Review

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# Addressing Risks Derived From the Commodification of Substances of Human Origin: A European Proposal Applicable Worldwide

Natividad Cuende, MD, MPH, PhD,[1] Anna Vilarrodona, MD,[2] Elena Vuelta, PhD,[3] Rosario Marazuela, MD, PhD,[4] Concha Herrera, MD, PhD,[5] Sergi Querol, MD, PhD,[2] Jacinto Sánchez-Ibáñez, MD,[6] Mar Carmona, Pharm,[4] Antonio Gayá, MD, PhD,[7] Jaume Tort, MD,[8] Dolores Hernández, MD, PhD,[4] and Beatriz Domínguez-Gil, MD, PhD[4]



**Abstract.** In view of the public consultation recently launched by the World Health Organization on Regulatory Convergence of Cell and Gene Therapy Products and the Proposal for a Regulation on substances of human origin (SoHO) repealing the European Union Directives on Blood and on Tissues and Cells, an opportunity arises to define an ethical and transparent framework of collaboration between industry and authorities responsible for SoHO-derived products, comprising medicines, medical devices, transfusion, and transplantation. The commodification of SoHO-derived medicinal products and medical devices entails important risks to the sustainability of healthcare systems and threatens the equitable access of patients to innovative therapies. It may also jeopardize the principle of altruistic donation of SoHO that is required for the treatment and survival of thousands of patients every year. This article puts forward several proposals aimed at reconciling the ethical principles of voluntary and unpaid SoHO donation and the noncommercialization of the human body with obtaining a profit that allows business activities, while ensuring high quality, safety, and efficacy standards of tissues and cells for clinical use.

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## BACKGROUND

The use of cells—stem, progenitor, or specialized cells—and tissues of human origin for therapeutic purposes has been growing significantly for several decades. It is not a new field of medicine as the first successful cornea transplant was performed over a century ago,[1] and the first successful transplants of hematopoietic stem cells from the bone marrow were carried out in the 1950s.[2] However, we are currently witnessing the development of new technologies that are revolutionizing medicine with the emergence of innovative therapies based on substances of human origin (SoHO).[3]

The regulation of SoHO-based therapies has evolved in recent years, giving rise to new categories of products that have been classified as medicines or medical devices in certain jurisdictions, as it is the case of the European Union (EU).

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*[1] Coordinación Autonómica de Trasplantes de Andalucía, Servicio Andaluz de Salud, Sevilla, Spain.*

*[2] Banc de Sang i Teixits, Vall d'Hebron Institute of Research (VHIR), Barcelona, Spain.*

*[3] Establecimiento de Tejidos Humanos, Fundación Clínica San Francisco, León, Spain.*

*[4] Organización Nacional de Trasplantes, Madrid, Spain.*

*[5] UGC de Hematología y Unidad de Terapia Celular, Hospital Universitario Reina Sofía, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), Universidad de Córdoba, Córdoba, Spain.*

*[6] Unidad de Criobiología-Establecimiento de Tejidos, Complejo Hospitalario Universitario A Coruña, A Coruña, Spain.*

*[7] Banco de Tejidos, Fundación Banco de Sangre y Tejidos de las Illas Balears, Instituto de Investigaciones Sanitarias Illes Balears (IdISBa), Palma de Mallorca, Spain.*

*[8] Organització Catalana de Trasplantaments, Barcelona, Spain.*

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*Correspondence: Natividad Cuende, MD, MPH, PhD, Coordinación Autonómica de Trasplantes de Andalucía, Servicio Andaluz de Salud, Avda de la Constitución 18, 41071 Sevilla, Spain. (natividad.cuende.sspa@juntadeandalucia.es).*



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These products coexist with tissue and cell (T&C) transplantation and transfusion medicine, subject to their own regulatory frameworks. Nevertheless, whether a SoHO-based product is considered one particular type of these products has important regulatory, organizational, and financial consequences, as well as relevant ethical implications.

The World Health Organization (WHO) has recently acknowledged the potential impact of novel SoHO-based products on global public health and the need, especially in low- and middle-income countries, to strengthen their regulatory capacity to provide oversight of these novel therapies. For that purpose, on December 2021, the WHO launched a draft for Public consultation[4] describing the components of such regulatory frameworks and aimed at ensuring convergence on minimum global standards for SoHO-based innovative products. Principles to be promoted by the WHO will likely mirror those that ground the EU legislation. In parallel, the European Parliament and the Council of the EU are currently debating a proposal for a Regulation on SoHO[5] that will repeal the EU Directives on Blood[6] and on T&C,[7] which at present are in force.

In this article, we analyze the risks derived from classifying SoHO-based therapies as medicinal products or medical devices that may be taken into consideration during the debate of the EU proposal for a Regulation on SoHO and during its future application by EU Member States. This exercise may also be helpful to non-EU countries that are currently revisiting or building their own legislation in this area, inspired by the previously mentioned WHO initiative. Moreover, although this analysis focuses on blood and their components and human nonreproductive T&C, certain emerging technologies applied to other SoHO, such as human organs,[8] could lead to reconsidering their regulatory framework, so it is crucial to contemplate this analysis from a global perspective.

