Commentary

The new SoHO Regulation. What should the blood system expect?

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In 2015, G. Folléa and K. Aranko published a paper setting out the "state of the art" of the four European Union (EU) blood directives[1] that entered into force between 2003 and 2005. According to the principle of subsidiarity, stating that the responsibilities of Member States include the management of health services, the EU directives focused more on the "product" and less on the "patient", leaving the responsibility to manage health care issues to the Member States themselves. The authors recognized that the EU blood directives certainly provided a solid regulatory basis for quality and safety of collection, testing, processing, storage and distribution of human blood and blood components. Nevertheless, scientific knowledge highlighted the need to consider a revision of these directives, promoting the implementation of a more patient- and donor-centered approach. The same considerations may be extended to the field of tissues and cells, in which the introduction of technical innovations as well as continuous scientific development necessitate updating of the related EU legislation.

Therefore, the EU Commission promoted several initiatives and funded joint actions and projects through the Public Health Programme (2014-2020)[2] with the specific aim of strengthening the Member States' capacity to oversee the field of blood transfusion and tissue and cell transplantation.

The first joint action, named Vigilance and Inspection for the Safety of Transfusion, Assisted Reproduction and Transplantation (VISTART)[3] was led from 2015 to 2019 by the two Italian competent authorities for Blood (the National Blood Center) and Organs, Tissues and Cells (the National Transplant Center) with the support of many Member States, technical organizations and external experts. The key objectives were to promote and facilitate the harmonization of the inspection, authorization and vigilance systems for blood, tissues and cells (BTC) including reproductive cells and to improve collaboration between Member States by increasing confidence in each Member State's overseeing activities. The initiative also aimed to increase the consistency and efficiency of the competent authorities through the introduction of EU level tools across BTC. VISTART was preliminary to another EU joint action aimed to facilitate a common approach to assess and authorize novel preparation processes[4]. Furthermore, in this context, the National Blood Center and the National Transplant Center proposed the implementation of the ongoing joint action "Piloting GAPP model approach for assessing and authorizing novel substances of human origin preparation PROcesses" (GAPP-PRO), which aims at testing and improving GAPP methodology through specific actions, and includes new SoHO, such as breast milk and serum eye drops[5]. Most of the deliverables (guidelines,

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tools) produced within these initiatives have contributed clearly to the revision process, providing input for the definition of some parts of Regulation (EU) 2024/1938 of the European Parliament and of the Council of 13 June 2024[3], published in July 2024 in the Official Journal. The act is both binding in its entirety and directly applicable in all Member States unless otherwise provided for in its paragraph 2; it shall apply from 7 August, 2027.

What are the main reasons why the EU Commission updated the BTC legislation?

The EU SoHO directives were published more than 20 years ago and no longer reflected the scientific and technical developments that have occurred since their adoption. An impact assessment, performed in 2019, identified five key areas in which the legal framework had shortcomings regarding the current situation: 1) patient protection from new risks, mostly arising from global epidemiological changes; 2) donor protection, including offspring from medically assisted reproduction; 3) oversight activities being approached differently by Member States, potentially producing unequal levels of quality and safety of the SoHO; 4) inadequate capacity of the legislation to deal with innovation; and 5) weakness of the EU system to guarantee the continuity of the supply of SoHO during emergencies.

The development of the new Regulation therefore started with the aim of producing one high-level act providing principles and measures for BTC, including medically assisted reproduction, that apply to regulatory authorities, to SoHO entities as well as to hospitals and clinics in which SoHO are used to treat patients.

SoHO entities are any entity legally established in the Member States carrying out one or more SoHO activities. SoHO establishments are those entities that carry out any of both processing and storage, release, import, and export. According to the Regulation, a SoHO competent authority shall formally authorize its own SoHO establishments, and may decide about the extension of licensing/authorization to its SoHO entities according to a documented risk-based assessment.

