Tampereen ammattikorkeakoulu

Navigating regulatory challenges for Substances of Human Origin in selected EU markets

Hanna Parviainen

THESIS
December 2024

Master's Degree Programme in Wellbeing Technology
Master of Health Care

TIIVISTELMÄ
Tampereen ammattikorkeakoulu
Hyvinvointiteknologian ylempi tutkinto-ohjelma
Sosiaali- ja terveysalan ylempi ammattikorkeakoulututkinto

PARVIAINEN, HANNA:
Ihmisperäisten kudostuotteiden sääntelyhaasteet EU:n valikoiduilla markkinoilla

Opinnäytetyö 56 sivua, joista liitteitä 4 sivua
Joulukuu 2024

Euroopassa ihmisperäisten kudostuotteiden sääntelyn hajanaisuus asettaa merkittäviä haasteita uusien innovatiivisten tuotteiden kehittämiselle ja markkinoille pääsylle. Opinnäytetyön tarkoituksena oli analysoida näiden tuotteiden sääntelyä valituissa EU-jäsenvaltioissa (Viro, Ranska, Saksa, Irlanti ja Tanska) ja tunnistaa suotuisimmat markkinat toimeksiantajayrityksen, Linio Biotechin, innovatiiviselle kudostuotteelle. Tutkimuksen tavoitteena oli tarjota käytännönläheisiä näkemyksiä sääntelypoluista ja markkinoille pääsyyn liittyvistä strategioista.

Tutkimus toteutettiin tapaustutkimuksena laadullisia menetelmiä hyödyntäen Menetelminä käytettiin kirjallisuuskatsausta se valvovien viranomaisten haastatteluja. Aineisto analysoitiin vertaillen viiden keskeisen kriteerin perusteella, jotka olivat kudostuotteen varastointiaika terveysdenhuollon yksikössä, kuljetuskäytännöt, lupaprosessit, laadunvalvontastandardit ja valvontamenettelyt.

Tulokset osoittivat merkittäviä eroja EU-direktiivien kansallisessa täytäntöönpanossa. Vaikka jäljitettävyys- ja laadunvalvontakäytännöt olivat laajalti yhdenmukaisia jäsenvaltioiden välillä, suurimmat erot liittyivät hyväksymisprosesseihin ja kuljetuskäytäntöihin. Saksa luokittelee useimmat kudostuotteet lääkkeiksi, mikä tiukentaa sääntelyä, kun taas Irlanti sallii suoran kuljettamisen klinikoille erityissopimuksilla. Nämä erot korostivat tarvetta mukauttaa markkinoille pääsyn strategiat maakohtaisiin vaatimuksiin.

Johtopäätöksenä todettiin, että Irlanti, Ranska ja Viro tarjosivat suotuisimmat sääntely-ympäristöt selkeiden hyväksymisprosessien ja laadunvalvontaa tukevien viitekehyksien ansiosta. Näiden löydösten perusteella Linio Biotech voi priorisoida markkinoille pääsyä ja ratkaista sääntelyyn liittyviä haasteita. Jatkotutkimuksessa tulisi laajentaa jäsenvaltioiden tarkastelua ja tutkia operatiivisia sekä markkinapohjaisia tekijöitä ihmisperäisten kudostuotteiden EU markkinoille viemisen tukemiseksi.

Asiasanat: ihmisperäinen kudostuote, säännöstely, markkinoille pääsy

ABSTRACT

Tampereen ammattikorkeakoulu
Tampere University of Applied Sciences
Master's Degree Programme in Wellbeing Technology

PARVIAINEN, HANNA:
Navigating Regulatory Challenges for Substances of Human Origin in Selected EU Markets

Master's thesis 56 pages, appendices 4 pages
December 2024

The objective of this study was to analyze the regulatory frameworks governing Substances of Human Origin (SoHO) products in five selected EU Member States – Estonia, France, Germany, Ireland, and Denmark – to identify optimal markets for Linio Biotech's SoHO product.

This study was conducted using a case study approach, integrating an integrative literature review with direct communication with competent authorities. The data were analyzed through a comparative framework to evaluate national implementations of EU directives based on key criteria, including storage duration at organization responsible for human application, direct shipment policies, regulatory approval processes, quality control standards, and vigilance measures.

The findings reveal significant variations in national implementations of EU frameworks, with traceability and quality control consistently aligned with EU directives, but notable differences in approval processes and shipment allowances. Ireland and France were identified as the most favorable markets due to their streamlined regulatory environments and alignment with Linio Biotech's operational capabilities.

These results highlight the importance of tailored market entry strategies to navigate the diverse regulatory landscape for SoHO products. Further research is required to explore broader market-based factors and the implications of the upcoming EU-wide SoHO Regulation.

Key words: substances of human origin, regulation, market entry

TABLE OF CONTENTS

1 INTRODUCTION

The regulation of Substances of Human Origin (SoHO) plays a critical role in ensuring the safety, quality, and traceability of products derived from human tissues and cells. These substances are indispensable in modern healthcare, supporting therapies ranging from regenerative medicine to advanced aesthetic treatments. However, introducing novel SoHO products to European markets is fraught with challenges due to the fragmented regulatory landscape within the European Union (EU).

Linio Biotech Ltd, a Finnish biotechnology company, faces this challenge as it seeks to expand the market reach of its innovative SoHO product, Tience® Currently distributed in Finland and Sweden, Tience® is designed for tissue regeneration and repair. However, its market entry into other EU countries is hindered by varying national implementations of EU directives, each with its own set of requirements for compliance and approval.

This thesis addresses the research problem of navigating regulatory barriers to enable successful access to EU markets for SoHO products. By focusing on five selected member states – Estonia, France, Germany, Luxembourg and Denmark – this study explores how different regulatory environments impact feasibility of market entry. It is important to note that the scope of this thesis is limited to regulatory aspects. Go-to-market planning and broader business feasibility considerations, while critical to the overall success of market expansion, are not addressed. These factors, alongside regulatory pathways, must ultimately be considered to assess the practicality of entering a new market.

Through its focus on regulatory challenges, this thesis aims to contribute to a deeper understanding of the complexities involved in bringing SoHO products to new markets within the EU. By providing insights into the regulatory frameworks of selected Member States, the study offers valuable guidance for Linio Biotech and similar organizations navigating these pathways. This work highlights the importance of regulatory compliance as a foundational step in expanding access to innovative treatments in the rapidly evolving field of regenerative medicine.

2 THEORETICAL FRAMEWORK

2.1 Substances of Human Origin (SoHO)

SoHO encompass a wide range of materials derived from the human body, including blood, organs, tissues and cells. These materials are essential in modern medicine and have applications that range from life-saving interventions, such as blood transfusions and organ transplants, to emerging regenerative therapies aimed at repairing or replacing damaged tissues in humans. The ability of SoHO to address critical healthcare needs highlights their importance in advancing medical science and improving patient outcomes. (WHO 2010, 1-2.)

Human tissue, the specific focus of this thesis. In this thesis, we will specifically focus on human tissue, which plays a crucial role in various applications. SoHO are integral to treatments such as blood transfusions, organ transplants, and regenerative therapies. The use of SoHO, particularly human tissue, is governed by stringent regulatory and ethical standards to ensure their safe and effective application. This chapter will explore the definition of SoHO, their diverse application in humans, and ethical considerations that must be addressed in their use. (EDQM 2022, 30-32, 34).

2.1.1 Definition and importance

SoHO refers to a variety of biological materials derived from the human body and intended for clinical application. Broadly speaking, these include blood, tissues, cells, and organs, but they can encompass any parts of the human body, as well as secretions or excretions, collected from living or deceased persons (ECDC, n.d.). These materials are indispensable to modern medicine, addressing a wide range of medical conditions and sometimes serving as the only available or lifesaving treatment. In many cases, the application of SoHO products significantly improves patients' quality of life.

This thesis specifically focuses on human tissue, a subset of SoHO, which includes materials such as skin, bone, cartilage, adipose tissue, and cardiac tissue used in various medical treatments.

The types of tissues that can be harvested from the human body and their respective medical use are illustrated in Figure 1. This visual representation highlights the broad utility of SoHO products and their critical role in advancing patient care.

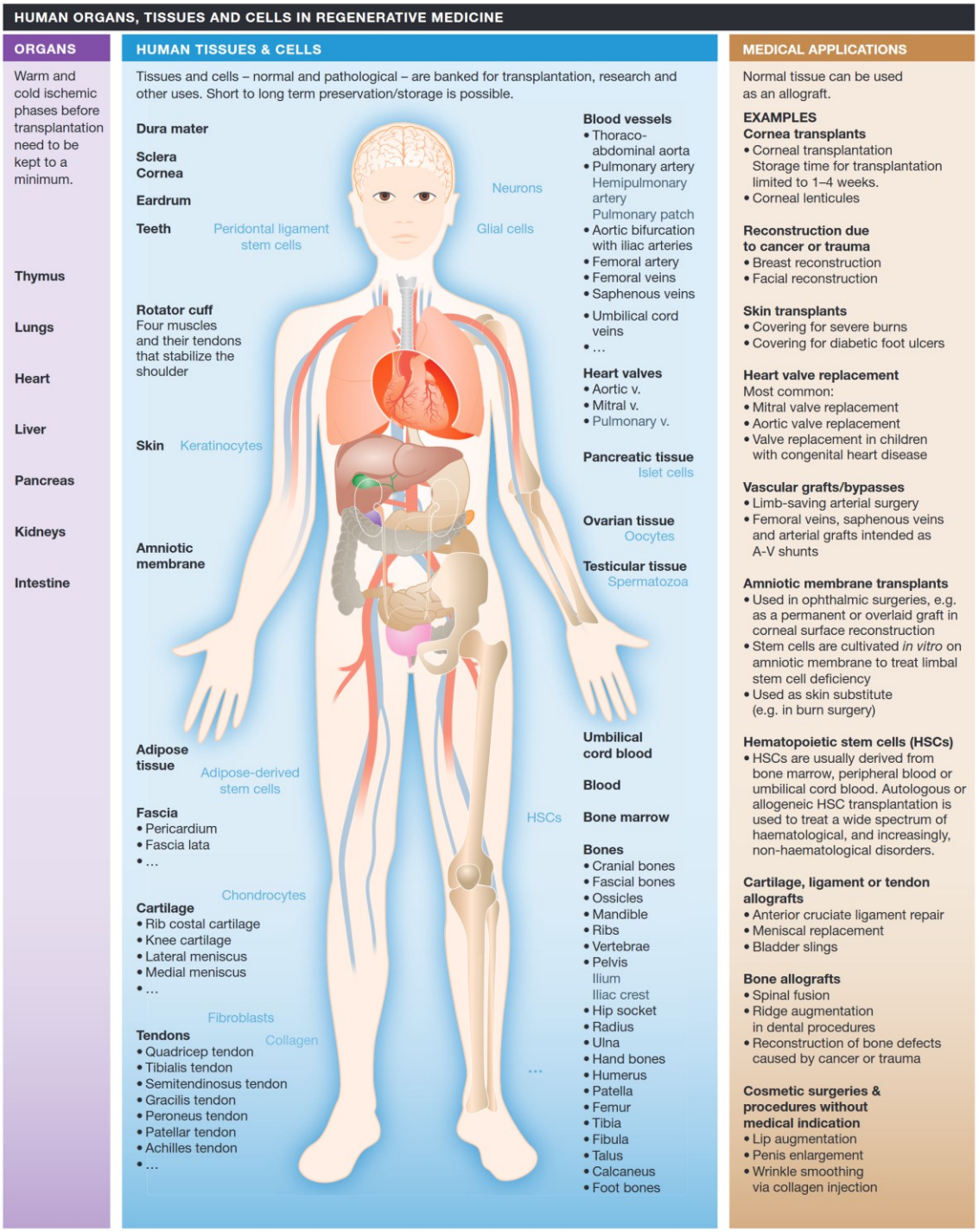

Figure 1. Types of tissues harvested from human body and their medical applications (Pirnay et al. 2015, 556).