## REGULATORY FRAMEWORK APPLIED TO SoHO-BASED PRODUCTS FROM THE EU PERSPECTIVE

### Definition of the Different SoHO-based Products

The different types of SoHO-based products according to the EU legislation are displayed in Figure 1. Human blood and somatic T&C, apart from being used for transfusion medicine or transplantation, can give rise to products classified as medicines or medical devices. Certain products that incorporate human T&C are regulated as medical devices.[9] Most types of advanced therapy medicinal products (ATMPs)[10] are SoHO-derived, such as somatic cell therapy medicinal products, ex vivo gene therapy medicinal products, tissue-engineering products and combined ATMPs that contain, as an integral part of the product, 1 or more medical devices. The limits between SoHO-based ATMPs, medical devices, T&C transplants,[7] and transfusion medicine[6] are sometimes difficult to establish as their definitions are not always clear-cut and there is certain overlap between all these products from a regulatory point of view.

A product made from human T&C is considered an ATMP in the EU based on 2 criteria: the T&C have been subject to substantial manipulation or are not intended to be used for the same essential function or functions in the recipient as in the donor. The ATMP Regulation[10] does not define what is meant by essential functions of T&C, though it does recognize that there may be several, nor does it specify what is meant by substantial manipulation, although the Regulation incorporates a nonexhaustive list of manipulations considered nonsubstantial (cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation, and vitrification). Furthermore, the interpretation of what are or are not essential functions is not always straightforward and may result in cases in which the classification of a product as a medicine may be controversial. An example[11] is shown in Figure 2.

On the grounds that the EU legislation, particularly the Regulation on ATMPs[10] and the Directives on T&C,[7] was considered incomplete with respect to certain products manufactured using derivatives of T&C of human origin that are or have been rendered nonviable, said products were included in the Regulation on Medical Devices,[9] which entered into force in May 2021. Thus, any device that, when placed on the market or put into service, incorporates as an

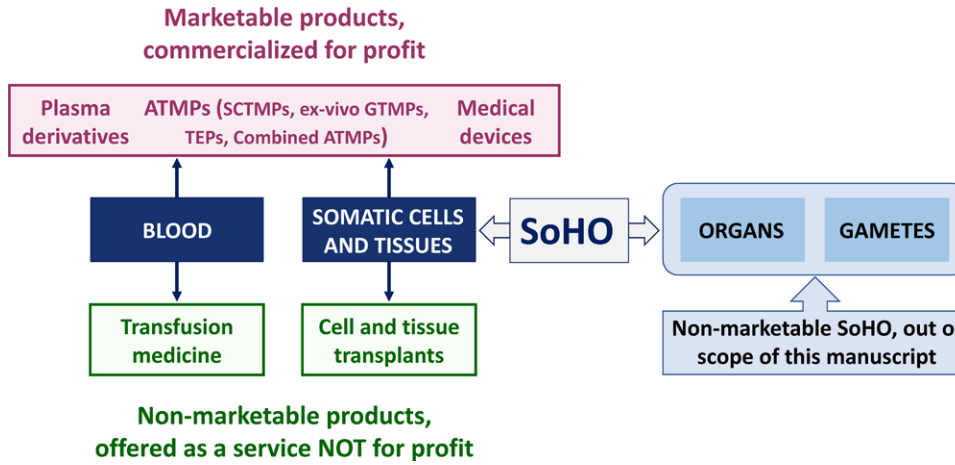


**FIGURE 1.** Products derived from substances of human origin (SoHO) according to the EU legislation. ATMP, advanced therapy medicinal product; GTMP, gene therapy medicinal product; SCTMP, somatic cell therapy medicinal product; TEP, tissue-engineered product.

integral part nonviable T&C of human origin or their derivatives that have a function ancillary to that of the device, must be evaluated and authorized as a medical device. However, the concept of ancillary function is not defined, and its interpretation may also be controversial. It should be noted that medical devices are considered goods in the EU legislation.

## Main Regulatory Implications for Different SoHO-based Products in the EU

Legislation governing blood or T&C donation applies regardless of its use for marketable or nonmarketable products. In fact, medicines and medical devices that use human blood or T&C as starting material are currently subject, respectively, to the EU Blood or the T&C



