the fields of transfusion medicine, transplantation, ATMPs and medical devices, both at supranational level, where relevant, and within each country. In order to perform balanced and well-informed risk-based assessments of novel therapies, taking into account the best available non-clinical and clinical evidence to date, as well as the quality and safety guarantees afforded by the different regulatory frameworks, it would be essential to establish multidisciplinary bodies that include experts from the four aforementioned fields. Their decisions should be duly justified according to proportionate risk-based criteria, considering their safety, quality and efficacy, as over-regulating carries important consequences.

4. To establish transparent and scientifically sound quality and safety standards for the donation, procurement and clinical use of SoHO that should be the same regardless of the final use of SoHO and be periodically revised taking into account the rapid developments in these fields. In this sense, the technical guides regularly published by the European Directorate for the Quality of Medicines & HealthCare (EDQM) of the Council of Europe[19,28,29] contribute to increasing the quality and safety of SoHO and to keeping requirements in this field up to date according to the best available scientific and clinical evidence, while also keeping in mind the protection of donors, recipients and offspring and the respect for fundamental human principles. Furthermore, they facilitate the implementation

of homogeneous standards throughout Europe and diminish duplication of efforts at the level of individual countries and SoHO establishments and entities, with a view to guaranteeing the safety and quality of SoHO applied to patients.

5. To regulate clinical research with SoHO in accordance with the level of complexity of the innovation and the potential risk for patients. In this area, the guidance provided by the GAPP Joint Action[30] should be considered.

6. To establish criteria and transparent mechanisms to assess and ensure not only the quality and safety but also the efficacy of new SoHO-based therapies prior to their incorporation into clinical practice as transplants and transfusion medicine. The capacity of transplant systems should be improved to ensure the oversight of research, evaluation of efficacy and incorporation of innovative SoHO-based products into clinical practice.

7. To promote mechanisms to foster development and innovation within tissue and blood establishments, which ensure citizens have access to SoHO-based therapies of greater added value, while safeguarding the sustainability of the system.

In conclusion, beyond its consequences in terms of equity in the access to innovative therapies and the sustainability of healthcare systems, the commercialisation of products derived from SoHO presents the challenge of reconciling respect for the principle of non-commercialisation of the human body with the profit generation that fosters innovation. This must be achieved without endangering the altruistic donation of SoHO for transplantation and, therefore, the treatment of patients whose survival and quality of life depends on those donations. The CD-P-TO has put together these proposals with the aim of contributing to that end and, ultimately, helping to bring new treatment opportunities to all patients.

References

1. European Union. Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. *Official Journal of the European Union* L 102; 2004 Apr 7: 48-58.

2. European Union. Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC. *Official Journal of the European Union* L 33; 2003 Feb 8: 30-40.

3. European Union. Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. *Official Journal of the European Union* L 324; 2007 Dec 10: 121-37.

4. European Union. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC. *Official Journal of the European Union* L 117; 2017 May 5: 1-175.

5. Cuende N, Herrera C, Keating A. When the best is the enemy of the good: the case of bone-marrow mononuclear cells to treat ischemic syndromes. *Haematologica* 2013;98(3):323-4.

6. European Medicines Agency Committee for Advanced Therapies. Reflection paper on classification of advanced therapy medicinal products. Ref: EMA/CAT/285241/2010 Rev.1. [available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/06/WC500187744.pdf, accessed 2022 Oct 10].

7. Izeta A, Herrera C, Mata R et al. Cell-based product classification procedure: What can be done differently to improve decisions on borderline products? *Cytotherapy* 2016 Jul;18(7):809-15.

8. Cuende N, Rico L, Herrera C. Concise review: bone marrow mononuclear cells for the treatment of ischemic syndromes: medicinal product or cell transplantation? *Stem Cells Transl Med* 2012 May;1(5):403-8.

9. Consolidated version of the Treaty on the Functioning of the European Union. *Official Journal of the European Union* C 326: 2012 Oct 26: 47-390.

10. Proposal for a Regulation on substances of human origin. European Commission [available from: https://health.ec.europa.eu/blood-tissues-cells-and-organs/overview/proposal-regulation-substances-human-origin_en, accessed 2022 Oct 12].

11. World Health Organization. WHO approach towards the development of a global regulatory framework for cell and gene therapy products. Ref: WHO/BS/2022.2424; [available from: https://cdn.who.int/media/docs/default-source/biologicals/bs2424_cgtp-document-for-2nd-public-consultation.pdf?sfvrsn=11a0c885_1, accessed 2022 Oct 10].