Beyond therapeutic applications, human tissue is essential in research and development. Studying human tissues in controlled environments enables researchers to better understand disease mechanisms, develop new treatments, and refine existing therapies. These contributions highlight the indispensable role of SoHO in advancing medical science and improving patient outcomes. (Nuffield Council on Bioethics, 2011, 191-193.)

2.1.2 Application of SoHO in humans

The medical use of SoHO spans from remarkable range of treatments, showcasing their versatility and vital role for healthcare. These applications can be categorized into lifesaving interventions, quality-of-life enhancements, and innovative approaches in regenerative medicine. By examining a few key examples, the diverse impact of SoHO in clinical settings becomes evident.

SoHO are often critical in emergency and life-threatening situations. Skin grafts, for instance, are used as temporary coverings for severe burns, where they reduce the risk of infection and promote healing. Similarly, bone grafts are essential in orthopedic surgeries, aiding in fracture repair, spinal fusion, and reconstruction of bone defects. Corneal transplants restore vision for patients with severe corneal damage or disease, providing a pathway to improved quality of life. Hematopoietic stem cell transplants, derived from bone marrow or peripheral blood, are indispensable in treating leukemia, lymphoma, and other blood disorders, often offering patients a chance at remission or cure. (EDQM 2022, 25-26.)

Beyond emergency care, SoHO significantly improve patients' quality of life by addressing chronic or degenerative conditions. Tendons and ligaments harvested from donors are used in reconstructive surgeries to restore mobility and alleviate pain caused by injuries or degenerative conditions. Heart valves, often retrieved from deceased donors, replace defective valves in recipients, extending life expectancy and enhancing cardiovascular health. (EDQM 2022, 26.)

Adipose tissue, harvested through liposuction procedure, is used in reconstructive applications to restore volume and regenerate tissues. It has been employed in breast reconstruction, scar treatment, and correction of soft tissue defects due to its rich concentration of growth factors essential for tissue repair and reconstruction. Sarkanen (2012) highlighted its ability to promote the development of new blood vessels and support healing processes, while López

et al. (2022) demonstrated its effectiveness in stimulating wound healing and improving scar quality. (EDQM 2022, 330-331.)

Advances in biotechnology have expanded the possibilities for SoHO, particularly in regenerative medicine. Bioengineered tissues, such as decellularized scaffolds, are increasingly being explored as potential solutions for addressing complex medical conditions by supporting tissue repair and regeneration. The decellularization-recellularization technique has shown promise in maintaining the structural and functional properties of biological tissues, enabling its application in diverse areas of medicine, including reconstructive surgery. (Yujia et al. 2023.)

Recent advancements include the improved preservation of vascular networks, optimization of preparation protocols, and integration of advanced biomaterials. These developments demonstrate the potential for creating structures that are of human origin and closely mimic the natural properties of human tissues, providing hope for addressing previously unmet medical needs. Regenerative medicine continues to evolve as an interdisciplinary field, offering innovative pathways to enhance patient care and outcomes. (Yujia et al. 2023.)

2.1.3 Ethical considerations

The ethical considerations surrounding the use of SoHO are multifaceted and deeply rooted in respect of human dignity and rights. Human tissues and cells, derived from living or deceased individuals, present unique ethical challenges due to the intimate nature of their source. The handling and disposal of these materials must always reflect respect for the human body and adhere to fundamental ethical principles.

Central to the ethical framework governing SoHOs is the principle of informed consent. According to the Oviedo Convention of Human Rights and Biomedicine (1997) and its Additional Protocol on transplantation of organs and tissues of human origin (2002), any intervention in the health field, including donation of tissues and cells, requires the free and informed consent of the donor. This

consent must be given without undue influence and with full understanding of the intended use, consequences, and risks of donation. The right to withdraw consent at any time is also protected, ensuring that donors retain autonomy over their bodily materials. (Council of Europe, 1997.)

The ethical standards for tissue and cell donation are reinforced by various international guidelines, including the World Health Organization (WHO) Guiding Principles on human cell, tissue and organ transplantation and the Declaration of Istanbul on Organ Trafficking and Transplant Tourism. These guidelines emphasize the importance of voluntary, unpaid donation and the prohibition of financial gain from the human body and its parts. The principle of altruism is paramount, with compensation. (CD-P-TO, 2022; WHO guiding principles.)

Conflicts of interest must be meticulously avoided in the donation process. Physicians involved in determining the death of a potential donor should not participate in the procurement or transplantation procedures to prevent any bias of undue influence. This separation ensures that decisions are made purely on medical and ethical grounds, safeguarding the integrity of the donation process. Additionally, living donors must receive impartial information from healthcare professionals not involved in the recipient's care, ensuring that their consent is fully informed and voluntary. (GAEBA 2018, 3-4.)

Financial aspects of donation are particularly sensitive. The Oviedo Convention explicitly prohibits financial gain from the human body and its parts, a principle reiterated in its additional protocol. While compensation for donors is allowed, it must not constitute a financial incentive. This distinction is crucial to maintaining the altruistic nature of donation and preventing exploitation. The Nuffield Council on Bioethics' report (2011) highlights the importance of distinguishing between altruist-focused interventions, which remove disincentives to donate, and non-altruistic focused interventions, which offer financial incentives. The latter are particularly problematic as they can undermine the ethical foundation of donation and lead to exploitation, especially in vulnerable populations. (Council of Europe 2018, 4-9; Nuffield Council of Bioethics 2011, 152-157.)

Equitable access to transplantation and medically assisted reproduction (MAR) is another critical ethical consideration. The demand for human tissues and cells often exceeds supply, raising questions of fairness and efficiency in their distribution. The Additional Protocol of Convention on Human Rights and Biomedicine mandates that allocation systems must be transparent, objective, and based on medical criteria, ensuring equity in access to transplantation services. This principle extends to MAR, where access should be structured to avoid discrimination and ensure that treatments are available to all who need them, regardless of socio-economic status. (EDQM 2022, 25-27.)

Transparency in the donation and application of SoHO is vital for maintaining public trust and ensuring ethical practices. This involves public access to comprehensive data on donation activities, allocation, and clinical outcomes while protecting the anonymity and privacy of donors and recipients. Transparency helps to identify and mitigate the risks, ensuring the safety and efficacy of treatments and fostering public confidence in the healthcare system.

The ethical considerations surrounding SoHO are not only theoretical but also require practical implementation within tissue establishments (TE). These establishments are responsible for handling human tissues and cells, and they are mandated to follow the ethical principles in their everyday operations.

As discussed before, one of the primary principles is informed consent. TEs must have robust systems in place to make sure that the consent is obtained in a manner that is free from coercion and fully informed. This involves detailed documentation processes where donors are provided with comprehensive information about the intended use of their donated tissue, risks involved and consequences of their donation.

2.2 **Regulatory framework**

The regulation of SoHO within the European Union is governed by a framework of directives aimed at ensuring safety, quality, and traceability. Central to this

framework is Directive 2004/23/EC, the EU Tissues and Cells Directive, which sets standards for the donation, procurement, testing, processing, preservation, storage, and distribution of human tissues and cells. This directive, implemented across all EU Member States, protects both donors and recipients by ensuring all handlings steps are conducted under controlled and safe conditions. (Directive 2004/23/EC.)

In addition to Directive 2004/23/EC, other directives include Directive 2006/17/EC, which specifies technical requirements for the donation, procurement, and testing of tissues and cells, and Directive 2006/86/EC, which outlines traceability requirements and notification of serious adverse reactions and events. These directives collectively ensure that all tissue and cell-based products, including SoHOs, meet uniform safety and quality standards across the EU, facilitating oversight of tissue establishments. (Directive 2006/17/EC; Directive 2006/86/EC.)

While Directive 2004/23/EC provides the overarching framework, it allows Member States to maintain national-specific regulations, provided these meets or exceeds the directive's minimum standards. This flexibility enables countries to implement directives in ways that best suit their healthcare systems while adhering to EU safety and quality thresholds.

2.2.1 EU Directives and regulations

Article 168 (4)(a) of the Treaty on the Functioning of the European Union (TFEU) grants the EU the authority to establish high quality and safety standards for SoHO (European Union, 2012). Recognizing the expanding medical field of tissues and cells, the EU aims for a common regulatory approach to promote cross-border exchanges and improve patient access.

Directive 2004/23/EC, known as the EU Tissue and Cells Directive (EUTCD), applies to the donation, procurement, testing, preservation, storage, and distribution of human tissues and cells intended for human use, including reproductive cells used in medically assisted reproduction procedures. This

directive establishes obligations for EU Member States' authorities, including supervision, authorization, inspection of tissue establishments, ensuring traceability, and maintaining a public register of national tissue establishments. It also sets rules on donor selection, consent, data confidentiality, and quality and safety standards. (Directive 2004/23/EC.)

Commission Directive 2006/17/EC specifies technical requirements for each step in preparation process of human tissues and cells, including donor selection criteria, laboratory tests, procurement, and reception procedures at tissue establishments (Directive 2006/17/EC). This directive was amended by Directive 2012/39/EC to update certain technical requirements (Directive 2012/39/EC). Additionally, Commission Directive 2006/86/EC includes requirements for traceability, notification of serious adverse reactions and events, and technical requirements for coding, processing, preservation, storage, and distribution of human tissues and cells (Directive 2006/86/EC).

