LAW360

Portfolio Media. Inc. | 230 Park Avenue, 7th Floor | New York, NY 10169 | www.law360.com
Phone: +1 646 783 7100 | Fax: +1 646 783 7161 | customerservice@law360.com

A Primer On EU's Updated Human Substance Regulations

By **Geneviève Michaux and Georgios Symeonidis** (August 6, 2024, 6:54 PM EDT)


Geneviève Michaux


Georgios Symeonidis

On July 17, the European Union adopted a regulation on standards of quality and safety for substances of human origin, or SoHOs, intended for human application. The SoHO regulation, which updates and replaces the EU Blood Directive[1] and the EU Tissue and Cells Directive[2] — collectively, the blood, tissues and cells legislation, or BTC legislation — will become applicable by mid-2027.

The SoHO regulation aims to protect donors, recipients and offspring from medically assisted reproduction by setting high standards of safety and quality for all substances of human origin used in healthcare and for all activities related to such substances falling into its scope of application.

It also seeks to improve EU harmonization and remove the current national divergences that impede cross-border exchange of and access to SoHOs.

Harmonization, however, is not guaranteed because the SoHO regulation does not prevent member states from maintaining or introducing more stringent protective measures — for example, the presence of qualified medical professionals where SoHO collection takes place — albeit compatible with EU law and proportionate to the risk to human health.

It is a complex legal framework that carries significant implications for all companies involved in the development and manufacture of medicinal products and medical devices using human-derived substances, such as blood, tissues, cells, bone marrow, etc.

The framework strengthens the safety and quality standards applicable to the starting and raw materials used for those products, imposes more obligations on entities active in the SoHO sector, and expressly addresses borderline products. Moreover, the SoHO regulation regulates the export and import of SoHOs, which is especially relevant for U.S. companies active on the EU market.

This article provides a general overview of the SoHO regulation and examines some of its aspects that are especially relevant for pharmaceutical and medical devices companies — U.S. companies in particular — using SoHOs to manufacture their products.

Scope of Application — SoHOs and SoHO Activities

The SoHO regulation covers all SoHOs — any substance collected from the human body, whether it

contains cells or not and whether those cells are living or not, including SoHO preparations resulting from the processing of such substance — intended for human application or used to manufacture products regulated by other EU legislations and intended for human application.

A SoHO is used for human application where it is being inserted, implanted, injected, infused, transfused, transplanted, ingested, transferred, inseminated or otherwise added to the human body in order to create a biological interaction with that body.

Some SoHOs were already covered by the BTC legislation: blood and blood components; tissues; cells including hematopoietic stem cells from peripheral blood umbilical-cord blood or bone marrow; reproductive cells and tissues; embryos; fetal tissues and cells; and adult and embryonic stem cells.

The SoHO regulation extends the scope to human breast milk (unless used exclusively for feeding one's own child, without processing), intestinal microbiota, blood preparations for use other than transfusion, and, more generally, any other SoHOs that could be applied to humans in the future.

However, it covers neither substances without any biological interaction with the body when used (e.g., wigs from human hair), nor solid organs unless they are removed from a SoHO donor for the purpose of separating tissues or cells for human application (e.g., heart valves from a heart or pancreatic islets from a pancreas).

The SoHO regulation also covers the SoHO activities — activities that have a direct impact on the quality, safety or effectiveness of SoHOs — that it enumerates. In essence, all activities related to SoHOs are regulated, from donor registration and testing, collection, processing, quality control to storage, distribution, import and export, clinical outcome monitoring, release, and clinical outcome registration.

Regulation of Products, Activities and Entities

The SoHO regulation is a very complex piece of legislation, and part of its complexity results from regulation not only of products and activities but also entities.

Regulation of Products

SoHO preparations are legally defined as a type of SoHO that (1) has been subjected to processing (any operation involved in the handling of SoHOs, including, but not limited to, washing, shaping, separation, decontamination, sterilization, preservation and packaging) and, possibly, one or more SoHO activities; (2) has a specific clinical indication; and (3) is intended for human application to a SoHO recipient or for distribution.

Examples of SoHO preparations include different types of plasma for transfusion, platelets, or stem cells for transplantation. Typically, SoHO preparations are used for treatment by transfusion, transplantation and medically assisted reproduction.

The SoHO regulation sets up a harmonized system for authorization of SoHO preparations. No SoHO preparation may be released for distribution or prepared and immediately applied without prior authorization except for the implementation of a clinical outcome monitoring plan as part of the authorization. A clinical outcome monitoring plan seeks generating additional evidence of safety and effectiveness required for the authorization.

