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Europe - The Proposal on "Substances of Human Origin Intended for Human Application" (SoHO Regulation) and Its Impact on Advanced Therapy (Gene, Cell, and Tissue) Medicinal Products

On July 14, 2022, the European Commission ("EU Commission") published a proposal to adopt an EU-wide Regulation on standards of quality and safety for substances of human origin intended for human application ("Proposal," available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=COM:2022:338:FIN).

This proposed regulation on substances of human origin ("SoHo Regulation") -- which is meant to update and replace the EU Blood Directive[1] and the Tissue and Cells Directive[2] (collectively, the "BTC Legislation") -- will set out high quality and safety standards for all substances of human origin intended for human application ("SoHOs") and for activities related to those substances. As such, it will be relevant not only for hospitals, blood transfusion centers, and the like, but also for pharmaceutical, device, and other companies involved with blood products and cell- and gene-therapy products.

This alert does not elaborate the Proposal in detail. Instead, after providing some general background and a description of the contemplated SoHO Regulation, it focuses on the impact on advanced therapy medicinal products ("ATMPs").

1. Legislative Background

The BTC Legislation, which was adopted at the beginning of the 2000's, sought to ensure the quality and safety of blood, blood components, tissues, and cells used for transfusion, transplantation or medically assisted reproduction.

A revision process started a few years ago, which highlighted several gaps and shortcomings of the BTC Legislation. In particular, (i) its transposition

into national law had led to discrepancies that fragmented the EU market, and (ii) the need to adapt it to increasing new ways to process and use BTC for medical purposes.

The revision thus opened several discussions that were relevant for companies involved with cell- and gene-therapy products and blood products. The current Proposal addresses some but not all those issues (although the situation may change during the legislative process).

2. EU vs National Rules

The EU Commission proposes replacing the BTC Legislation by a "regulation," i.e., a legal tool directly applicable in all Member States, to achieve higher harmonization.

The SoHO Regulation would ensure a higher, but not full, harmonization since the Member States would be expressly authorized to maintain or introduce certain stringent national measures. Member States remain competent, for example, to decide on ethical (use, or limitation of use, of specific types of SoHOs or specific uses of SoHOs) and organisational (allocation of certain SoHOs) matters or to implement the principle of voluntary unpaid donation.

Those national restrictions, however, would have to be evidence-based, compatible with EU law, and proportionate to the risk to human health, and they would have to be transparent and notified to the EU Commission.

3. General Description and Main Changes

The SoHO Regulation would be complex legislation that would (i) regulate SoHO-related products, activities and entities, (ii) organize the supervision of those products, activities and entities at the national level, (iii) ensure continuous supplies of SoHOs, in particular those which are critically important to patients, and (iv) ensure the protection of donors, recipients and offspring from medically assisted reproduction. The Explanatory Memorandum contains a summary of each of the 14 chapters – See the Appendix at the end of this alert.

The SoHO Regulation would introduce the following main changes to the current regime:

- Broader scope of application - see below.
- Quality and safety standards specific to SoHO preparation and treatment would be extended to protect donors and offspring born from medically assisted reproduction.
- The safety standards provided by the Proposal would mostly be continuously developed by scientific expert bodies in order to swiftly include new evidence and update safety requirements.
- SoHO entities conducting activities that affect the safety and quality of SoHOs would have to register with the national competent authorities. Additional requirements would apply where those activities include SoHO processing and storage.
- In the case of a critical SoHO (SoHO for which an insufficient supply will result in serious harm or risk of harm to patients), SoHO entities would have to alert the competent authority in case of sudden fall in supply and may have to implement emergency plans.
- An EU SoHO platform would be created to provide better sharing of information and transparency among competent authorities and SoHO entities. Exchange of best practices and joint inspections of SoHO entities, would be promoted/supported by the EU Commission.
- A SoHO Coordination Board would be set up to coordinate the implementation of the SoHO Regulation and its delegated and implementing acts.

As a general rule, the future SoHO Regulation would become applicable after a two-year transition period. However, some products would benefit from a more lenient regime, and national blood and tissues establishments which have been

designated, authorized, accredited, or licensed under the BTC Legislation before the date of application of the SoHO Regulation, would be deemed to be SoHO Establishments under the SoHO Regulation (provided that they meet the legal definition of SoHO Establishment; otherwise, they would become "mere" SoHO Entities).