In 2015, two new directives were adopted to further enhance the regulatory framework. Directive 2015/565/EC provides detailed requirements on the coding of human tissues to enhance the traceability (Directive 2015/565/EC), while directive 2015/566/EC establishes procedures for verifying equivalent standards of quality and safety for imported tissues and cells (Directive 2015/566/EC).

The EU directives oblige Member States to encourage voluntary and unpaid donation of tissues and cells and ensure that procurement is carried out on a non-profit basis. Promotion and publicity activities for financial gain of tissue donation are prohibited. The directives provide clear provisions on donor information, consent, data anonymity, and instruct Member States to adopt measures to ensure data security and prevent unauthorized modifications to files and records. (Cuende et al 2023, 870-872; Directive 2004/23/EC.)

In 2019, the EU conducted an evaluation of its blood and tissues and cells legislation to assess whether the existing regulations had achieved their original objectives and remained fit for the purpose considering significant technological advancements in the sector. The evaluation identified several gaps and shortcomings, prompting the European Commission (EC) to undertake revision

of legislation to ensure it is up to date, fit for purpose and future-proof (Revision of the EU legislation on blood, tissues and cells - European Commission 2024). This resulted in EC proposing a new regulation in 2022 to address these shortcomings, emphasizing stronger safety standards, updated traceability requirements, and streamlined procedures to foster innovation in the sector (EC 2022). This proposal was adopted in 2024, marking a significant step toward a more cohesive and modernized regulatory environment for SoHO within the EU. The new Regulation 2024/1938 will apply from August 2027 (EC 2024.)

The EC has supported various projects to aid EU Member States in implementing these directives. These projects have strengthened collaboration among health authorities and professional associations, ensuring continuous input from field practice into the regulatory framework. Table 1 below summarizes some of these projects. (EDQM 2022, 44-45.)

Table 1. Projects supported by EC to aid Member States implementation of directives (EDQM 2022, 44-45).

Project	Description
European Quality System for Tissue Banking (EQSTB)	Focused on key requirements for tissue banking, developing a registry, training programs, and audit models
EUSTITE (European Standards in Training and Inspection of Tissue Establishments)	Developed guidance in training for EU Competent Authorities on inspection and vigilance procedures
EUROCET	A platform collecting and publishing annual activity data on donation, processing, and human applications of tissues and cells
EuroGTP (European Good Tissue Practices)	Developed guidelines for good tissue practices and personnel training
SoHO V&S (SoHO Vigilance & Surveillance)	Addressed harmonization of terminology and documentation for adverse events and reactions
VISTART (Vigilance and Inspection for the Safety of Transfusion, Assisted Reproduction, and Transplantation)	Promoted harmonization of inspection, authorization, and vigilance systems for blood transfusions and tissues and cells
EuroGTP-II (Good Tissue Practices for demonstrating safety and quality through recipient follow up)	Developed technical guidance to assess the quality and safety of novel tissue and cell therapies
TRANSPOSE (TRANSfusion and transplantation: protection and SElection of donors)	Harmonized European donor selection and protection policies

GAPP (Facilitating the Authorization of Preparation Process for blood, tissues and cells)	Facilitated the development of a common approach to assess and authorize preparation processes in blood and tissue establishments

Within the EU, the European Directorate for the Quality of Medicines & HealthCare (EDQM) is instrumental in upholding the standards for SoHO. The EDQM is responsible for developing and maintaining quality standards that are recognized across Europe. They offer technical guidance and resources. Although these standards encompass all stages of handling human tissues and cells in a similar manner than in the directives, they are not legally binding. This is going to change in 2027 when the regulation is coming into effect making it mandatory. (EC 2023.)

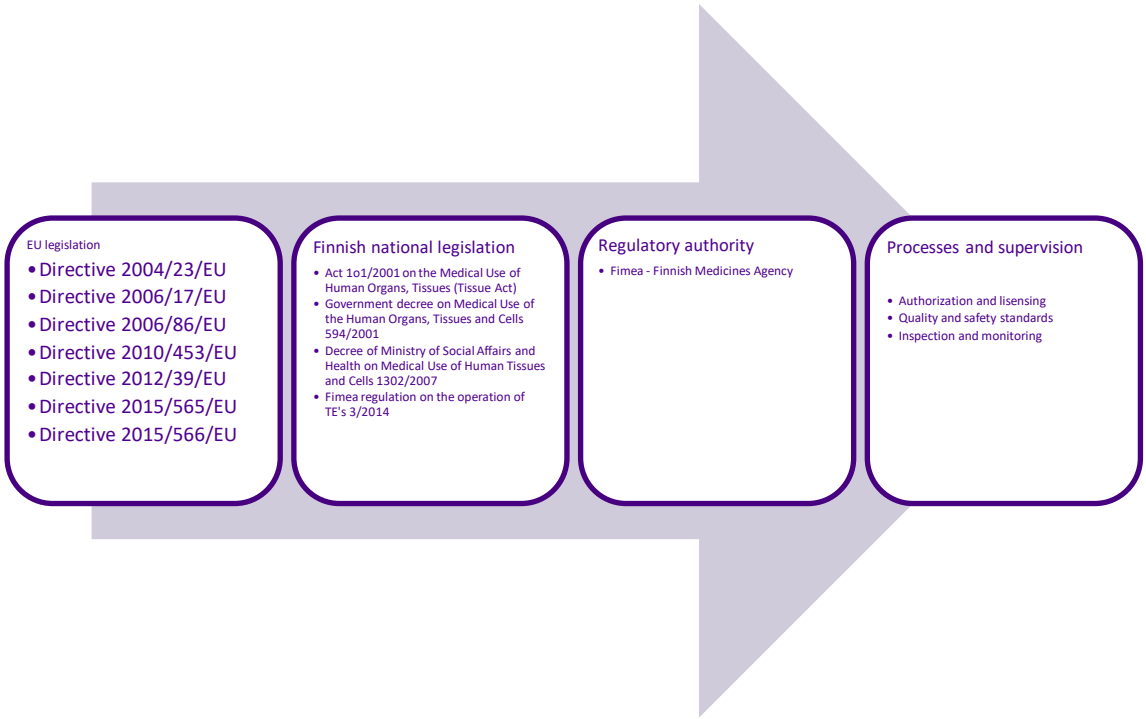

Figure 2. Implementation of SoHO regulations in Finland.

2.2.2 General principles and commonalities

Across EU Member States, the regulation of SoHO is guided by overarching principles aimed at ensuring safety, quality and traceability. These principles are fundamental to protecting donors and recipients while maintaining public trust in the healthcare system. Despite national variations in the implementation of EU directives, these core tenets serve as a common foundation for regulatory practices.

Safety is prioritized through stringent donor selection criteria, rigorous testing procedures, and robust processing standards. Directive 2004/23/EC mandates that all human tissues and cells undergo extensive screening to minimize the risk of transmitting diseases. Additionally, technical requirements outlined in directive 2006/17/EU ensure that procurement and testing procedures meet consistent quality thresholds across Member States. (Directive 2004/23/EC; Directive 2006/17/EC.)

Quality is ensured though standardized processes for handling, processing, and storing SoHO. TE's must comply with Good Tissue Practices (GTP) and adhere to detailed protocols for maintaining the integrity of biological materials. These standards are vital for ensuring that tissues and cells retain their functional and structural properties during preservation and transport. (EDQM 2023, 8-9.)

Traceability is another cornerstone of SoHO regulation. Directive 2006/86/EU requires that all SoHO materials be traceable from do not to recipient and vice versa. This comprehensive traceability framework includes coding systems, record-keeping, and vigilance measures to ensure that any adverse events or safety concerns can be promptly addressed. The introduction of Single European Codes (SEC), which is an internationally recognized coding system, has further enhanced traceability, enabling seamless tracking of SoHO products across the borders. (EDQM 2022, 182-185.)

Table 2. Single European Code for tissues and cells (2015/565/EU, Annex VII).

Donation Identification Sequence			**Product Identification Sequence**			
Tissue establishment code		Unique donation number	Product code		Split number	Expiry date (yyymmdd)
ISO country code	Tissue establishment number		Product Coding System identifier	Product number		
2 alphabetic characters	6 alpha-numeric characters	13 alpha-numeric characters	1 alphabetic character	7 alpha-numeric characters	3 alpha-numeric characters	8 numeric characters

In addition to these legally binding principles, several non-binding best practices provide supplementary guidance to TEs. The EuroGTP II project, for example, has developed frameworks for assessing the quality and safety of novel SoHO products, emphasizing the importance of standardization and post-market surveillance. These best practices, while not legally mandated, play a critical role in harmonizing procedures and promoting innovation across the EU. (EDQM 2022, 215.)

By adhering to these general principles and leveraging both binding and non-binding guidelines, EU Member States can ensure the ethical and effective use of SoHO in medical treatments. These shared regulatory foundations facilitate cross-border collaboration and support the development of innovative therapies, ultimately benefiting patients across Europe.

2.2.3 Challenges and gaps in current regulations

The regulation of SoHO in the EU has made significant progress in ensuring the safety and quality of blood, tissues, and cells (BTC). However, the current legislative framework faces several challenges and gaps, particularly in adapting to evolving medical technologies and internationalization of healthcare.

In 2019 a study was conducted by an external contractor to provide an independent evidence base for the European Commission’s evaluation of the current EU legislation on blood, tissues, and cells (BTC). The primary aim was to assess the effectiveness of the existing directives in ensuring the safety and quality from donor to recipient, and to determine if the legislation remains for the purpose considering evolving medical and technological advancements (EC

2019, 6). This kind of evaluation is the basis for understanding and identifying the areas that need improvement to support the development and market entry of innovative SoHO products.

The study methodology was comprehensive, addressing 14 high level evaluation questions outlined in Blood, Tissues, and Cells Evaluation Roadmap. The independent study team conducted an extensive review of 222 literature sources and gathered qualitative and quantitative data through targeted telephone interviews with a broad range of stakeholders. Additionally, focus groups were held to discuss the importance of the assisted reproductive technology sector and the coherence evaluation theme. Two validation focus groups further refined the emerging findings. A stakeholder event brought together over 200 experts from the BTC field, along with other stakeholders. Targeted data collection actions, including questionnaires sent to national Competent Authorities (CA) and professional associations, addressed remaining evidence gaps. The findings were based on thorough analysis and triangulation of data from these various sources, and the draft report was peer reviewed by three independent experts to ensure accuracy and comprehensiveness. (EC 2019, 6-7.)