Authorizations are granted by national competent authorities, based on a benefit-risk assessment and scientific data, to SoHO entities located in their territory and are valid throughout the EU.

However, an EU member state may decline to recognize an authorization given by another EU member state, where it has adopted more stringent rules for a specific SoHO preparation and compliance therewith is not yet demonstrated by the responsible SoHO entity.

Regulation of Activities

SoHO activities are regulated through the SoHO lifecycle. Specific standards are set for the quality and safety of each SoHO activity, and the quality management system to be implemented by SoHO entities must consider each SoHO activity conducted by the SoHO entity.

Regulation of Entities

Entities involved in SoHO activities are subject to obligations, which vary depending on the nature of the entity.

SoHO entities are entities established in the EU that carry out one or more SoHO activities. They must register with their national competent authority. SoHO entities must appoint a responsible person for ensuring compliance of SoHO activities, implement procedures to ensure the traceability and coding of SoHOs, organize a vigilance system, etc.

SoHO entities must also conduct a self-assessment of whether they qualify as a critical SoHO entity, i.e., their activity contributes to the supply of a critical SoHO, since special rules apply to entities dealing with so-called critical SoHOs — SoHOs for which an insufficient supply will result in serious harm or risk of serious harm or in a serious interruption in the manufacture of products regulated by other EU legislation.

SoHO establishments are a subcategory of SoHO entities that carry out any of the following SoHO activities: processing and storage; release; import; and export. National SoHO-competent authorities may decide that other SoHO entities must also be authorized such as SoHO entities that (1) have a significant influence on the safety and quality of the SoHO due to the scale, criticality or complexity of their SoHO activities or (2) carry out activities in connection with multiple SoHO establishments.

Besides being authorized rather than registered, SoHO establishments must comply with stricter requirements including the appointment of a physician — entrusted with, for example, procedures and policies for SoHO donor eligibility criteria, allocation of SoHOs, and clinical data collection — and a releasing officer, if applicable, and they are regularly inspected by SoHO-competent authorities.

Autologous Use

Currently, compliance with the donation, procurement and testing requirements set out in the BTC legislation leads to long and costly procedures for companies involved in the development, manufacturing and distribution of autologous products, which, however, are not truly necessary since the tissues and cells are collected from one individual for subsequent application to the same individual. The SoHO regulation removes this disproportionate administrative burden.

Where a SoHO intended for autologous use — human application of a SoHO collected from a person to the same person — is processed and stored before human application, the SoHO regulation applies, e.g.,

authorization of the SoHO preparation and release, because of contamination risks.

If the SoHO is neither processed nor stored before human application, the SoHO regulation does not apply. If the SoHO is processed but not stored, the SoHO preparation authorization must specify the quality control parameters to be monitored during the processing, and no release before human application is necessary.

The same rules generally apply to within-relationship use of SoHOs, i.e., the use of reproductive SoHO for medically assisted reproduction between persons with an intimate physical relationship.

In addition, when a closed-system medical device is used in an autologous context, e.g. hemodialysis at bedside or at home, or red-cell salvage during surgery, the SoHO regulation does not apply, provided that the closed-system medical device has been CE marked. If it is not CE marked, the SoHO regulation does apply to the processing of a SoHO at bedside or in the same surgical procedure.

Import and Export of SoHOs

The SoHO regulation facilitates the circulation of SoHOs within the EU through harmonized standards and requirements and regulates the import of SoHOs from third countries through equivalent standards. Both EU and international circulation are key aspects for companies involved in the manufacturing of SoHO-based medicinal products and medical devices.

Import of SoHOs from third countries — activities to carry out to bring SoHOs into the EU from a third country before their release — is more strictly regulated than the other SoHO activities. Imported SoHOs must meet quality, safety and effectiveness standards equivalent to the EU standards, so the importer must have procedures in place to ensure that the quality, safety and effectiveness of imported SoHOs are equivalent to those of authorized SoHO preparations.

An EU pharmaceutical or medical devices company that imports SoHOs into the EU for manufacturing purposes qualifies as a SoHO establishment. An importing SoHO establishment is required for a SoHO establishment that imports SoHOs, except in case of import of human plasma that is intended for the manufacture of medicinal products and is included in a plasma master file. Importers are authorized under the pharmaceutical rules.

However, imports may be authorized for immediate application (1) to a specific SoHO recipient upon a clinically justified request from a SoHO entity or (2) where health is seriously endangered without such import.