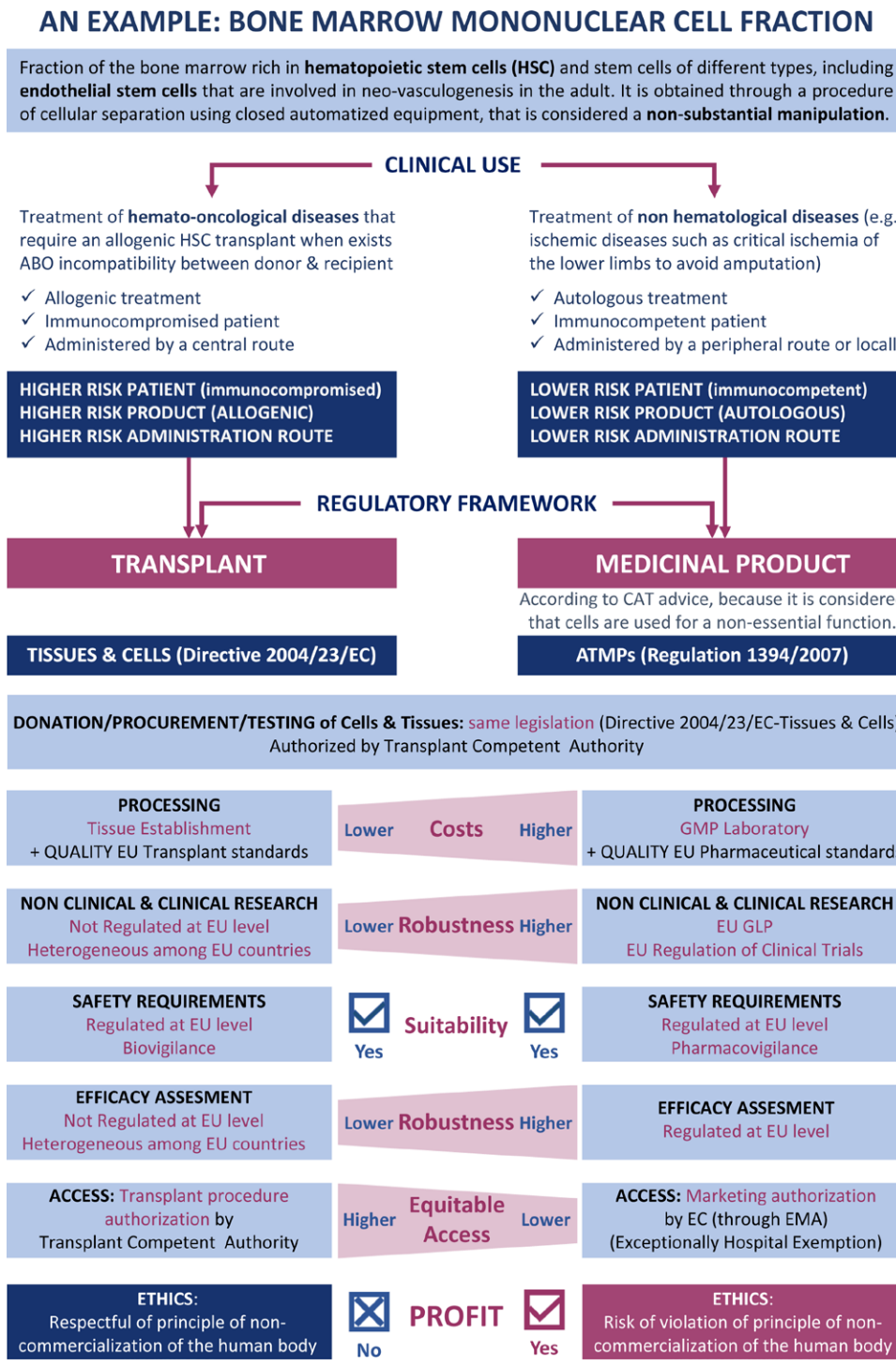


**FIGURE 2.** Example of the controversial classification of bone marrow mononuclear cells as advanced therapy medicinal product (ATMP) when used for the treatment of nonhematological diseases. Main differences in regulation of ATMPs and of cells and tissue transplants and their consequences are summarized. ATMP, advanced therapy medicinal product; CAT, committee for advanced therapies; EC, European Commission; EMA, European Medicines Agency; EU, European Union; GLP, good laboratory practice; GMP, good manufacturing practice.

Directives regarding donation, procurement or collection, testing, and traceability activities. In a near future, those activities will be subject to the new EU Regulation on SoHO now under discussion.[5] Beyond these activities, whether a SoHO-based product is considered an ATMP or a medical device instead of a transplant or transfusion has important implications from a regulatory point of view (Figure 2), mainly in the following aspects: the requirements for the production or manufacturing, and for the nonclinical and clinical development, the manner to assess efficacy and the way in which the products are made accessible to patients.[12]

The EU Directives on blood and T&C[6,7] only set common quality and safety standards applicable to SoHO, because of the powers that Member States have conferred to the EU through Article 168 of the Treaty on the Functioning of the EU.[13] Therefore, the legislation governing research and efficacy assessment for the incorporation of new modalities of transfusion medicine and T&C transplants into the clinical setting remain to each country's discretion.

With regard to how to access these products once their quality, safety, and efficacy or usefulness have been assessed, products considered to be transplants or transfusion medicine are incorporated into healthcare practice, as a therapeutic procedure with an established clinical indication, in health centers, services, and establishments which, in most countries, must be expressly authorized by the competent authorities to carry out each specific procedure. For ATMPs, the general rule is that they can be administered to patients if a company obtains marketing authorization from the European Commission, with the exception of a possible hospital exemption in cases of nonindustrially manufactured medicines prepared on a non-routine basis in order to comply with an individual medical prescription for a custom-made product for an individual patient.[14] In the case of medical devices, marketing them in the EU requires obtaining the CE Declaration of Conformity (or CE marking, where CE stands for Conformité Européene, which means European Conformity) issued by a notified body, so that it can be guaranteed that the design, manufacture, marketing, and distribution requirements are met.[9] Importantly, the legal framework for SoHO-based products considered as transplants and transfusion medicine does not allow profit, in contrast to that for SoHO-based products considered as medicines or medical devices.