The study found out that while the original objectives of the EU legislation remain valid, the legislation has struggled to adapt to sectoral changes, rendering it insufficient to meet current and future needs. Despite this, the legislation has successfully ensured a high level of human health protection and raised quality standards across Member States. National authorities have been established to oversee activities, and complementary technical guidelines have clarified the legislation. However, the need for ongoing interpretation of specific aspects of law has increased workloads for establishments, national authorities, and Commission services. (EC 2019.)

Several issues were identified, including gaps in law, such as the absence of donor protection measures, and challenges posed by internationalization and innovations not foreseen when legislation was drafted. The study also highlighted inefficiencies and disproportionate burdens caused by outdated tests, deferral criteria for donors, a two-year inspection interval, and air quality requirements in

cleanrooms. These requirements often do not cost-effectively contribute to patient safety and negatively impact the availability of some SoHO.

Furthermore, there is a lack of consensus on which EU legal framework applies to certain substances, leading to incoherence in safety and quality requirements and oversight. This issue is exacerbated when BTC become starting materials for medicinal products or medical devices. This study also noted potential inconsistencies with other EU legal frameworks, such as data protection, communicable diseases, value-added tax, and the Charter of Fundamental Rights. (EC 2019, 8-12.)

Despite these challenges stakeholders agreed that the Directives have added significant value by introducing harmonized quality and safety standards across Member States. However, differing national interpretations and the ability of Member States to implement more stringent measures have created barriers to cross-border exchanges and harmonization, undermining the progress towards the objectives of the EU legislation. (EC 2019, 8-12.)

The SoHO Regulation will enhance harmonization across Member States, streamline authorization processes, and reduce administrative burdens, thereby enabling faster and safer market entry for innovative therapies. Additionally, the regulation’s focus on digital-ready policies and improved crisis preparedness will support the resilience and continuity of SoHO supply chain will assist in faster market entry.

Martens and Arifacig (2024) highlight that blood transfusions, plasma, and tissues and cells play a vital role in the production of medicinal products as they do in SoHO products. Consequently, donations through blood and tissue establishments are crucial to maximizing the patient’s benefits. They argue that SoHO Regulation is anticipated to positively influence innovation in the blood and tissue donation sector, fostering increased access to novel and innovative therapies.

One of the key features of the SoHO Regulation is the establishment of the SoHO Coordination Board (SCB). According to Martens and Arifacig (2024),

the SCB is designed to address the issue of borderline classification of substances, products, or activities by providing opinions on these subjects. This consultation procedure aims to ensure coherence and consistency in regulatory decisions, thereby supporting a more harmonized and efficient regulatory environment.

2.3 SoHO product sector

2.3.1 SoHO potential and future opportunities

The SoHO product sector in the EU holds significant potential due to continuous advancements in basic science, technology, and medicine. These advancements create opportunities for the development of novel tissue and cell preparation processes, including changes to donor selection, procurement, processing, storage, and distribution methodologies, as well as new clinical applications. Ensuring the quality, safety, and efficacy of these novel processes and applications is paramount to safeguarding the health of donors and recipients. EDQM 2023, 8; EDQM 2022, 214.)

Several key elements should be considered to maximize the potential and future opportunities in the SoHO sector:

1. **Clinical need as a driver**: The development of novel processes and applications for tissues and cells should be predominantly driven by clinical need. This ensures that innovations are aligned with the actual requirements of healthcare providers and patients, leading to more effective and targeted treatments
2. **Stakeholder collaboration**: The involvement and close cooperation between TEs, clinicians representing ORHAs, and health authorities are essential. A clear structure identifying the responsibilities of each party and how they interact must be established and documented. This collaborative approach ensures that the principles are comprehensively addressed.
3. **Comprehensive risk analysis**: The development and evaluation of novel processes and applications should be underpinned by comprehensive risk analysis. This analysis should consider both the risks and clinical

benefits of the innovation. Evaluation may include in vitro, in vivo, and, where indicated, clinical evaluation and patient follow up according to the level of risk identified. This systematic approach helps to mitigate potential risks and validate the clinical performance of new therapies.

4. **Standardization and validation**: Standardization and validation are critical for unlocking the full potential of the SoHO sector. By establishing standardized methodologies and validation protocols, TEs and health authorities can ensure the consistent quality and safety of SoHO products. This not only facilitates regulatory approval but also builds trust among healthcare providers and patients. Standardized processes enable more efficient and reliable production, reducing variability and enhancing the reproducibility of results. Validation studies rigorously test new processes and applications, providing necessary evidence to demonstrate their safety and efficacy. The systematic approach helps to mitigate risks and ensures that innovative therapies meet the highest standards before they reach the market. By focusing on standardization and validation, the SoHO sector can accelerate the development and adopt novel therapies, ultimately improving patient outcomes and advancing medical science.

While some processes and applications may be new to specific TEs, they may not be his sector is significant for developing innovative treatments that address a wide range of medical conditions. The increasing demand for such treatments underscores the vast potential of the SoHO sector. (EDQM 2023, 8; EDQM 2022, 214-217.)

2.3.2 Challenges and opportunities

The SoHO product market faces significant challenges, primarily due to its fragmented regulatory landscape. While the EU aims to harmonize regulations, its Member States often impose additional national requirements, complicating compliance. This forces companies to invest heavily in understanding legal frameworks, delaying market entry and increasing costs.

Ethical and legal complexities further complicate market dynamics. Issues such as informed consent, donor privacy, and the use of embryonic stem cells highlight sensitive ethical dilemmas. For instance, concerns about biopiracy and ethical sourcing of tissues has drawn public scrutiny, making compliance essential for approval and acceptance. (Pirnay et al. 2015.)

As has been discussed previously, SoHO products are highly regulated and there are ethical implications to be taken into consideration when thinking of development of a novel product. EDQM guidance (European Directorate for the Quality of Medicines & HealthCare (EDQM) s.a., 214) states that clinical need should be predominant driver when new products and applications are designed. Directive 98/44/EC offers a framework for innovation and growth in the SoHO sector. Evaluating potential products against its patentability criteria – especially in genetic engineering, cell therapy, and tissue engineering – can secure intellectual property rights, attract investment, and provide competitive advantages. Adherence to ethical guidelines, such as avoiding human cloning or germline modifications, is essential for regulatory approval and public trust.

The directive also supports funding proposals by demonstrating the potential of returns on investment through patented innovations. Patented SoHO products can differentiate themselves in the market, appealing to health care providers and patients. Strategic partnerships with research institutions, biotech companies, and healthcare organizations can further accelerate development and commercialization. By leveraging Directive 98/44/EC and integrating ethical compliance, the SoHO sector can foster innovation, secure growth, and improve patient outcomes. (98/44/EC).

3 OBJECTIVES AND PURPOSE OF THE THESIS AND RESEARCH QUESTIONS

3.1 The company commissioning the thesis

This thesis work was commissioned by Linio Biotech, a Finnish biotechnology company specializing in innovative SoHO products for regenerative medicine and aesthetics. Founded in 2021, the company focuses on revolutionizing regenerative aesthetics with safe, effective and natural solutions for tissue regeneration and skin repair.

Its flagship product, Tience®, promotes tissue regeneration, repairs skin damage, and enhances aesthetics naturally, positioning Linio Biotech as a pioneer in the field. Currently distributed in Finland and Sweden, the company aims to expand into new European markets. (Tience, N.d.)

To support this expansion, Linio Biotech commissioned this thesis to analyze and compare regulatory frameworks for SoHO in selected EU countries. The research provides strategic insights to identify feasible markets for Tience® while ensuring regulatory compliance.

3.2 The objective, purpose and research questions

The objective of this study is to evaluate the regulatory landscapes of selected EU Member States to identify opportunities and challenges for introducing innovative SoHO product into new markets. The purpose of this study is to provide insights and guidance for navigating regulatory pathways, enabling the effective and compliant introduction of SoHO product into selected EU markets by examining regulatory requirements in the selected European countries. The findings will guide Linio Biotech in making informed decisions in compliance and market entry, thus supporting the market entry and their compliance decisions, thus supporting the successful market expansion of Tience®.

The research questions:

1. How can the regulatory requirements for introducing a SoHO product to selected European markets be determined?
2. Which of these countries have the most favorable regulatory environment for the new tissue products?

4 METHODS

4.1 Research approach

This thesis was carried out as a case study, and it was conducted using qualitative methods.

According to Laine, Bamberg, and Jokinen (2007), a case study is not merely a single method but rather a collection of different methods, which can be collectively referred to as a research approach. This comprehensive approach enables an in-depth exploration of complex phenomena within their real-life context. It is particularly well-suited for investigating the regulatory landscape for SoHO products in the EU, where interplay between harmonized EU directives and diverse national implementations demands a detailed, contextualized analysis.

One key component of this study is the integrated literature review. This distinctive form of research synthesizes existing literature to generate new insights and perspectives on a particular topic. According to Torraco (2005), an integrated literature review involves a systematic approach to collecting, analyzing, and synthesizing previous research. This enables researchers to identify patterns, gaps, and trends within the existing body of knowledge. Importantly, this method goes beyond summarizing studies; it critically evaluates and integrates findings to provide a new conceptual framework or theoretical model. Whittemore (2008) further outlines the steps for conducting an integrative review, which include problem identification, literature search, data evaluation, data analysis, and presentation. These steps ensure that the review is systematic, thorough, and transparent, providing a solid foundation for further research and practice.

In addition to the integrated literature review, this study interviews with Competent Authorities from selected European countries. Combining these methods within the case study approach allows for a nuanced understanding of regulatory frameworks and the factors influencing market access for SoHO products. Unlike

surveys or experimental methods, a case study is particularly effective for exploring complex, context-specific phenomena, such as the interplay between EU regulations and national laws.

This research focuses on identifying how regulatory requirements for introducing SoHO products can be determined across different European countries. It further explores the methods used to assess these requirements and how they vary between countries. Additionally, the study evaluates which countries offer the most favorable regulatory environments for new SoHO products.

As part of the writing and editing process, AI tools such as ChatGPT-4 and Copilot were used to enhance the clarity and coherence of the text. Both of them were used in similar manner; for generating suggestions for different sections of text, grammar correction and improvements in flow of the text. The AI-generated content was reviewed and edited to ensure the accuracy and relevance to the topic researched. The use of AI tools aimed to complement, not replace, the researchers critical thinking and expertise in the topic.

4.2 **Data collection methods**

This study employed two primary data collection methods: conducting an integrated literature review of relevant regulatory frameworks and contacting the competent authorities in selected EU Member States. Together, these methods provided comprehensive insights into the regulatory landscape for SoHO. The list of competent authorities can be found on the official website of the EU (Appendix 1.). Within that list are the addresses to each member state's competent authority's official webpage.