4. Scope of Application

The scope of application of the Proposal is threefold and covers SoHO products, SoHO activities, and SoHO donors and recipients.

Products: The Proposal mentions three categories of products.

- SoHOs intended for human application.

  A SoHO would be legally defined as "any substance collected from the human body in whatever manner, whether it contains cells or not and whether those cells are living or not". Thus, SoHOs include blood, blood components, tissues, cells (including haematopoietic peripheral blood, umbilical-cord blood and bone-marrow stem cells, reproductive cells and tissues, foetal tissues and cells and adult and embryonic stem cells) and any substance of human origin such as human breast milk, intestinal microbiota, blood preparations not used for transfusion, and any other SoHO that may be applied to patients in the future.

  Organs are expressly excluded except when they are removed from a donor for the purposes of separating tissues or cells for human application (for example, heart valves from a heart or pancreatic islets from a pancreas).

  Human application is defined as "inserted, implanted, injected, infused, transfused, transplanted, ingested, transferred (as in transfer to the uterus or fallopian tube of a woman), inseminated or otherwise added to the human body in order to create a biological, mechanical or physiological interaction with that body". Therefore, the placing of a substance on the body when it does not have any biological or physiological interaction with that body (for example, wigs made from human hair), is not covered.

- SoHO preparations, i.e., a particular type of SoHO that (a) has been subjected to one or more SoHO activities, including processing, in accordance with defined quality and safety parameters; (b) meets a pre-defined specification; and (c) is intended for application to a recipient for a specific clinical indication or is intended for distribution for manufacture of a product regulated by other Union legislation, or as the starting and raw material thereof.

- Products manufactured from SoHOs and intended for human application.

SoHO Activities: A SoHO activity is defined as "an action, or series of actions, that has a direct impact on the safety, quality or efficacy of SoHOs, as listed in Article 2(1)". The list includes: SoHO donor recruitment; SoHO donor history review and eligibility assessment; SoHO testing of donors for eligibility or matching purposes; collection of SoHOs from donors or patients; processing of SoHOs; quality control testing of SoHOs; storage of SoHOs; SoHO release; distribution of SoHOs; import of SoHOs; export of SoHOs; human application of SoHOs; SoHO clinical outcome monitoring. On the other hand, the SoHO Regulation would not cover research using SoHOs that does not involve application to the human body such as in-vitro research or research in animals.

5. Impacts on ATMPs

Tissues and cells are used in the manufacture, or as the starting and raw materials, of ATMPs, and ATMPs are regulated generally by the EU general pharmaceutical legislation (Directive 2001/83 and Regulation 726/2004) and specifically by the ATMP Regulation (Regulation 1394/2007).

Interaction between the SoHO Regulation and Pharmaceutical Law. – Currently, the tissues and cells to be used in ATMPs must comply with the donation, procurement, and testing requirements set out in the BTC Legislation.

Article 2 (3) of the Proposal provides that:

- for SoHOs that are used to manufacture medicinal products regulated by EU pharmaceutical law, or as the starting and raw material thereof, only the provisions applicable to SoHO donor recruitment, donor history review and eligibility assessment, testing of donors for eligibility or matching purposes, and collection of SoHOs from donors or patients apply;

- however, all provisions of the SoHO Regulation apply to SoHO release, distribution, import and export before their distribution to an operator regulated by EU pharmaceutical law.

Of note, the same principle applies to medical devices and foodstuffs manufactured using SoHOs.

Autologous Use. – In the case of autologous use, the requirement to comply with the donation, procurement, and testing requirements set out in the BTC Legislation leads to long and costly procedures, which are not truly necessary since the tissues and cells are collected from one individual for subsequent application to the same individual. The same applies to the labelling and traceability requirements.