As previously mentioned, the limits between the different SoHO-based products are sometimes difficult to establish, but how they are classified leads to major organizational, economic, and regulatory implications and may also rise important ethical issues that are described further ahead. In spite of this, there is an absence of bodies at the EU level, and frequently at the national level, that convey experts from all fields under which SoHO-derived products can be included, to allow consensual decisions on the classification of products. Moreover, the European Medicines Agency's Committee for Advanced Therapies is the only body at the EU level that can be directly consulted by stakeholders who develop these type of products (Figure 3). This situation can lead to an overclassification of novel SoHO-based products as ATMPs and even to recategorizing as medicines certain procedures that are regulated under a different legal framework and that are currently considered standard clinical practice, for example, the use of amniotic membrane for corneal repair or the infusion of donor lymphocytes.[15,16]

A reason behind this reality might be the lack of an EU homogenous approach to the regulation of research and evaluation of efficacy in the field of transplantation and transfusion medicine, because this has been left to each EU Member State. In some countries, Medicine Agencies, aiming at ensuring a high level of protection of patients, may tend to label 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.

## RISKS ARISING FROM THE COMMODIFICATION OF SoHO-DERIVED PRODUCTS

When SoHO-based products are classified as medicines or medical devices, we move into the realm of the commoditization of derivatives of SoHO, such that their availability is largely determined by their commercialization by pharmaceutical and biotech companies. It is important to note that, although it is true that basic and clinical research on ATMPs and regenerative medicines, unlike what happens with traditional drugs, is mainly led by academic and government sponsors,[17] the biopharmaceutical industry plays a necessary role in driving, not only financially, the development and arrival into the markets of many SoHO-based therapies. However, this marketing activity may entail significant ethical challenges and thus risks for the global donation and transplantation system, not just of blood, T&C but also organs, which are vital for the treatment of thousands of patients every year. In addition, the consequences for both the sustainability of healthcare systems and patients' equitable access to these treatments must be evaluated.

### Risk of Violation of the Principle of Noncommercialization

Obtaining T&C or blood components, whether from patients themselves or from a third person, to manufacture ATMPs or medical devices is regulated by either the transplantation or blood regulations, depending on the starting product, which do not allow profiteering. However, once manufactured, SoHO-based medicines and medical devices, unlike what happens with transplants, are marketed by companies that pursue financial benefit. In 2010, the 63rd World Health Assembly (WHA), confident that the voluntary and unpaid donation of organs and T&C from deceased or living donors contributes to ensuring the continuation of a vital community resource, adopted the WHO Guiding Principles on Human Cell, Tissue, and Organ Transplantation. The WHA urged Member States to promote the development of altruistic, voluntary, and unpaid donation systems, combat the pursuit of financial gain, and promote a transparent and fair allocation system for these SoHO guided by clinical criteria and ethical norms, as well as equal access to transplantation services in accordance with national capacity, which is the foundation for public support and voluntary donation.[18,19]

Following this, at the 70th WHA in 2017, a report by the WHO Secretariat, developed through a global consensus