The methodology for literature review in this thesis involves a systematic analysis of the regulatory frameworks governing SoHOs within the EU and selected Member States. The primary objective is to identify and compare specific regulatory criteria across different countries to understand which of these countries have the most favorable regulatory framework for SoHO to enter their market.

4.3 **Literature selection process**

The literature review systematically analyzed regulatory frameworks at the EU and national levels to identify the most favorable market environments for SoHO products. Sources for the review included:

- Official EU directives and amendments
- National legislation for the selected countries, obtained through competent authority websites and databases

The selection of literature was guided by specific inclusion and exclusion criteria to ensure relevance and quality.

Table 3. Inclusion and exclusion criteria.

INCLUSION CRITERIA	EXCLUSION CRITERIA
• Documents published from 2004 onwards, as Directive 2004/23/EC serves as the foundational regulation for SoHO products in EU • Only official EU directives, amendments and national laws will be included as they give the requirements SoHOs must fullfill • EU-level directives and laws from six selected Member States • Documents available in English or with official translations to English	• Documents published before 2004 are excluded, as they precede Directive 2004/23/EC and are no longer relevant to the current regulatory framework • Academic articles, industry white papers, or non-regulatory reports are excluded unless they provide critical context directly related to directives or laws • Older versions of directives

4.3.1 Integrated literature review

The integrated literature review focused on systematic analysis of regulatory frameworks governing SoHO products at both EU and national levels. Its objective was to identify and compare specific regulatory criteria across selected countries to determine which offer the most favorable environment for market entry. Sources included official EU directives, amendments, and national legislation obtained through competent authority websites and legal databases.

In the context of this thesis, the integrated literature review methodology is applied to examine the regulatory landscape for SoHO within the EU. This approach is suitable for this study as it allows for a comprehensive analysis of regulatory frameworks across different countries, highlighting both commonalities and differences. By synthesizing EU directives and selected Member States legislation, this review aims to generate new insights into the regulatory challenges and opportunities for SoHO.

The selection of criteria for this review is based on factors that impact on the introduction of a SoHO product into a new market. These criteria include the time a SoHO product is allowed to be stored in the organization responsible for human application (ORHA), and whether direct shipment of the product to ORHA is possible or if the SoHO product must be stored in and distributed from TE in said country. The comprehensive list of criteria will be introduced in Table 4.

Table 4. Criteria for comparative analysis of regulatory frameworks.

Criteria	Definition/Explanation
Storage duration at ORHA	Maximum allowable time a SoHO product can be stored at the ORHA
Direct shipment	Whether SoHO products can be shipped directly to ORHA or require distribution via TE
Regulatory approval process	Steps required to obtain approval for new SoHO product, including timelines and involved agencies
Quality control and standards	Specific testing, documentation, and certification requirements to ensure product safety and compliance

SoHO vigilance and surveillance	Measures for monitoring and reporting adverse events or reactions to SoHO products

The comparative analysis involves identifying legislation concerning SoHO products, systematically comparing the extracted information across the selected countries, and evaluating the regulation environments. This analysis will highlight which countries provide the most favorable conditions for the introduction of new SoHO products, considering factors such as regulatory clarity, ease of compliance, and support for innovation. The findings will be presented in structured format, with detailed discussion of each criterion and differences and similarities across countries.

The selection of criteria for this review was informed not only by an initial exploratory analysis of EU directives, amendments, and national legislation governing SoHO products but also discussions within the Linio Biotech. These sources provided insights into regulatory aspects that significantly impact the introduction and management of SoHO products across different markets. Additionally, feedback from competent authorities during preliminary communications helped refine the criteria to focus on the most relevant regulatory elements.

The final set of criteria – presented in Table 4. – was chosen because they represent critical factors that influence compliance, operational efficiency, and patient safety. These criteria also align with the objectives of this study, ensuring a comprehensive and structured evaluation of the regulatory frameworks in selected countries.

After conducting the integrated literature review, direct communication with competent authorities in the selected countries provided additional context and real-time insights into the interpretation and implementation of regulatory frameworks. This dual approach – combining literature review with expert feedback – ensured a comprehensive understanding of the regulatory landscape.

4.3.2 Contacting Competent Authorities

To gather accurate and up-to-date information about national regulatory practices, the competent authorities of five European countries – Estonia, France, Germany, Luxembourg, and Denmark – were contacted. These authorities are responsible for overseeing the implementation of EU directives and national laws related to SoHO products.

The list of Competent Authorities was obtained from the official EU website, which provides links to each Member State's official CAs webpage (Appendix 1). Communications were conducted via emails and phone calls between January and October 2024, focusing on five criteria mentioned earlier.

The purpose of this interaction was to clarify how each country interprets and applies EU directives, identify potential gaps and variations in national regulations, and understand the practical implications for market access. The responses were recorded and analyzed alongside data from the literature review to provide a holistic understanding of the regulatory environment.

The response rate from competent authorities was 100%, with variations in the level of detail provided. Some responses included comprehensive insights into national regulations, while others referred to publicly available documentation. The collected data was used to complement the findings from the literature review, focusing on the five evaluation criteria. Due to the business sensitive nature of the responses, specific details from Competent Authorities are not included in this thesis. However, the insights obtained were synthesized into broader themes to maintain confidentiality while supporting the study's objectives.

4.4 Data analysis techniques

This study employed a cross-country comparative approach to analyze the data collected through the integrated literature review and communications with competent authorities. This method allowed for a systematic evaluation of

regulatory frameworks across selected EU Member States, focusing on commonalities, differences, and specific regulatory requirements that influence the introduction of SoHO products.

The analysis process involved organizing data based on the five evaluation criteria: storage duration at ORHAs, direct shipment policies, regulatory approval processes, quality control and standards, and SoHO vigilance and surveillance measures. These criteria were selected to ensure that the analysis remained relevant to the study's objectives, addressing both the regulatory clarity and operational feasibility. The following section elaborates on the criteria used for the analysis and the rationale for their selection.

4.4.1 Criteria and categories for analysis

The integrative literature review in this study employed a criteria-based approach to systematically analyze and synthesize regulatory frameworks governing SoHO products. Five key criteria (see Table 3.) were identified based on their relevance to regulatory compliance and operational feasibility.

Data from EU directives, amendments, and national laws were categorized under each criterion to enable systematic comparison. For instance, storage duration was examined in terms of specified limits, and quality standards were analyzed for the degree of alignment with EU directives. This thematic categorization provided structure for synthesizing diverse data sources while identifying patterns and discrepancies.

By applying a structured framework, the integrative literature review highlighted regulatory challenges and opportunities across the selected EU Member States. This approach ensured a comprehensive understanding of the regulatory landscape, enabling the identification of favorable Member States as a market for SoHO products while highlighting gaps in existing regulations.

4.4.2 Comparative analysis of regulatory frameworks

The comparative analysis in this study aimed to evaluate how regulatory frameworks for SoHO products are implemented across selected EU Member States. Using a cross-country comparison approach, data from EU directives and national laws were systemically examined against five evaluation criteria: storage duration at ORHA, Direct shipment policies, regulatory approval processes, quality control and standards, and vigilance and surveillance measures. This method facilitated the identification of both commonalities and divergences in regulatory requirements.

The findings were organized using a structured table to provide a comprehensive overview of regulatory practices in each country. While some criteria, such as vigilance and surveillance, exhibited minimal variation across countries due to harmonized EU directives, others, such as approval processes and direct shipment policies, revealed significant differences in national implementation. For example, Ireland permits direct shipment under specific conditions, while Estonia mandates distribution through a licensed TE.

The results of this analysis are detailed in chapter 5.3, where summary table and discussion of key differences and similarities are presented. This structured presentation emphasizes the implications of cross-country regulatory variations and their impact on the operational feasibility and market entry strategies for SoHO products.

Table 5. provides an overview of the key legal frameworks and their scope, highlighting primary laws that underpin the regulatory requirements in each Member State. This summary serves as a reference for understanding the cross-country variations discussed in the following chapters.

Table 5 National legislation governing SoHO products.

Country	Key national legislation	Legislation code	Brief description/scope
Estonia	Medicinal Products Act	RT I, 2005, 2,4 (Consolidated as of 2023)	Governs the import, storage, and distribution of tissues and cells, requiring authorization from the State Agency of Medicines
	Special Regulation on Tissues, Cells, and Organs	§ 44 (2023)	Details traceability requirements, including the SEC and donor identification
France	Public Health Code	Code de la santé publique (CSP), Article L.1243-2	Establishes ASNM as the competent authority for SoHO activities, requiring authorization for storage, distribution, and therapeutic use
Germany	Medicinal Products Act (Arzneimittelgesetz, AMG)	AMG (2023)	Classifies most tissue-derived products as medicinal products, requiring compliance with GMP and pharmacovigilance
	Transplantation Law (TPG)	TPG (1997, last amended 2022)	Regulates donation, procurement, and transplantation of tissues and organs
Ireland	European Communities (Quality and Safety of Human Tissues and Cells) Regulation	S.I. No. 185 of 2006	Implements EU directives, emphasizing storage, traceability, and adverse event reporting
	HPRA Guidelines for Tissues and Cells	HPRA Guidance (Website-based)	Provides practical instructions for implementing legislation, including service agreements and SEC requirements
Denmark	Act on Procurement, Processing, and Distribution of Human Tissue and Cells	No specific coding	Nationally implemented EU legislation governs the preparation, storage, and use of SoHO products, overseen by the Danish Medicines Agency

Building on the foundational frameworks outlined in Table 5., the comparative analysis identifies both commonalities and divergences in the regulatory requirements for SoHO products across the selected Member States. These variations significantly influence the operational feasibility and market entry strategies for companies like Linio Biotech.

5 RESEARCH RESULTS

5.1 Overview of findings

This research revealed significant variation in the regulatory frameworks for SoHO products across the five selected EU Member states. While overarching EU directives provide a harmonized baseline, national implementations differ significantly in areas such as approval processes, whether direct shipment to the ORHA is possible or not, and storage requirements. These differences underscore the importance of tailoring market entry strategies to each country's unique regulatory landscape.

5.2 Detailed analysis of regulatory frameworks

This section examines the findings for each of five evaluation criteria.

5.2.1 Storage duration at ORHA

The duration for which SoHO can be stored at an ORHA varies. In Estonia, storage duration is determined by the TE and communicated to ORHA. France follows similar practices but have made decision on certain SoHO products that could be stored at the ORHA up to one year. In discussion with Denmark's CA it was found out that the maximum time for SoHO products to be stored at ORHA is 48 hours, although Danish law does not give explicit timeline. By contrast, Germany does not have specific storage requirements for SoHO products, as most are classified as medicinal products.