The Proposal specifically addresses the issue of autologous use. First, it defines autologous use as "collection of SoHO from one individual for subequent application to the same individual, with or without further SoHO activities between collection and application". Then, it provides that in cases of autologous use of SoHOs:

- where SoHOs are processed and stored before application, the SoHO Regulation fully applies. Full application is justified by the risks of cross-contamination, loss of traceability or damage to the biological properties inherent to the substance, and necessary for efficacy in the recipient.
- where SoHOs are processed and not stored before application, only the provisions on vigilance, SoHO rapid alerts, SoHO entity registration, SoHO preparation authorisation, and activity data collection and reporting, apply. The objective is to ensure that the SoHO is demonstrated to be safe and effective for the recipient.
- where SoHOs are not processed and not stored before application, the SoHO Regulation does not apply. Such an application would not be proportionate to the limited quality and safety risks arising in such a setting.

Furthermore, in cases where SoHOs, SoHO preparations, or products manufactured from SoHO, are used to manufacture medicinal products regulated by EU pharmaceutical law (or as the starting and raw material thereof) which are exclusively for autologous use, only the provisions applicable to SoHO collection from patients apply.

Borderline Products. – Under the 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 (non-homologous use), they are regulated as medicinal products (i.e., as ATMPs); otherwise, they fall under the scope of the BTC Legislation.

During the revision process, many stakeholders underlined the lack of legal clarity on the delineation with other EU legal frameworks, including the ATMP Regulation, and some even reported a negative impact on supply and patient access. Other stakeholders however requested to avoid changes regarding the delineation of borderline products as that could create a risk of overlapping between the different applicable framework.

The EU Commission apparently agreed with the latter as the Proposal does not modify the qualification/criteria of borderline products. To the contrary, it states that the delineating criteria for borderline products are sufficiently defined in other legal frameworks.

However, the Proposal sets out rules to ensure, in case of doubt about the regulatory status of a particular substance, product or activity under the SoHO Regulation, consultations among the relevant national and EU authorities or an opinion from the SoHO Coordination Board ("SCB"). If the consultations are not successful, the national competent authority must ask an opinion from the SCB.

National decisions on regulatory status must be communicated to the SCB, which would keep a compendium of its opinions, the opinions of other competent authorities, and the decisions of national authorities, for reference purposes.

In addition, in order to ensure consistent decisions across all Member States with regard to borderline cases, the Proposal empowers the EU Commission to, on its own initiative or at the duly substantiated request of a Member State, decide on the regulatory status of a particular substance, product or activity under the SoHO Regulation.

SoHO Entities. – A SoHO entity is legally defined as "an organisation legally established in the [EU] that carries out one or more of the SoHO activities set out in Article 2(1)". SoHO entities are subject to several obligations, including to register with the national competent authority and, if they import SoHOs from third countries, to be specifically authorized for that activity. Export of SoHOs to third countries is not subject to prior authorization, but, as a general rule, compliance with the SoHO Regulation is required.

Therefore, an EU pharmaceutical company that exports SoHOs for manufacturing purposes in a third country or imports SoHOs for manufacturing purposes in the EU, qualifies as SoHO entity and is subject to those obligations.

Hospital Exemption. – The most controversial provisions of the ATMP Regulation concern the so-called "hospital exemption". Like compounded preparations, an ATMP *"which is prepared on a non-routine basis according to specific quality standards and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient"* is exempted from the application of the pharmaceutical legislation.

The hospital exemption is subject to national law, and reports show that in some Member States, hospitals were allowed using the concept too widely (i.e., on a "routine" basis), thereby competing in part with pharmaceutical companies that develop ATMPs under the (more stringent) ATMP Regulation.

The EU Commission could have subjected ATMPs developed under the hospital exemption to the SoHO Regulation, but chose not to, at least expressly.

6. Conclusion

In conclusion, the Proposal has a limited impact on ATMPs and ATMP companies because the Proposal does not expressly address some issues that were raised during the revision process. However, the legislative process has only started, and some stakeholders may insist on the future regulation addressing those issues as well, thereby increasing the importance of the SoHO Regulation for the ATMP industry. Moreover, the EU Commission's Explanatory Memorandum preceding the Proposal, stresses that the current action feeds into the ongoing revision of the European pharmaceutical legal framework, in particular regarding the regulatory delineation between the BTC sector and the pharmaceutical sector, the delineating criteria being set by definitions in the pharmaceutical framework.