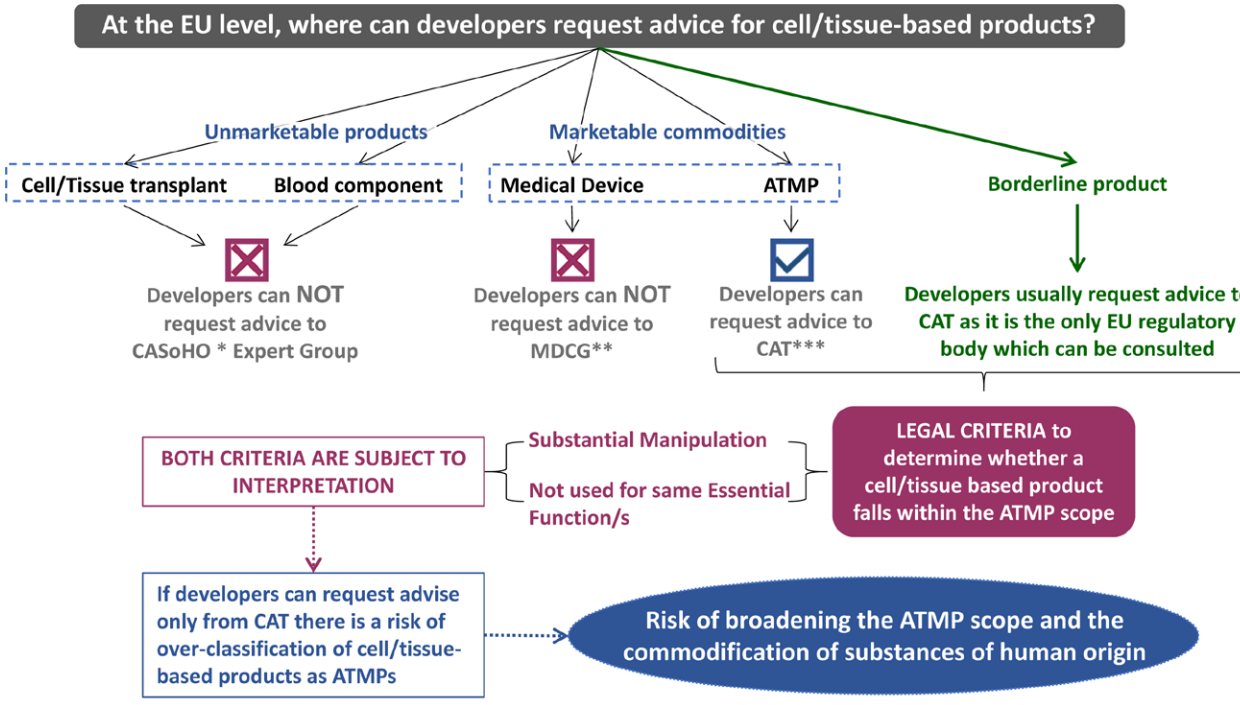


**FIGURE 3.** Institutions at European Union (EU) level, where developers of cell/tissue-based therapies can request advice and potential consequences. ATMP, advanced therapy medicinal product.

process, was presented, named *Principles on the donation and management of blood, blood components and other medical products of human origin*.[20] The report defines medical products of human origin as all biological materials that are derived wholly or in part from the human body and intended for clinical application. Recognizing the unique origin of these medical products, the human body, the report sets out 10 principles to promote ethical practices in the donation and management of medicinal products of human origin, which can be grouped into 3 pillars: (1) protecting the donor, both in terms of their state of health and of human dignity, and avoiding the exploitation of the vulnerable—in this regard, it emphasizes that the best model is noncommercial and financially neutral donation; (2) assessing, controlling, and reducing the risk that is inherent to the transfer of biological material between individuals; and (3) ensuring equity in access to these treatments. The report specifies that "some medical products of human origin, specifically those that undergo an extensive manufacturing process, (...) may be regulated as pharmaceuticals (...) or as medical devices. Regardless of how particular medical products of human origin are classified, all forms of regulation should explicitly address requirements specific to those medical products, such as donor protection. In practice, close collaboration among regulators internationally and among regulatory bodies within countries, and oversight of the various steps from procurement of the human biological material through to clinical application of the final product will be necessary to ensure efficiency and maintenance of standards across the whole process of preparing and using medical products of human origin."

For its part, the World Medical Association, in October 2017, approved a declaration on organ and tissue donation to promote policies applicable to donation from deceased and living donors that should be based on the ethical principles of altruism, autonomy, beneficence, equity, and justice, emphasizing that organs and tissues should not be sold for profit.[21]

The principle of noncommercialization is a firm foundation of the Council of Europe's legal acquis, established in the Convention on Human Rights and Biomedicine (also known as the Oviedo Convention) and its Additional Protocol on Transplantation.[22,23] The Convention states that "the human body and its parts shall not, as such, give rise to financial gain." In order to reaffirm this principle and reinforce its implementation, the Council of Europe has produced a Guide stressing the importance of preserving this principle to protect the dignity of the individual and promote the altruistic donation of SoHO.[24] However, the Convention only prohibits that human body material "as such" gives rise to financial gain. Moreover, the Explanatory Memorandum to the Oviedo Convention[25] specifies that "Under this provision organs and tissues proper, including blood, should not be bought or sold or give rise to financial gain for the person from whom they have been removed or for a third party, whether an individual or a corporate entity such as, for example, a hospital. However, technical acts (sampling, testing, pasteurization, fractionation,

purification, storage, culture, transport, etc), which are performed on the basis of these items, may legitimately give rise to reasonable remuneration." It is true that the manufacture of ATMPs involves the processing of blood or T&C used as starting material. Similarly, the manufacture of a medical device containing nonviable T&C of human origin in turn involves processes that manipulate the biological starting material. However, it is still a SoHO that has been donated within a regulatory framework contrary to profit but that will later give rise to a medicinal product or medical device that will be marketed with a clear financial benefit for companies, which could constitute a violation of the principle of noncommercialization of SoHO, especially if the profit made is not reasonable or proportionate. We must acknowledge that what constitutes a reasonable remuneration for the services provided has never been clearly defined, not only in the transplant or medical product setting but also in the research one, and this loophole can be exploited to turn altruistic donations into disproportionate profits. This situation creates a tension between the altruistic principles of blood and T&C donation and industry's profit motivations.[26]

Finally, donor compensation is worth mentioning as a potential additional ethical issue related to the noncommercialization principle. Donor compensation for loss of earnings and reimbursement of justifiable expenses is ethically appropriate.[25] Nevertheless, the lack of an unequivocal definition of compensation and the potential competition between companies and not-for-profit tissue banks to gain access to limited and precious SoHO might give rise to differences in financial compensation schemes that could partly determine the final destination of the donated human body material.[26]