5.2.2 Direct shipment of the SoHO product

The policies regarding direct shipment of SoHO products vary significantly among the selected countries, reflecting the differences in regulatory interpretations and operational frameworks. Estonia prohibits direct shipment altogether, requiring

that all SoHO products be distributed through licensed TEs. This ensures centralized oversight but adds logistical complexity for international suppliers. Conversely, Ireland permits direct shipment under specific conditions. To quality, TEs must obtain authorization from the SRPA and establish service level agreements with the clinics receiving the products. These agreements must define responsibilities for transportation, traceability, serious adverse event reporting, and recall procedures. Germany, on the other hand, does not allow direct shipment for most products, as these are classified as medicinal products and are subject to stringent pharmaceutical regulations. The variation in policies underscores the need for companies to adapt distribution strategies to meet country-specific requirements, balancing regulatory compliance with operational efficiency.

5.2.3 Regulatory approval process

The regulatory approval process for SoHO products exhibits significant variation across selected countries, highlighting the differing interpretations and implementations of EU directives. In Estonia, a classification request must be submitted to the State Agency of Medicines, accompanied by relevant documentation. Once the product is classified as a SoHO product, the agency's notification requirements mandate reporting within five working days of product transportation. Similarly, Ireland requires TEs to submit product details, a list of intended clinics using the product, draft service level agreements, and examples of the SEC to the HPRA. This process ensures that essential compliance aspects, such as traceability and safety standards, are met before approval is granted. France, under the oversight of the ANSM, demands an authorization process that encompasses storage, preparation, and distribution, with specific therapeutic indications outlined in the documentation. In contrast, Germany classifies most tissue-derived products as medicinal products, requiring adherence to pharmaceutical standards, such as compliance with GMP and pharmacovigilance regulations.

5.2.4 Quality control and standards

Quality control and standards for SoHO products are integral to ensuring their safety and efficacy, yet the approaches vary across the studied Member States. Estonia's framework emphasizes that licensed TEs are responsible for defining storage conditions and adhering to traceability requirements outlined in national regulations. Similarly, Ireland mandates service level agreements to specify responsibilities for quality control measures such as transportation, traceability, and serious adverse event reporting. France enforces compliance with additional requirements, such as stricter viral inactivation protocols, to enhance product safety.

5.2.5 SoHO vigilance and surveillance

Vigilance and surveillance systems for SoHO products are fundamental to ensuring patient safety and maintaining the quality of tissues and cells throughout their lifecycle. All the studied Member States have established measures to comply with EU directives, emphasizing the importance of serious adverse event reporting, traceability, and robust monitoring systems. While some national nuances exist, this criterion exhibited the least variation among the studied countries. Overall, the framework for vigilance and surveillance is largely uniform across the countries.

5.3 Comparative analysis

The comparative analysis of the regulatory frameworks for SoHO products across the selected EU Member States highlights both consistencies and disparities in their implementation of EU directives. A summary table (Table 6) illustrates key regulatory criteria and their interpretations across five countries.

Table 6. Comparative analysis of regulatory frameworks by country

Member State	Storage duration	Direct Shipment	Approval process	Quality control	Vigilance and surveillance
Estonia	Determined by tissue establishment; ORHAs must follow set conditions	Not allowed: must go through a licensed TE	Classification request with documents submitted to State Agency of Medicines; notification within 5 working days of transportation	Storage and distribution by licensed establishments; traceability requirements outlined in regulations	Comprehensive: traceability includes SEC, donor ID, transplantation data, and distribution.
France	Not explicitly mentioned; regulated by CA approved TEs.	Allowed only via authorized French TEs	ANSM (French CA) authorization for preparation, storage, and distribution; authorization lists therapeutic indications and preparation processes	Compliance with Directive 2004/23/EU; products must be for therapeutic purposes only. Stricter requirements for viral inactivation of SoHO product	Overseen by ANSM; applies Directive 2004/23/EU to ensure quality and safety standards
Germany	Not applicable	Not applicable	Most tissue-derived products are classified as medicinal products of ATMPs, requiring compliance with Directive 2001/83/EU and Regulation (EU) 1394/2007. This imposes stricter approval processes, including GMP standards and pharmacovigilance requirements.	Not applicable	Not applicable
Ireland	Retention of traceability data for minimum of 30 years by hospitals and clinics	Allowed with HPRA (Irish CA) approval, provided a service level agreement is in place.	Submission of product details, list of ORHAs intended to offer the treatment, draft of service level agreements, and SEC example to SPRA for approval, borderline product review if applicable	Service agreements must specify responsibilities for transport, traceability, SARE reporting, and recall	Hospitals and clinics reporting and retention of traceability data for 30 years; guidance available on HPRA website
Denmark	Not explicitly mentioned in the response; presumed to follow EU standards (48hrs at ORHA)	Allowed if criteria for homologous use and minimal manipulation are met.	Product that is not classified as a medicinal product or ATMP; must comply with minimal manipulation and homologous use per EU definitions	Not explicitly detailed; presumed to follow EU Directive 2004/23/EU	Oversight by Danish Patient Safety Authority.

5.3.1 Summary table of findings

The comparative analysis of regulatory frameworks reveals both alignment and divergence in how EU Member States implement directives for SoHO. Traceability emerges as a consistent priority, with all countries requiring robust systems that include SEC, donor identification, and detailed record-keeping. Similarly, quality control measures largely adhere to EU directives, though certain countries, like France, impose additional national requirements, such as stricter viral inactivation standards. Surveillance and vigilance measures, including serious adverse reaction reporting, are also common feature across the selected countries, though their scope and implementation vary depending on the national CA.

Despite these commonalities, notable differences highlight the challenges of cross-country compliance. For example, approval processes vary significantly, with Germany classifying most tissue derived products as medicinal products, subjecting them to stringent regulations under pharmaceutical regulations. In contrast, countries like Ireland and Denmark follow EU definitions, distinguishing between medicinal products and minimally manipulated SoHO. Similarly, policies on direct shipment diverge: Ireland allows it under specific agreements with their CA, while Estonia mandates distribution through licensed TEs. Storage duration, while often following general EU recommendations, is not uniformly specified and is sometimes left to the discretion of TEs, as seen in Estonia.

These differences illustrate the complexity of navigating SoHO regulation within the EU. Understanding both the overarching patterns and unique national requirements is critical for tailoring market entry strategies and fulfilling compliance requirements in diverse regulatory environments.

6 DEVELOPMENT PROPOSALS FOR LINIO BIOTECH

6.1 Identification of optimal markets

The comparative analysis of regulatory frameworks reveals distinct opportunities for Linio Biotech in entering new EU markets with its SoHO product. The optimal markets are those with streamlined regulatory processes, favorable operational conditions, and alignment with Linio Biotech's product characteristics.

- **Ireland:** Ireland offers a well-defined pathway for SoHO products through its CA, the HPRA. Direct shipment to ORHAs is allowed under specific conditions, including service level agreements detailing responsibilities for traceability, adverse event reporting, and recalls. The regulatory environment in Ireland is conducive to efficient market entry, making it top priority for Linio Biotech.
- **Denmark:** Denmark present promising opportunity for Linio Biotech due to its pragmatic approach to SoHO regulation. Direct shipment is allowed under the strict 48hr storage rule at ORHA. This could be leveraged with efficient logistics and planning from the ORHA.
- **France:** France has a robust framework for SoHO vigilance and surveillance but imposes additional safety measures, such as stricter viral inactivation standards. While the regulatory process is more complex, collaboration with authorized TE can facilitate market entry.
- **Estonia:** Estonia's prohibition of direct shipment and reliance on TE distribution could pose logistical challenges. However, its regulatory clarity and well-defined traceability requirements make it a potential future market.
- **Germany:** Germany's classification of most tissue-derived products as medicinal products introduces a higher compliance burden, including adherence to GMP and pharmacovigilance requirements. This complexity makes Germany not a viable option for market entry.

6.2 **Implications for Linio Biotech Ltd**

The findings of this study have significant implications for Linio Biotech strategic planning and market entry effort. The comparative analysis revealed both opportunities and challenges in navigating the regulatory frameworks of the selected EU Member States. These insights provide actionable guidance for prioritizing markets and tailoring operational strategies to ensure compliance and efficiency.

For Linio Biotech, Ireland emerges as a particularly favorable market due to its streamlined approval process, which permits direct shipments to clinics under specific agreements with the HPRA. This regulatory flexibility minimizes logistical complexity and aligns well with Linio Biotech's existing operational capacities. Additionally, the requirement for robust service level agreements with clinics provides a clear framework for ensuring compliance and managing responsibilities, such as traceability and adverse event reporting.

In contrast, Estonia's requirement to distribute SoHO products exclusively through licensed TEs presents additional logistical hurdles. While this may complicate market entry, Estonia still offers opportunities due to its transparent regulatory requirements and predictable approval processes. France, despite its stricter standards, also remains a viable market if partnership with French TE can be established. Denmark and Germany, however, present more significant challenges. Germany's classification policy for tissue-derived products and compliance requirements make it not viable option. Meanwhile, Denmark's policies, though generally aligned with EU directives, lack the feasible solution for storage with a strict timeline of 48 hours storage for ORHAs.

By focusing on markets with clearer regulatory frameworks and operational advantages, such as Ireland and France, Linio Biotech can optimize its initial market entry efforts. These insights underscore the importance of aligning strategic decisions with regulatory realities to maximize efficiency, minimize risks, and build a foundation for sustainable growth in the EU.

6.3 **Recommendations for market entry**

To successfully navigate the diverse regulatory landscapes of the EU Member States, Linio Biotech should adopt a strategic and prioritized approach. Ireland and France present the most favorable pathways for compliance and market access. These two markets should be targeted first, leveraging their regulatory clarity and potential for collaboration.

Building strategic partnerships with local TEs will be crucial, particularly in France, where collaboration with authorized establishments is a prerequisite for market entry. Although no French TEs are currently authorized for adipose tissue, starting material for Linio Biotech's product, initiating discussion with TE partner have them apply for amendment to their license would solve this issue. Similarly, in Ireland, drafting a service level agreement that covers all the necessary requirements can create strong market foundation.

Regulatory preparedness is another critical area of focus. Linio Biotech must ensure that its documentation and compliance capabilities align with the specific requirements of each target market. Developing internal expertise and systems to meet these demands will position the company as a reliable and compliant partner.

Tailoring distribution strategies to align with country specific requirements will also be essential. For instance, Estonia mandates distribution through licensed TEs, necessitating logistical adjustments. By evaluating these variations and planning its distribution network accordingly, Linio Biotech can enhance operational efficiency and meet market demands effectively.