The Proposal is opened for feedback until **September 8, 2022**.

King & Spalding's lawyers in Europe and the U.S. advocate for clients to address strategic and compliance considerations affecting product classification, standards, and business terms. Please contact us to discuss the proposed SoHO Regulation, its interplay with the pharmaceutical and other EU regulatory regimes, and convergence with U.S. provisions applicable to cells, tissues, blood, and related products for commercial use.

[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.

APPENDIX –SUMMARY OF THE SOHO REGULATION CHAPTER BY CHAPTER

(excerpt from the Explanatory Memorandum)

The new Regulation, repealing the Blood Directive 2002/98/EC and the Tissues and Cells Directive 2004/23/EC, and their implementing legislation, is structured around obligations for the different stakeholders: the national competent authorities, the entities handling SoHOs, and the Commission. It includes specific requirements for all organisations that carry out activities that can affect the safety, quality or efficacy of SoHOs used for human application and describes obligations for designated authorities that will verify the proper implementation of the provisions. It will consist of the following main chapters:

Chapter I: General provisions

Chapter I contains general provisions of this Regulation. It defines the subject matter and the scope of application of the Regulation. In recognition of the importance of ensuring safety and quality of SoHOs that are not defined by the terms 'blood', 'tissue' or 'cell', such as breast milk and intestinal microbiota, and to future-proof the legislation in this regard, the scope is defined by the broader term SoHOs. Solid organs continue to be regulated by Directive 2010/53/EU and are excluded from the definition of this term. This chapter contains the definitions of the different elements of the Regulation and of the terminology used throughout the text. Furthermore, it introduces the description of SoHO activities and describes the possible more stringent measures set by Member States, in line with Article 168(4)(a) of the TFEU. Certain exclusions are described, along with the partial applicability of this Regulation when SoHOs are used to manufacture products regulated by other Union legislation, or as the starting and raw material thereof.

Chapter II: Competent Authorities

Chapter II contains the provisions regarding competent authorities for SoHOs, which are responsible for the SoHO supervisory activities. It covers the designation of competent authorities, the possibility to delegate certain SoHO supervisory activities, and general principles for their functioning (independence and impartiality, transparency). It also defines their general responsibilities and obligations. It covers the communication between competent authorities (within the SoHO sector) and consultation and cooperation with authorities of other regulated sectors. It lays down general obligations for authority personnel and provides for competent authorities obligations regarding Commission controls.

Chapter III: SoHO Supervisory Activities

Chapter III covers all activities competent authorities undertake vis-à-vis SoHO entities or processes, with the obligation to maintain a register of SoHO entities and a procedure for their registration; the obligation to have a system for the authorisation of SoHO preparations, and a procedure for these authorisations, with provisions for conducting the assessment of SoHO preparations, possibly in a joint process with one or more competent authorities, and further specific obligations for SoHO preparation assessors. This Chapter also covers the obligation to have an authorisation system for SoHO establishments (specific in case of importing SoHO entities) and a procedure for their authorisation (SoHO establishments/importing SoHO entities). It stipulates the obligations for inspections of SoHO establishments and other SoHO entities, possibly via joint inspections, and the specific obligations for inspectors. It provides for the obligations for competent authorities regarding data publication, traceability, vigilance and, SoHO Rapid Alerts.

Chapter IV: General Obligations on SoHO Entities

Chapter IV outlines all the general obligations on SoHO entities, namely their registration, the nomination of a Responsible Person if they release SoHOs for clinical use, the obligations regarding export of SoHOs. It also lays down the obligation for authorisation of SoHO preparations, and the procedure for application for such authorisation. It also covers the obligations for importing SoHO entities regarding their authorisation, and the application for such authorisation. It provides for the obligations for SoHO entities regarding activity data collection and reporting, traceability and coding, the obligation to apply the Single European Code to SoHOs distributed for human application (except for some specific SoHOs), and vigilance notifications.

Chapter V: General Obligations on SoHO Establishments

Chapter V lays down the general obligations on SoHO establishments, a sub-set of SoHO entities that process and store SoHOs. It provides for their authorisation and the application procedure for such authorisation, the obligation to have a Quality Management system in place, and the obligation to designate a physician responsible for specific tasks.