## Risk of Invalidating the Consent Given by the Donors and Jeopardizing the Altruistic Donation of SoHO

According to the European and WHO principles, donation of SoHO must be voluntary and unpaid.[6,7,27] Consent for donation of SoHO must also be informed, even in countries with opt-out models—because opting out is applicable to the donation of organs or other SoHO for the specific purpose of transplantation. The consent given by donors could be invalidated if they have not been made aware of the final destination of the substance obtained and the potential subsequent profit for companies, especially if such profit is not proportionate. More worryingly, a disproportionate profit could jeopardize the altruistic donation of SoHO for transplantation and thus the treatment of patients whose survival and quality of life depends on such donations. This danger stems from the fact that the general public may believe that their altruistic donation can result in a disproportionate financial gain for pharmaceutical or biotech companies. If this became public, it could lead to a loss of trust in the transplantation field and people could decide to opt out of organ donation.[26]

## Risk of Unnecessary Increased Costs

The consideration of SoHO-based products as medicines implies their processing in accordance with guidelines on good manufacturing practice for ATMPs.[28] This entails higher costs than their processing in accordance with the applicable requirements when the products are considered transplants, not only in terms of production but also of structure, because pharmaceutical laboratories instead of tissue establishments are required. The pharmaceutical industry generally argues that it is better for SoHO-based products to be processed under pharmaceutical quality standards. However, there is no scientific basis for this assertion, and the application of these pharmaceutical standards may be unnecessary or even deleterious.[29] A clear example has been shown in Figure 2 referring to the bone marrow mononuclear fraction. It does not seem reasonable that the same product is processed in tissue establishments under transplantation standards for its allogenic use—administered by central venous route—into high-risk immunosuppressed patients diagnosed with hematological diseases, but it must be processed under good manufacturing practice for ATMPs when used autologously—through a lower risk route of administration—into immunocompetent patients diagnosed with ischemic syndromes. This entails applying pharmaceutical quality standards, such as performing a sterility test based on the European Pharmacopoeia instead of a standard microbiological culture, among others, without any scientific basis, leading to potentially avoidable cost increase.[30]

In the case of nonviable T&C that may be considered as medical devices, compliance with the regulatory requirements defined for their design, manufacture, authorization, and postmarket surveillance may also lead to increased costs, all without a solid argument that makes evident a higher quality and safety of SoHO compared with what already established by the European Directives and the Council of Europe Guides for the Quality and Safety of T&C,[31] the reference guide for European tissue establishments.

In case of borderline products, and especially for those products derived from SoHO not involving any substantial manipulation, considering the economic impact of their classification becomes even more important. The increased cost resulting from the application of quality standards for medicines or medical devices to human T&C has a different impact on companies and not-for-profit tissue establishments and may even represent an advantage for the former, because of their greater economic capacity and ability to cope with costs increases, which will subsequently be passed on in the price, thus eliminating the competition of public not-for-profit organizations.

In addition, the commercialization of ATMPs and medical devices entails higher costs derived from marketing activities—the greatest compared with other large companies[32]—including the fees for obtaining and holding patents and licenses for commercialization, that also have an impact on their prices, unlike the area of transplantation where there is no commercialization. Furthermore, it should be taken into account that Medicine Agencies are responsible for assessing the risk–benefit ratio for patients' health as a requirement for a medicinal product to be authorized but in general terms without incorporating the cost perspective (the price is then negotiated by bodies other than the agencies). Thus, if a medicinal product demonstrates beneficial effects, applying the highest pharmaceutical quality standards, irrespective of the cost involved,

may lead to a more favorable balance and make authorization more likely. Finally, as previously mentioned, medicine agencies may tend to overclassify some products as medicinal products in the belief that pharmaceutical standards, even in those cases where they might not be strictly necessary, lead to increased patient protection, which inevitably means an increase in costs.



## Risk to the Sustainability of Health Systems

The economic benefit that the commercializing of products based on human T&C entails, beyond the implications previously analyzed due to the possible conflict with the principles that govern donation and transplantation and that are contrary to profit, leads to healthcare systems being forced to assume higher costs in order to provide SoHO-based treatments when they are considered medicines or medical devices. The pharmaceutical sector is one of the most lucrative, if not the most lucrative industry sector, beyond even the banking industry.[32,33] It is also estimated that in the year 2020, medicines represented 14.9% of health expenditure in Europe, while medical devices, with a European market estimated in 140 billion euros in that same year, represented 7.6% of health expenditure.[34]

ATMPs, whether they have been fully developed by the industry or licensed through academia, fetch very high prices once they obtain marketing authorization.[35] Prices of marketed ATMPs range from several tens of thousands of euros to 3 million dollars per treatment, which is the price of the most expensive drug in the world.[36]