Maintaining open communication channels with CAs will further support the company's regulatory efforts. Regular engagement will help Linio Biotech stay informed about regulatory updates, clarify classification expectations, and address potential challenges proactively. Flexibility and adaptability will also be vital as the regulatory environment evolves. Continuous assessment of real-world challenges and feedback from local stakeholders will enable the company to refine its strategies and ensure sustainable success in new markets. By adopting

these measures, Linio Biotech can effectively navigate the complexities of the EU regulatory landscape and enhance its reputation as a trusted provider of innovative SoHO products.

6.4 **Addressing regulatory challenges**

Navigating the regulatory complexities in the EU demands a strategic, adaptive approach. Linio Biotech must align its processes with specific requirements of each target market while maintaining compliance with overarching EU directives.

To address the variability in distribution models, Linio Biotech should tailor its strategy to each market. For example, Estonia's requirement for distribution through licensed TEs necessitates identifying suitable local partners, while Ireland's allowance for direct shipment offers greater flexibility, provided service level agreements are in place. A market specific approach will optimize regulatory compliance and operational efficiency.

Traceability and vigilance systems must be robust and harmonized to meet EU and national requirements, including the use of SEC and adherence to 30-year data retention policies. Clear workflows for adverse event reporting will further reinforce Linio Biotech's adherence to vigilance standards, providing confidence to both regulators and clinical partners.

To address quality control challenges and overcome regulatory and logistical barriers, Linio Biotech could standardize its internal procedures to align with the strictest national requirements, such as the enhanced viral inactivation standards mandated in France, while building strategic partnerships with local TEs, clinicians administering SoHO products. This dual approach would ensure compliance across all target markets, fosters trust among stakeholders, and positions the company as a reliable and well-prepared market entrant, ultimately supporting long-term support success in the EU SoHO market.

7 CONCLUSIONS

7.1 Summary of key findings

While EU directives provide a harmonized baseline, the analysis revealed critical differences in national implementations, particularly in areas such as approval processes, direct shipment policies, and storage duration requirements. These variations reflect not only the unique regulatory environments of each country but also the challenges faced by companies attempting to navigate them.

Traceability and quality control emerged as consistent priorities, with all countries adhering to EU-mandated standards, including the use of SEC. However, the stricter national requirements in some countries, such as enhanced viral inactivation protocols in France, illustrate how Member States can impose additional conditions that require careful planning and adaptation.

The findings of this thesis align closely with those emphasized in the 2019, as discussed in chapter 2.2.3. Both studies underscore critical gaps in the current regulatory framework for SoHO products, particularly in the harmonized implementation of EU directives and the challenges these pose for market entry. For instance, the 2019 study pointed out to the variability in national interpretations of EU regulations, a conclusion echoed by the findings of this research, which revealed significant differences in approval processes. direct shipment policies, and storage duration requirements across Member States.

These shared observations highlight a persistent need for regulatory reform to support innovation in the SoHO sector. The upcoming SoHO Regulation, as discussed, offers a promising pathway for addressing these challenges. By establishing a more adaptable and harmonized legal environment, the regulation has the potential to facilitate not only the development of novel SoHO products but also their successful market entry, thereby advancing patient outcomes and healthcare innovation.

In summary, this research provides a detailed account of the current regulatory landscape for SoHO products, identifying both barriers and opportunities. By

addressing these barriers, Linio Biotech and similar organizations can effectively navigate the complex regulatory environment and contribute to the growth of this innovative sector.

7.2 **Evaluation of research objectives and methodology**

This study successfully achieved its objectives by identifying and analyzing the regulatory frameworks governing SoHO products across selected Member States. The research questions were addressed comprehensively through systematic examination of five key criteria. These findings provide actionable insights into how regulatory frameworks differ among Member States and their implications for market entry strategies.

The results align with the prior studies discussed in the theoretical framework (chapter 2), particularly the 2019 study, which emphasized challenges in harmonizing EU directives with national regulations. This alignment reinforces the reliability of the findings and highlights the relevance of addressing persistent gaps in the current regulatory framework for SoHO products.

Regarding reliability and validity, the research methods were extensive enough. The study employed an integrated literature review and direct communication with CAs, ensuring balanced and comprehensive data collection process. However, the variability in responses and challenges in accessing up-to-date legislation required reliance on interpretation and secondary sources in certain cases, introducing potential limitations. Nevertheless, cross-referencing and validation with official resources mitigated these issues, supporting the credibility of the findings.

Ethically, the research adhered to high standards by leaving out the actual correspondence with CAs due to the business sensitive nature of the information shared. By avoiding the inclusion of commercially sensitive data, the analysis remained impartial and free from biases. The study’s findings are thus both reliable and ethically sound, contributing meaningfully to the field of regulatory research.

7.3 **Contributions to the field**

This thesis adds to the body of knowledge on regulatory pathways for SoHO products in the EU. By focusing cross-country comparison, it offers a structured framework for understanding the regulatory landscape, identifying both opportunities and obstacles for market entry. The use of a criteria-based approach, combined with an integrated literature review and communications with CAs, ensures a comprehensive perspective on the topic.

The study's findings provide actionable insights for stakeholders in the SoHO sector, including TEs, regulatory authorities, and policymakers. By highlighting areas where national regulations diverge or exceed EU standards, the thesis underscores the importance of harmonized regulatory practices and offers a foundation for future initiatives aimed at aligning Member State practices more closely with EU directives. Additionally, the methodology employed in this study could be adapted for future research on other regions or product categories, further broadening its relevance and utility.

7.4 **Future research directions**

Future research should expand the scope to include a broader range of Member States, providing more comprehensive analysis of EU-wide trends and regulatory practices. Investigating operational and market-based factors alongside regulatory compliance would also yield a more holistic understanding of the challenges and opportunities in bringing SoHO products to market. Additionally, studies focusing on the impact the of the upcoming SoHO Regulation could provide valuable insights into its effectiveness and areas for further improvement.

This research emphasizes the need for greater standardization and transparency in regulatory practices across the EU. Future studies should explore methods to streamline communication between businesses and CAs and investigate tools or platforms that could enhance the accessibility and clarity of regulatory information. By addressing these areas, future research can support the

development of a more cohesive and supportive regulatory environment for SoHO products across the EU.

REFERENCES

Act on Requirements for Quality and Safety in the Handling of Human Tissues and Cells. Denmark. Act. No. 273. 2006. Accessed: 1.11.2024. https://laegemiddelstyrelsen.dk/en/publications/2012/annual-report-human-on-tissues-and-cells-2011/~/media/3753F2FF5378466387D731260AD3F4E1.ashx.

Article L1243-2 - Code de la santé publique. Légifrance. Accessed 1.12.2024 https://www.legifrance.gouv.fr/codes/article_lc/LEGIARTI000025104376/

Blood, Tissues, Organs. n.d. HPRA. Web page. Accessed: 2.12.2024. https://www.hpra.ie/homepage/blood-tissues-organs

Charter of Fundamental Rights of the European Union. Official Journal of the European Union. 26.10.2016. Accessed: 18.11.2024. http://data.europa.eu/eli/treaty/char_2012/oj/eng

Council of Europe. 1997. Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (ETS No. 164). Accessed: 18.11.2024. https://www.coe.int/en/web/conventions/full-list?module=treaty-detail&treatynum=164

Commission Decision 2010/453/EU. 3.8.2010. Commission Decision establishing guidelines concerning the conditions of inspections and control measures, and on the training and qualification of officials, in the field of human tissues and cells provided for in Directive 2004/23/EC of the European Parliament and of the Council. Accessed: 8.12.2024 http://data.europa.eu/eli/dec/2010/453/oj/eng

Commission Directive 2004/23/EC. 7.4.2004. Directive of European parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage, and distribution of human tissues and cells. Official journal of the European Union. Accessed 7.7.2024. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32004L0023

Commission Directive 2006/17/EC. 8.2.2006. Implementing Directive 2004/23/EC as regards certain technical requirements for the donation, procurement and testing of human tissues and cells. Official Journal of the European Union. Accessed: 7.7.2024. https://eur-lex.europa.eu/eli/dir/2006/17/oj/eng

Commission Directive 2006/86/EC. 24.11.2006. Implementing Directive 2004/23/EC as regards traceability requirements, notification of serious adverse reactions and events, and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells. Official Journal of European Union. Accessed: 7.7.2024. http://data.europa.eu/eli/dir/2006/86/oj/eng

Commission Directive 2012/39/EC. 26.11.2012. Amending Directive 2006/17/EC as regards certain technical requirements for the testing of human tissues and cells. Accessed:8.12.2024 http://data.europa.eu/eli/dir/2012/39/oj/eng.

Commission Directive (EU) 2015/565. 8.4.2015. Amending Directive 2006/86/EC as regards certain technical requirements for the coding of human tissues and cells. Accessed: 30.11.2024 http://data.europa.eu/eli/dir/2015/565/oj/eng.

Commission Directive (EU) 2015/566. 8.4.2015 implementing Directive 2004/23/EC as regards the procedures for verifying the equivalent standards of quality and safety of imported tissues and cells. Accessed 30.11.2024. http://data.europa.eu/eli/dir/2015/566/oj/eng

Cuende, N., Vilarrodona, A., Vuelta, E., Marazuela, R., Herrera, C., Querol, S., Sánchez-Ibáñez, J., Carmona, M., Gayá, A., Tort, J., Hernández, D. & Domínguez-Gil, B. 2023. ”Addressing Risks Derived From the Commodification of Substances of Human Origin: A European Proposal Applicable Worldwide”. *Transplantation*, 107, 4, pp. 867–877. Accessed: 1.12.2024 https://doi.org/10.1097/TP.0000000000004527.

Directorate-General for Health and Food Safety (European Commission) & ICF. 2019. *Study supporting the evaluation of the EU legislation on blood and tissues and cells: Final Report*. Publications Office of the European Union. Accessed:20.11.2024. https://data.europa.eu/doi/10.2875/674510.

ECDC. 2023. Substances of human origin. Accessed: 10.7.2024 https://www.ecdc.europa.eu/en/substances-human-origin

European Committee on Organ Transplantation (CD-P-TO). 18.11.2022. *Risk of Commodification of Substances of Human Origin – A Position Statement of the European Committee on Organ Transplantation of the Council of Europe (CD-P-TO)*.