Chapter VI: SoHO Donor Protection

Chapter VI contains the provisions related to the protection of SoHO donors, with standards, and how to implement these standards concerning donor protection.

Chapter VII: Recipient and Offspring Protection

Chapter VII contains the provisions related to the protection of patients treated with SoHO (recipients) and offspring from medically assisted reproduction, with standards, and how to implement these standards concerning recipient and offspring protection. It also stipulates conditions for the release of SoHOs for human application, and conditions for exceptional release.

Chapter VIII: Supply Continuity

Chapter VIII lays down provisions to ensure the continuity of supply of SoHOs. It covers the obligation for Member States to have national SoHO emergency plans (for SoHOs that are critically important for patients) and the responsibilities of competent authorities and entities regarding supply alerts for critical SoHOs. It also stipulates the conditions for derogation from the obligations to authorise SoHO preparations in emergencies, provides for additional emergency measures taken

by Member States and finally lays down the obligation for SoHO entities carrying out activities with critical SoHOs to have an emergency plan in place.

Chapter IX: SoHO Coordination Board

Chapter IX establishes the SoHO Coordination Board (SCB) to support Member States in the coordination of implementation of this Regulation and the delegated and implementing acts adopted pursuant to it. This chapter also provides for the composition of the Board and how its functioning is organised.

Chapter X: Union Activities

Chapter X outlines the activities organised at Union level, regarding training and exchange of competent authorities' personnel, the Commission controls in Member States, and the support provided by the Commission to support the implementation of the Regulation. It also refers to the cooperation with the EDQM, which should address procedures for the development and revision of technical guidelines, including evidence gathering, guideline drafting and public consultation.

Chapter XI: EU SoHO Platform

Chapter XI describes the EU SoHO Platform that will support information sharing between authorities and with SoHO entities, and outlines its general functionalities.

Chapter XII: Procedural Provisions

Chapter XII contains the procedural provisions of the Regulation with regard to confidentiality and data protection obligations. It furthermore contains provisions regarding the exercise of delegation, the urgency procedure and the committee procedure. Finally, it lays down the penalties applicable to infringements of the provisions of this Regulation to be set by Member States.

As regards delegated acts, following the adoption of the proposal, the Commission intends to create an expert group in line with decision C (2016) 3301 in order to advise and assist it in the preparation of delegated acts, as well as on issues related to implementation of the Regulation as regards:

(a) preparing opinions at the request of the Commission on the regulatory status of a substance, product or activity (and consulting equivalent advisory bodies established in other relevant Union legislation);

(b) providing expertise relevant for the development of technical guidelines, other guidelines and technical methods to the Commission;

(c) reviewing reports on activity data and on vigilance data prior to publication by the Commission;

(d) contributing to the continuous monitoring of technical progress and assessment of whether the safety and quality requirements set out in this Regulation are adequate to ensure safety and quality of SoHOs and SoHO preparations and the safety of SoHO donors;

(e) supporting the Commission to exchange views with Union or international level professional associations working in the field of SoHOs on issues of general interest in relation to the applicability of the provisions of this Regulation;

(f) providing expertise to the Commission for the development of guidelines, standards or similar on an international level for SoHOs and their quality and safety, when appropriate;

(g) advising the Commission on the appropriate content and format of Union training programmes for competent authority personnel and supporting the performance of training activities;

(h) providing advice and expertise on the preparation of delegated acts.

The expert group should also provide technical advice to the Commission when it considers that the EDQM guidelines are not sufficient to meet a standard for donor protection or a standard for recipient and offspring protection as provided for in this Regulation.

Chapter XIII: Transitional Provisions

This Chapter sets the transitional provisions applicable to establishments and SoHO preparations authorised under the former BTC legislation. It stipulates the status of SoHO stored before the application of this Regulation. Finally, it contains the transitional measures related to the date of adoption of certain delegated and implementing acts.

Chapter XIV: Final Provisions

The final chapter stipulates the repeal of Directives 2002/98/EC and 2004/23/EC. It also sets the provision for the evaluation of the Regulation, and its dates of entry into force and application.