Few ATMPs have already obtained marketing authorization, and most of them are aimed at treating rare diseases,[37] but their high prices may compromise the sustainability of healthcare systems, especially as medicines for more prevalent diseases become available on the market, as we have seen in the case of other types of medicines, particularly when there is no alternative treatment.[38] Additionally, it does not seem that the high prices of medicines are always completely justified. The cases in which an excess price has been demonstrated are not exceptional.[39-41] Indeed, the price of medicines does not directly respond to the investment made by pharmaceutical companies in their research, development, manufacture, and marketing, although such investment is highly unknown due to the reluctance of the pharma sector to disclose this information.[42] Furthermore, the profitability of large pharmaceutical companies has been shown to be statistically much higher compared with that of other large companies in terms of gross profit margin and net income margin.[33]

ATMPs are not strangers to this reality, with prices that bear no obvious relation to their aggregated costs of development and manufacturing.[43] A recent example is the academic chimeric antigen receptor (CAR) T-cell therapy granted hospital exemption by the Spanish Agency of Medicines and Medical Devices after demonstration of quality, safety, and efficacy. This academic CAR-T is reimbursed by the Spanish National Healthcare System at one third the price of the commercial CAR-Ts available in Spain.[44] The reimbursement price was established after considering not only manufacturing costs, including those arising from the collection of the starting material, depreciation of equipment, failure of production or unused manufactured drugs, among others, but also and importantly adding an incentive for research.[45] In fact, CAR-T cell production in an academic nonprofit setting under specific conditions could cost nearly 10 times less than the price of the commercial products.[46] Lower manufacturing cost is expected in large pharmaceutical companies due to their manufacturing capacity on a larger scale, although they have to face higher logistics costs to the extent that manufacturing does not take place near hospitals. It is out of the question that companies must have economic benefits that allow them to attract investors. Nevertheless, the huge difference between the manufacturing cost and the price of commercial ATMPs might be partially due to a disproportionate profit made by marketed SoHO-derived products.

Due to the high price of innovative medicines, in 2017, the Organization for Economic Cooperation and Development was asked by the health ministers of every member country to produce a report on how to incorporate innovation into health systems while preserving their sustainability.[47]

## Risk to Patient Accessibility to SoHO-based Therapy

It is important to emphasize that the origin of SoHO lies in the altruistic and sometimes complex act of donation, which means that they are sometimes of limited availability. Currently, most commercialized SoHO-based ATMPs are made from autologous cells, but a shift to allogeneic sources is anticipated in upcoming commercial ATMPs. This is one more compelling reason that reinforces that patients' access to treatment must be governed by the principle of equity and not be exclusively determined by the marketing bases of the industry.

The commercialization of SoHO-derived products introduces a different approach to the development of therapies based on T&C of human origin, and especially to the way in which these treatments are accessed, because, unlike transplantation, companies are required to obtain and hold marketing authorization. After being placed in the market, it is up to health authorities of individual countries to decide whether to publicly fund such treatments and at what prize, so there is currently significant variation in ATMP reimbursement across EU countries, which means that there is variability in patient access to certain treatments that are publicly funded only in some jurisdictions.[35] The high price of certain medicinal products and medical devices can compromise accessibility, because not only certain products may not be publicly funded but also, even if funded, the high cost may force to limit the number of patients who receive funded treatment and prioritize those who might benefit the most.[43]

Additionally, it is also important to keep in mind the possible financial toxicity as a result of rising expenditures related to increasingly expensive therapeutics entering the market. This financial toxicity, initially described for cancer treatment, is especially concerning in countries where the private health insurance model plays a significant role, even for insured patients as they are experiencing higher out-of-pocket healthcare costs, leading to poorer financial well-being, quality of life, psychosocial health, and outcomes.[48,49]

Finally, patient access to these treatments may be compromised by a lack of supply when companies unilaterally decide to stop manufacturing certain products in order to move toward the development and marketing of more lucrative medicinal products or to shift marketing to more lucrative territories, as has already happened

in the growing field of ATMPs[50,51] and frequently occurs in more traditional biotechnology fields such as vaccines against infectious diseases, resulting in recurrent supply shortages.[52,53]

## PROPOSALS TO ADDRESS THE RISKS ARISING FROM THE COMMODIFICATION OF SoHO-DERIVED PRODUCTS

The analysis of the risks arising from the commodification of SoHO-derived products should not be seen as restricted to the EU region. Challenges are global and need to be addressed on a worldwide scale. The Proposal for a Regulation on SoHO repealing the EU Union Directives on Blood and on T&C,[5] currently under discussion, represents a unique opportunity, especially when regulatory convergence is promoted by the WHO and low- and middle-income countries are encouraged to regulate cell and gene therapy products adapting the framework developed by other regions such as the EU. We echo the proposals made by the European Committee on Organ Transplantation to avoid the commodification of SoHO included in a recently adopted position statement[54] (Table 1). The European Committee on Organ Transplantation is the steering committee in charge of organ, cell, and tissue transplantation activities at the European Directorate for the Quality of Medicines within the Council of Europe, which includes 46 member states, 27 of which are members of the EU. These proposals are aligned with those reflected in a previous position statement agreed upon within the South Alliance for Transplant,[55] a formal collaboration agreement between health authorities in the field of transplantation of 7 European countries. The proposals aim at preserving the ethical principles of SoHO donation and the accessibility of patients to innovative therapies in view of the future EU Regulation, although most of these proposals are applicable in other jurisdictions. Moreover, worldwide harmonization would be desirable to safeguard the competitiveness of the EU pharmaceutical and biotechnological industry as well as the accessibility of the European citizens, which might be at risk if similar rules do not apply in other territories.