The application for authorization must include (1) the license or the like granted by the third-country authority for activities related to SoHOs and (2) written agreements entered into between the SoHO establishment and one or more third-country suppliers, which impose both equivalence of the quality, safety and effectiveness of the SoHO to be imported and inspections by national SoHO-competent authorities.

Indeed, SoHO-competent authorities may inspect any third-country supplier — an organization, located outside the EU, which is contracted to supply SoHOs or to perform activities that might influence the quality and safety of the SoHO imported — when examining the application, in particular in cases of regular and repeated import of SoHOs from the same non-EU supplier.

The importing SoHO establishment is responsible for the physical reception, visual examination and verification of the SoHOs before release. Those tasks, however, can be delegated to the SoHO entity when the SoHO is meant for a specific recipient. Indeed, imported SoHOs may not be physically received by the SoHO establishment but sent directly to the SoHO entity for human application or an operator for manufacturing.

The EU Commission will adopt delegated acts to set out obligations and procedures for importing SoHO establishments and to verify equivalent standards for imports of SoHOs. The latter may be an issue for imports of blood, tissues and cells from countries applying standards that are not considered as equivalent by the EU Commission.

U.S. companies active on the EU market will have to ensure that SoHOs exported to the EU meet safety and quality standards that are equivalent to such EU standards and thus will have to impose and to check that their U.S. suppliers comply with this requirement.

U.S. companies will also have to ensure and check that their EU partners comply with the SoHO regulation in the EU. Overall, this will trigger additional costs and may delay the export of SoHOs to the EU.

Export of SoHOs to third countries is not specifically addressed by the SoHO regulation. An EU pharmaceutical or medical devices company that exports SoHOs to a third country also qualifies as a SoHO establishment.

Exported SoHOs must comply with the SoHO regulation except if the export is triggered by an express request from a third-country physician or authority who acknowledges noncompliance with applicable rules. Compliance is confirmed by a release before export.

Applicable Legislation

The SoHO regulation expressly covers SoHOs intended for human application and SoHOs used to manufacture medicinal products and medical devices. SoHO preparations are regulated by the SoHO regulation, but one may wonder about the application of the SoHO regulation to medicinal products and medical devices.

One of the most significant impacts of the SoHO regulation on pharmaceutical and medical device sector concerns products using SoHOs and SoHO preparations as starting materials because the SoHO regulation governs the sourcing of, and activities with, those SoHOs and SoHO preparations.

SoHOs can be collected, and SoHO preparations can be used, for manufacturing medicinal products,[3] e.g., advanced therapy medicinal products,[4] medical devices,[5] and investigational medicinal products.

In such cases, the authorization requirement for SoHO preparations is not applicable and only the provisions of the SoHO regulation regulating certain SoHO activities apply to the SoHOs. This limited application of the SoHO regulation does not seem to concern investigational medical devices since they are not expressly mentioned.

Under the previous regime, tissues and cells to be used in ATMPs had to comply with the donation, procurement and testing requirements set out in the BTC Legislation. The same logic applies under the SoHO regulation.

The SoHO regulation applies to the registration, history review and medical examination, and testing of SoHO donors, as well as to the collection and release of SoHOs up to their distribution to the manufacturer of the medicinal product or the medical device, e.g., the moment that the SoHO is released to the manufacturer.

Release is defined as "a process through which it is verified that a SoHO meets defined quality and safety criteria and fulfils the conditions of any applicable authorization, before distribution or export."

Afterward, the pharmaceutical or medical device legislation starts applying. The SoHO regulation also applies to the storage, distribution, import and export of SoHOs if those activities are carried out.

In the case of medicinal products or medical devices for autologous therapeutic use, the SoHO regulation only applies to the testing and collection of the SoHO.

Qualification of Borderline Products

The determination of the legal status of products is a prerequisite for regulatory compliance. In the past, blood, tissue and cell-based products have been requalified as advanced therapy medicinal products, or ATMPs, which required manufacturers to comply with a new, more stringent legal regime.

During the legislative process, the European Commission stressed that the SoHO regulation feeds into the ongoing revision of the European general pharmaceutical legislation, in particular regarding the regulatory delineation between the SoHOs and pharmaceutical sectors, and that the delineating criteria between medicinal products and SoHO preparations are set by the definitions in the pharmaceutical framework.

Therefore, the SoHO regulation does not include criteria for borderline products. Nevertheless, it recognizes the high level of interaction and interdependence among the different relevant legislations and the importance of avoiding discrepancies and overlaps, and contains rules designed to secure harmonization in the national handling of borderline products.