12. Council of Europe. Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine [available from: https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/164, accessed 2022 Oct 10].

13. World Health Organization. WHO guiding principles on human cell, tissue and organ transplantation. [available from: https://apps.who.int/iris/bitstream/handle/10665/341814/WHO-HTP-EHT-CPR-2010.01-eng.pdf?sequence=1&isAllowed=y, accessed 2022 Oct 10].

14. European Union. Directive 2010/45/EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation. *Official Journal of the European Union* L 207; 2010 Aug 6: 14-29.

15. WMA Statement on organ and tissue donation. Ferney-Voltaire: World Medical Association [available from: https://www.wma.net/policies-post/wma-statement-on-organ-and-tissue-donation/, accessed 2022 Oct 10].

16. Boo M, van Walraven SM, Chapman J et al. Remuneration of hematopoietic stem cell donors: principles and perspective of the World Marrow Donor Association. *Blood* 2011;117(1):21-5. doi: https://doi.org/10.1182/blood-2010-07-298430.

17. Council of Europe. Guide for the implementation of the principle of prohibition of financial gain with respect to the human body and its parts from living or deceased donors [available from: https://rm.coe.int/guide-financial-gain/16807bfc9a, accessed 2022 Oct 10].

18. European Commission. Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products. EudraLex. The Rules Governing Medicinal Products in the European Union. Volume 4. Good Manufacturing Practice [available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2017_11_22_guidelines_gmp_for_atmps.pdf, accessed 2022 Oct 10].

19. Council of Europe. European Directorate for the Quality of Medicines & HealthCare (EDQM). *Guide to the quality and safety of tissues and cells for human application* [available from: https://www.edqm.eu/en/guide-to-the-quality-and-safety-of-tissues-and-cells-for-human-application1, accessed 2022 Oct 10].

20. Nuijten M. Pricing Zolgensma – the world's most expensive drug. *J Mark Access Health Policy* 2022;10(1): 2022353. https://doi.org/10.1080/20016689.2021.2022353.

21. Ronco V, Dilecce M, Lanati E et al. Price and reimbursement of advanced therapeutic medicinal products in Europe: are assessment and appraisal diverging from expert recommendations?. *J Pharm Policy Pract* 2021;14(1):30.

22. Gonçalves E. Value-based pricing for advanced therapy medicinal products: emerging affordability solutions. *Eur J Health Econ* 2022 Mar;23(2):155-63. https://doi.org/10.1007/s10198-021-01276-2.

23. Trias E, Juan M, Urbano-Ispizua A, Calvo G. The hospital exemption pathway for the approval of advanced therapy medicinal products: an underused opportunity? The case of the CAR-T ARI-0001. *Bone Marrow Transplant* 2022;57:156-9. https://doi.org/10.1038/s41409-021-01463-y.

24. Organisation for Economic Co-operation and Development. Ensuring health system sustainability and access to innovation [available from: https://www.oecd.org/els/health-systems/Ensuring-health-system-sustainability-and-access-to-innovation.pdf,accessed 2022 Oct 10].

25. MolMed informs on its decision to withdraw the Conditional Marketing Authorization of Zalmoxis [press release] [available from: https://pipelinereview.com/index.php/2019101172535/DNA-RNA-and-Cells/MolMed-informs-on-its-decision-to-withdraw-the-Conditional-Marketing-Authorization-of-Zalmoxis.html, accessed 2022 Oct 10].

26. World Health Organization. WHO Principles on the donation and management of blood, blood components and other medical products of human origin [available from: https://apps.who.int/iris/bitstream/handle/10665/274793/A70_19-en.pdf?sequence=1&isAllowed=y, accessed 2022 Oct 10].

27. Common representation of Substances of Human Origin's (CoRe SoHO consortium 2016; EU Transparency Register number 501652723968-72).

28. Council of Europe. European Directorate for the Quality of Medicines & HealthCare (EDQM). *Guide to the preparation, use and quality assurance of blood components* [available from: https://www.edqm.eu/en/blood-guide, accessed 2022 Oct 10].

29. Council of Europe. European Directorate for the Quality of Medicines & HealthCare (EDQM). *Guide to the quality and safety of organs for transplantation* [available from: https://www.edqm.eu/en/guide-quality-and-safety-of-organs-for-transplantation, accessed 2022 Oct 10].

30. GAPP Joint Action. Facilitating the Authorization of Preparation Process for blood, tissues and cells [available from: https://www.gapp-ja.eu, accessed 2022 Oct 10].