Although some companies and industrial associations claim that SoHO donors can be remunerated,[56] we believe it is essential that the Proposal for a Regulation on SoHO is not modified in this regard due to the previously exposed ethical arguments. We should also be aware that, should a double route be allowed for the donation of SoHO depending on the final destination (altruistic donation of SoHO for transfusions and transplants versus remunerated donation of SoHO for commercial products), the transplantation field would be seriously threatened. Donor protection must be ensured by reinforcing the principles of altruism and solidarity that govern the donation of SoHO in the EU. This entails not allowing the remuneration of subjects who donate SoHO, whatever their final destination (including the preparation of medicines and medical devices) and future application, even within clinical trials. It will also require donor's informed consent on the final use of these substances, explicitly specifying the destination of the donated biological material, whether for research or treatment purposes, and the possibility of subsequent profit for a third party.

Similarly, mechanisms to regulate profits in relation to medicinal products and medical devices manufactured from SoHO should be established. To this end, a transparent pricing model that allows a proportionate profit for pharmaceutical and biotechnology companies should be sought. It should also be determined a possible economic return to contribute to the sustainability of donation programs and transformation of source materials. These proposals would facilitate societies' access to treatments that would not exist without their participation through the unpaid donation of this starting material.

Also important is considering the need for a proportional gain so as not to stifle the progress of cell therapies that will require pharma and market-driven financial support. A cost-based pricing model developed for cancer drugs[57] has recently been applied for ATMPs in order to make compatible a fair profit for companies with sustainability and affordability.[58] According to the model, the price is based on the costs of research and development (R&D)—adjusted for risk of failure and cost of capital—drug manufacturing, sales, marketing, the eligible patient population during patent protection, and a reasonable profit margin for the industry linked to the level of clinical benefit. Applying this model, the prices could be set between a third and a fifth of the current ones in the examples analyzed. Nevertheless, the sensitivity analysis showed that the assumed R&D expenses can have a tremendous impact on the calculated price, especially when the number of eligible patients is low. The lack of transparency from pharmaceutical companies regarding R&D expenses and the costs of drug manufacturing[42] is here emphasized as one limitation for the application of the model.[58] Moreover, as other authors have already pointed out, when R&D costs are calculated, they can be overestimated if the contribution of external research from large public academic medical centers with public funding and subsidies to companies are not taken into account.[49] In connection with this issue, it is worth mentioning that >50% of clinical trials with ATMPs and regenerative medicines worldwide are currently sponsored by academic and government institutions.[17]

In terms of accessibility and sustainability, it would be important to strengthen the role of academic and government institutions, including tissue establishments. A paradigmatic example is represented by the case of academic CAR-T cells, which are not only more affordable but are also used in indications not covered by commercial CAR-T cells.[59] It would be advisable to promote regulatory frameworks worldwide that facilitate the complementary use of noncommercial products with demonstrated quality, safety, and efficacy.[60]

Finally, it is imperative to improve the coordination and transparency in the classification of products obtained from SoHO and to avoid their potential overclassification as products subject to commercialization, even by revisiting existing definitions, so many SoHO-based products that are now labeled as medicines may be considered transplants whose future regulation[5] aims to strengthen innovation. In parallel, the transplant regulatory framework in the EU and other regions must be reinforced beyond the establishment of high quality and safety common

**TABLE 1.**

**Proposals to avoid the commodification of Substances of Human Origen of the Council of Europe's Committee on Organ Transplantation[54]**

1. To preserve and reaffirm the principle of noncommercialization 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 programs and the transformation of source materials could be sought. This approach would facilitate societies' 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, included 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 coordination 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 nonclinical 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 4 aforementioned fields. Their decisions should be duly justified according to the proportionate risk-based criteria, considering their safety, quality, and efficacy, as overregulating 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 and HealthCare (EDQM) of the Council of Europe 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 should be considered (Facilitating the Authorization of Preparation Process for Blood, Tissues and Cells, https://www.gapp-ja.eu).
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.

ATMP, advanced therapy medicinal product; SoHO, substances of human origin; T&C, tissues and cells.



standards. 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.

## CONCLUSIONS

We acknowledge the essential role of industry and market driven financial support in developing and making many innovative SoHO-based therapies available. Nevertheless, the commercialization of products derived from SoHO has consequences in terms of patients' equitable access to innovative therapies and sustainability of healthcare systems. More importantly, it faces us with the complex challenge of reconciling the respect for the principle of noncommercialization of the human body with the obtaining of a profit that allows business activities, all without putting at risk the altruistic donation of SoHO for transplantation and, therefore, the treatment of patients whose survival and quality of life depends on those donations. Our proposals may contribute to that end and help to bring new treatment opportunities to our patients.

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