Express Borderline Provisions

Products may combine medical devices and SoHOs. On the other hand, combinations of medicinal products and SoHOs do not seem possible since a product is either a medicinal product or a SoHO preparation.

Under the EU ATMP regulation, when cells and tissues are substantially manipulated or are used in the donor for an essential function different from the essential function in the recipient, the product qualifies as an ATMP. Therefore, the SoHO regulation focuses on combinations of medical devices and SoHOs.

In the case of products combining a nonviable SoHO or a derivative and a medical device, each element of the combination must comply with the relevant requirements, i.e., the SoHO preparation component must be authorized under the SoHO regulation and the medical device must be CE marked.

Where a nonviable SoHO or a derivative incorporates, as an integral part, a medical device and the action of the nonviable SoHO is the primary action, the SoHO regulation applies to the combination, and the SoHO-competent authority must verify that the medical device has been certified by a notified body under the EU Medical Devices Regulation.

Where the action of the nonviable SoHO is ancillary, the Medical Devices Regulation applies to the combination, and a SoHO-competent authority can be asked to provide an opinion on the conformity of the SoHO preparation to the SoHO regulation.

Borderline Processes

It is for the EU member states to decide on the regulatory status of products, on a case-by-case basis.

However, in cases of uncertainty about the regulatory status of a substance, product or activity under the SoHO regulation, the national SoHO-competent authorities must consult with the national authorities from other relevant regulatory frameworks and may or must — when consultations are not successful — request an opinion of the SoHO coordination board or another EU competent authority. The member state must justify its decision when it deviates from the coordination board's opinion.

Furthermore, the European Commission has the authority to determine, upon a duly substantiated request of an EU member state or on its own initiative, the regulatory status of a substance, product or activity to ensure consistency across member states.

The coordination board is entrusted with the publication and update of a compendium of EU and national opinions and decisions for reference purposes.

Principle of Voluntary Unpaid Donation

Currently, the BTC legislation expressly sets out the principle of voluntary unpaid donation that prohibits financial incentives to donors but allows reimbursement of expenses and compensation.

This principle, however, is implemented very differently among member states, and the shortage of plasma during the COVID-19 crisis drew the EU Legislature's special attention on the issue.

Under the SoHO regulation, EU member states remain competent to regulate the compensation and reimbursement of living donors, but the principle of financial neutrality has been expressly introduced in the SoHO regulation.

Since this principle prohibits financial gain or loss as a result of donations, the EU member states allowing compensation and reimbursement of donors must establish transparent criteria, including fixed rate allowances and upper limits, and ensure that compensation schemes do not result in competition among SoHO entities for recruiting SoHO donors.

While the principles of voluntary unpaid donations and financial neutrality have so far been applied to blood and blood components, they may prove relevant for other SoHOs in the future, for example, as more allogenic gene and cell therapy products are developed.

Transitional Measures

On Aug, 6, the SoHO regulation entered into force and the three-year transitional period for the application of the SoHO regulation started. Until Aug. 7, 2027, the EU Commission will adopt a series of measures to implement certain provisions such as import of SoHOs and traceability requirements.

National blood and tissues establishments that have been designated, authorized, accredited or licensed

under the BTC legislation before Aug. 7 are deemed to be registered as SoHO entities or authorized as SoHO establishments, respectively.

Entities carrying out SoHO activities that were not expressly addressed in the BTC legislation have until Aug. 7, 2025, to comply with the SoHO regulation except for the registration of SoHO entities, application for authorization of a SoHO establishment or a SoHO preparation by Nov. 7, 2025, and compliance with the standards for donor protection and recipients and offspring protection.

Similarly, SoHO preparations resulting from tissue and cell preparation processes designated, authorized, accredited or licensed by an EU member state under the national laws implementing the BTC legislation before Aug. 7 are deemed to be authorized under the SoHO regulation.

The same applies to blood components that were verified by SoHO-competent authorities as complying with applicable quality and safety requirements of the BTC legislation or that were otherwise designated, authorized, accredited or licensed under national legislation.

SoHOs in storage before Aug. 7 may continue to be released and distributed for two years, provided that they were fully compliant with the applicable EU legislation and national law in force at the time of collection.

SoHOs in storage but distributed before Aug. 7 and kept under appropriate control conditions until that date, can still be used. If they have not been distributed, they may only be released if the SoHO recipient's benefit outweighs the risks and no alternative SoHOs are available.

Geneviève Michaux is a partner and Georgios Symeonidis is an associate at King & Spalding LLP.

[1] 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.

[2] 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.

[3] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

[4] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products.

[5] Regulation (EU) 2017/745 of the European Parliament and of the Council.