European Communities (Quality and Safety of Human Tissues and Cells) Regulation. Ireland. S.I. No.185 of 2006. Accessed: 2.11.2024. https://www.irishstatutebook.ie/eli/2006/si/185/made/en/print

European Society of Human Reproduction and Embeyology (ESHRE) N.d. Ethics and Law. Accessed: 18.11.2024 https://www.eshre.eu/Specialty-groups/Special-Interest-Groups/Ethics-and-Law/

European Centre for Disease Prevention and Control. 2024. *ECDC framework relating to substances of human origin (SoHO): May 2024*. Publications Office. LU. Accessed: 7.7.2024 https://data.europa.eu/doi/10.2900/082755

European Commission. 2023. Directorate General for Health and Food Safety. European health union: new rules for greater safety and quality of blood, tissues, and cells. Publications Office. Accessed: 1.12.2024. https://data.europa.eu/doi/10.2875/51561

European Directorate for the Quality of Medicines & HealthCare (EDQM) Guide to the quality and safety of tissues and cells for human application, 5th edition. 2022a. Accessed: 7.7.2024.

European Union. 2012. Consolidated version of the Treaty on the Functioning of the European Union. Official Journal of the European Union C 326. Accessed: 17.11.2024. http://data.europa.eu/eli/treaty/tfeu_2012/oj/eng

Fimea, n.d. Kudoslaitosten valvonta. Web page. Accessed: 9.7.2024. https://fimea.fi/valvonta/kudos-_ja_verivalvonta/kudoslaitosten_valvonta.

Global Alliance of Eyebank Associations (GAEBA). The Barcelona Principles – An Agreement on the Use of Human Tissue for Ocular Transplantation, Research and Future Technologies. 2018. Accessed 18.11.2024. https://www.gaeba.org/wp-content/uploads/2018/05/GAEBA-2018-The-Barcelona-Principles-FINAL.pdf

Laine, M., Bamberg, J. & Jokinen, P. 2007. Tapaustutkimuksen taito. Helsinki: Gaudeamus Helsinki University Press.

Laki ihmisen elimien, kudoksien ja solujen lääketieteellisestä käytöstä. 1.9.2001. Accessed: 13.8.2024. https://www.finlex.fi/fi/laki/smur/2001/20010101.

López, J.F., Mikkola, A., Sarkanen, J.-R., Kaartinen, I.S., Kuokkanen, H.O. & Ylikomi, T. 2022. Adipose tissue as a source of growth factors to promote wound healing: a human study of skin graft donor sites. Journal of Wound Care, 31, 4, p. 282–292. URL: https://doi.org/10.12968/jowc.2022.31.4.282.

Martens, M. & Arifagic, L. 2024. SOHO ALERT: A Comprehensive Guide to the Proposed Regulation on Substances of Human Origin - interplay with the ATMP Legislation. Blog post. Accessed 20.11.2024. https://biotalk.twobirds.com//post/102jaws/soho-alert-a-comprehensive-guide-to-the-proposed-regulation-on-substances-of-hum

Medicinal Products Act (Arzneimittelgesetz, AMG). Germany. Consolidated version 2023. Accessed 1.11.2024. https://www.gesetze-im-internet.de/amg_1976/

Medicinal Products Act. Riigi Teataja. Riigi Teataja. 2004. Estonia. Accessed: 2.11.2024. https://www.riigiteataja.ee/en/eli/ee/516052016002/consolide/current

Nuffield Council on Bioethics. N.d. Human bodies: donation for medicine and research. Accessed:18.11.2024 https://www.nuffieldbioethics.org/publication/human-bodies-donation-for-medicine-and-research/.

Pirnay, J., Baudoux, E., Cornu, O., Delforge, A., Delloye, C., Guns, J., Heinen, E., Van den Abbeel, E., Vanderkelen, A., Van Geyt, C., van Riet, I., Verbeken, G., De Sutter, P., Verlinden, M., Huys, I., Cockbain, J., Chabannon, C., Dierickx, K., Schotsmans, P., De Vos, D., Rose, T., Jennes, S. & Sterckx, S. 2015. Access to human tissues for research and product development. EMBO reports, 16, 5, s. 557–562. Accessed: 2.12.2024. https://doi.org/10.15252/embr.201540070.

Public Health - European Commission 2024. URL: https://health.ec.europa.eu/index_en. Luettu: 8.12.2024.

Sarkanen, J.-R. 2012. Engineering vascularized soft tissue. Doctoral thesis. Tampere University Press. Accessed: 3.12.2024 https://trepo.tuni.fi/handle/10024/66939.

Special Regulation on Tissues, Cells, and Organs § 44. Estonia. Consolidated version 2023. Accessed 2.11.2024. https://www.riigiteataja.ee/en/eli/ee/530102013003/consolide/current

Tience®. N.d. Web page. Accessed: 6.10.2024 https://tience.com/the-science/.

Tight, M. 2017. Understanding Case Study Research: Small-scale Research with Meaning. SAGE Publications Ltd. 1 Oliver's Yard, 55 City Road London EC1Y 1SP. URL: https://doi.org/10.4135/9781473920118. Luettu: 10.7.2024.

Torraco, R.J. 2005. Writing Integrative Literature Reviews: Guidelines and Examples. Human Resource Development Review, 4, 3, pp. 356–367. Accessed: 17.11.2024. https://www.proquest.com/docview/221810269/abstract/3A10CB9F3AC2421CPQ/1

Webb, C. & Roe, B. 2007. Reviewing Research Evidence for Nursing Practice: Systematic Reviews. John Wiley & Sons, Incorporated. Newark, UNITED KINGDOM. URL: http://ebookcentral.proquest.com/lib/tampere/detail.action?docID=351408. Luettu: 19.11.2024.

Whittemore, R. 2007. Reviewing Research Evidence for Nursing Practice: Rigour in Integrative Reviews. p. 149-156. Blackwell Publishing Ltd. Oxford, UK. Accessed: 20.11.2024 https://doi.org/10.1002/9780470692127.ch11.

World Health Organization (WHO) guiding principles on human cell, tissue and organ transplantation. 2010. Accessed: 18.11.2024. https://iris.who.int/bitstream/handle/10665/341814/WHO-HTP-EHT-CPR-2010.01-eng.pdf?sequence=1&isAllowed=y

Yujia, S., Guanhuier, W., Yonghuan, Z., Liu, N., Fangfei, N., Zhao, Z., Li, H. & Yang, A. 2023, "Application of decellularization-recellularization technique in plastic and reconstructive surgery", *Chinese medical journal,* vol. 136, no. 17, p. 2017-2027. Accessed: 2.12.2024. https://www.proquest.com/docview/2860449194?accountid=14242&parentSessionId=5VKvzh1Iv0fwHZ4k6xBSDU4%2BrTe77%2BNVSEIITBRK%2FzU%3D&pq-origsite=primo&sourcetype=Scholarly%20Journals

APPENDICES

Appendix 1. CAs for tissues and cells (Public Health - European Commission n.d.).

1 (4)

Competent Authorities for Tissues and Cells

Member States	Competent Authorities	Website of the Competent Authorities
Austria	Austrian Federal Office for Safety in Health Care	https://www.basg.gv.at/en/home/
Belgium	Federal Agency for Medicines and Health Products	https://www.famhp.be/en.
Bulgaria	Bulgarian Executive Agency for Transplantation	http://www.bgtransplant.bg/iat/index.php
Croatia	Ministry of Health	https://zdravstvo.gov.hr/
Cyprus	Ministry of Health	https://www.moh.gov.cy/moh/moh.nsf/index_en/index_en?OpenDocument
Czech Republic	Ministry of Health State Institute for Drug Control	https://www.mzcr.cz/en https://www.sukl.cz/en
Denmark	Danish Patient Safety Authority	https://stps.dk/en
Estonia	State Agency of Medicines	http://www.ravimiamet.ee/
Finland	Finnish Medicines Agency (Fimea)	http://www.fimea.fi/web/en

 France	Ministry of Health Agence nationale de sécurité du médicament et des produits de santé (ANSM) Agence de la Biomédecine	http://solidarites-sante.gouv.fr/ http://ansm.sante.fr/ https://www.agence-biomedecine.fr/
 Germany	German Federal Ministry of Health Paul-Ehrlich-Institut	https://www.bundesgesundheitsministerium.de/en/?L=1 https://www.pei.de/EN/home/node.html
 Greece	Ministry of Health Hellenic Transplant Organisation and Bone Marrow Department Hellenic National Authority for Medically Assisted Reproduction – Ministry of Health	http://www.moh.gov.gr/ http://www.eom.gr/ www.eaiya.gov.gr
 Hungary	Ministry of Human Capacities	http://www.kormany.hu/en/ministry-of-human-resources
 Ireland	Health Products Regulatory Authority	https://www.hpra.ie/
 Italy	Ministry of Health National Blood Centre Centro Nazionale Trapianti (CNT)	http://www.salute.gov.it/portale/home.html http://www.centronazionalesangue.it/ http://www.trapianti.salute.gov.it/cnt/cnt.htm
 Latvia	State Agency of Medicines	https://www.zva.gov.lv/

 Lithuania	Ministry of Health National Transplants Bureau – Ministry of Health State Health Care Accreditation Agency – Ministry of Health	http://sam.lrv.lt/ http://ntb.lrv.lt/ http://www.vaspvt.gov.lt/en
 Luxembourg	Ministry of Health	http://www.sante.public.lu/fr/index.php
 Malta	Ministry of Health - Superintendence of Public Health	https://deputyprimeminister.gov.mt/en/sph/Pages/Superintendence-of-Public-Health.aspx
 Poland	National Centre for Tissues and Cells Banking Polish Transplant Coordination Centre – Poltransplant Department of Mother and Child – Ministry of Health	http://www.kcbtik.pl/ http://www.poltransplant.org.pl/ https://www.gov.pl/zdrowie/
 Portugal	Instituto Português do Sangue e da Transplantação Direção-Geral da Saúde (DGS) Conselho Nacional de Procriação Medicamente Assistida	http://ipst.pt/ https://www.dgs.pt/ http://www.cnpma.org.pt/
 Romania	National Transplant Agency Ministry of Health	https://www.transplant.ro/ http://www.ms.ro/
 Slovakia	Ministry of Health	http://www.health.gov.sk/Index.aspx

 Slovenia	Agency for Medicinal products and Medical Devices of the Republic of Slovenia Slovenija-transplant	http://www.jazmp.si/ http://www.slovenija-transplant.si/
 Spain	Organización Nacional de Trasplantes (ONT) National Commission on ARTs	http://www.ont.es/Paginas/Home.aspx http://www.cnrha.msssi.gob.es/
 Sweden	Health and Social Care Inspectorate Medical Products Agency National Board of Health and Welfare	https://www.ivo.se/ https://lakemedelsverket.se/ http://www.socialstyrelsen.se/
 The Netherlands	Ministry of Health, Welfare and Sport Health and Youth Care Inspectorate	https://www.government.nl/ministries/ministry-of-health-welfare-and-sport https://www.igj.nl/