Only SoHO establishments are in charge of the so-called "preparation processes", which shall be formally approved and authorized by the SoHO competent authority. The latter shall have in place and maintain a system for receiving and processing any application submitted by its own SoHO establishment, in order to decide about its approval. The preparation process dossier shall also include a clinical outcome-monitoring plan to demonstrate not only the safety but also the efficacy of the new product. The plan shall be approved preliminarily by the competent authority in case the scientific evidence and clinical data provided as part of the benefit-risk assessment, carried out by the applicant, are not sufficient, or in case in which the risk is more than negligible. The preliminarily approved clinical-outcome monitoring plan shall be the basis for the collection of further evidence to allow for the assessment and authorization of the new SoHO preparation or a new indication for the SoHO preparation. Again, a risk-based approach shall support the decision about the extension of the clinical monitoring plan, which shall be proportionate to the level of risk identified, where needed.

Other major changes include a range of new measures, which fill some gaps in the BTC directives. In relation to innovation, the new Regulation covers other substances such as human breast milk, microbiota and serum eye drops, as well as bedside preparations, which present similar safety and quality concerns being of human origin. Prospectively, new SoHO for human application could fall within the scope of new legislation regarding their preparation and authorization rules, supported by the definition of technical standards and specifications in the European Directorate for the Quality and Medicines and HealthCare (EDQM) guidelines. These guidelines are already widely applied in BTC fields, but they will become the primary means to meet EU standards of quality and safety for SoHO. Both EDQM and the European Centre for Disease Prevention and Control (ECDC), consistently with their mandate, will provide authoritative technical guidelines for the safety and quality of SoHO and the protection of donors, recipients, and offspring, reflecting high-quality and state-of-the-art scientific evidence, to help BTC professionals to meet the minimum best standards required. In this way, any new scientific and technical evidence can be considered more rapidly than waiting for an amendment of the Regulation and so safety requirements can be kept up to date (e.g., donor selection criteria, testing for infectious or non-infectious diseases).

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In order to strengthen the capacity of BTC systems to guarantee continuity of supply both during routine circumstances and during critical situations, SoHO entities will be asked to report their annual activity data at the European level to facilitate the improvement of donation rates of Member States or mitigate shortages, if they occur. A new task for the Member States is to identify SoHO entities working with critical SoHO, intended as those SoHO "*for which an insufficient supply will result in serious harm or risk of serious harm to recipients' health*". Critical entities shall have documented plans to address emergencies in the case of a fall in supply.

To support Member States' interconnection and harmonization of best practices in SoHo fields, the new Regulation puts forward the creation of an EU SoHO Platform, a central digital tool for authorities and stakeholders to facilitate data exchange in the sector. The EU Commission will host the platform, providing a central hub for access to information regarding SoHo entity registrations, authorizations, technical guidelines, and aggregated data on donations, clinical use and adverse reactions, all in line with data protection rules.

Furthermore, the Regulation establishes the creation of an advisory body that will support Member States in the implementation of the Regulation itself. The SoHO Coordination Board has the task of developing common practices for inspection and vigilance, of providing advice on the applicability of the Regulation, and of supporting competent authorities in the supervision of the sector. The SoHO Coordination Board will also improve cross-sector coherence, facilitating interconnection with other legal frameworks, such as those governing medical devices and pharmaceutical ones, regarding regulatory borderline issues that might arise from the introduction of innovation.

The new Regulation represents a primary law in the EU constitutional framework. Hence, it does not require transposition into national law by the Member States. Anyway, "*it does not prevent Member States from maintaining or introducing more stringent protective measures*". However, if Member States do so, they must make such measures publicly available for reasons of transparency. Furthermore, the Member States shall demonstrate that the national measures provide standard requirements with the same high level of quality and safety and that they are proportionate to the risk to human health.

Will the new Regulation have an impact on the blood system?

Yes, it definitely will. One positive impact will be the existence of an effective mechanism to adapt transfusion activities quickly to scientific and technical developments. Another will be the availability of effective tools for preparing and supporting the system to address critical situations promptly. Nevertheless, blood systems should recognize that a new model for managing manufacturing activities needs to be implemented in order to save resources for improving quality and safety and guaranteeing the best blood therapy for patients.

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