Regulatory Positioning of an Innovative Biomaterial for Regenerative Medicine: TissYou Project

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Abstract: New technologies make it possible to industrialize objects that can reconstruct in-vivo like extracellular matrices. Actually, these scaffolds exhibit properties mimicking physiological tissue. The project presented here aims at the industrial production of a new bicomposite biomaterial for skin regeneration. This "TissYou" matrix is produced by electrospining two polymers, silk fibroin and polycaproclactone, using an innovative process. The state of progress of the project leads us today to have in our hands a functional prototype on the way to becoming a finished product. In order to ensure the transition of this product from R&D to a possible medical device, the regulatory roadmap that awaits the future product should be prepared as soon as possible. Consequently, and relying on the European regulation and its annexes, our main objective is to demonstrate that the product meets the definition of a medical device, to precisely define the class to which it belongs, to start a risk analysis process and definition of the standards that should be applied in the subsequent qualification of the product. In order to stabilize the perimeter of the future indication of the product, we will also present a questionnaire deployed among professionals in order to collect their user needs.

1 INTRODUCTION

The TissYou project aims to the industrial production of an innovative bicomposite biomaterial intended for skin regeneration. This biomaterial is produced by electrospining, with two polymers, silk fibroin (natural) and polycaproclactone (synthetic), thanks to an innovative process.

The electrospinning technique is a technology allowing the production of polymeric fibers with controlled dimension in terms of composition, size, diameter and orientation in the three dimensions (Liu et al. 2021). This technology is the result of a process developed at the end of the 19th century (Boys et al. 1887). Today, researchers have more than a hundred years of experience on this technology, which is experiencing enormous interest; in the wild field of biomaterials (Wang et al. 2019). The basic electrospining technique (Aidana et al. 2021) is based on the use of a system (Figure 1) consisting of a syringe containing a polymer or a mixture of polymers in solution in a solvent (A) and a needle (B)

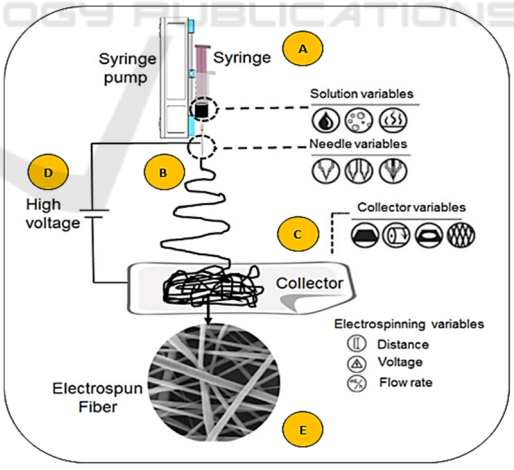

Figure 1: Electrospining technique (from Liu *et al*., 2021). (A) Polymers solubilised in a syringe. (B) Needle. (C) Collector. (D) Electric field. (E) Biomaterial.

allowing the exit of the polymer towards a collecting surface (C). An electric field is applied between the needle and the collector (D) and induces the

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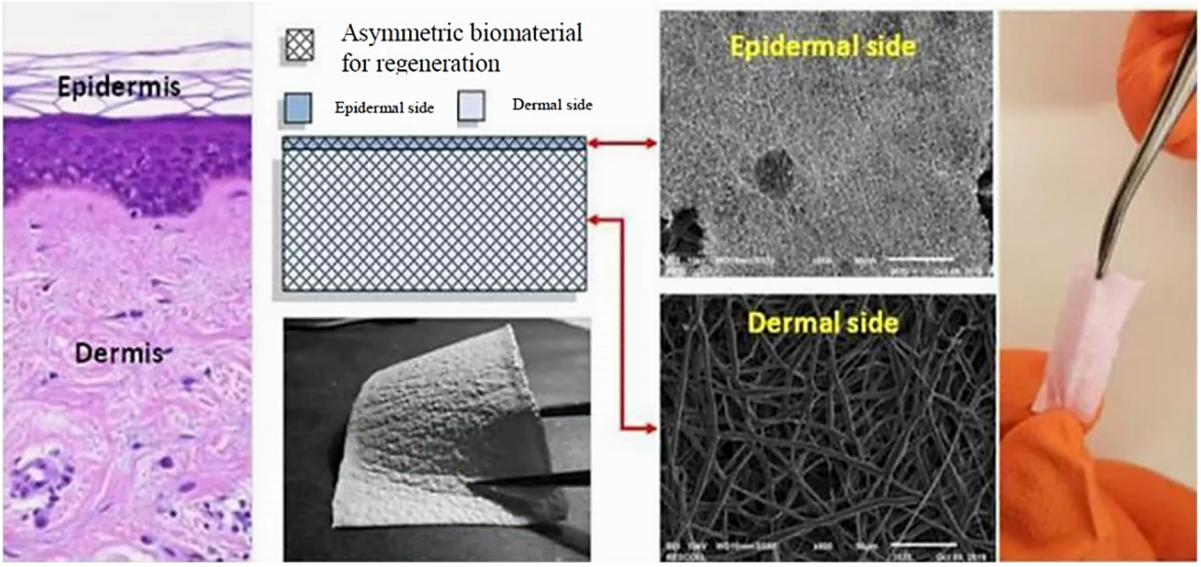

Figure 2: Concept of TissYou product composed of an epidermal and a dermal side to mimic human skin architecture.

formation of "solid" fiber from the raw material in solution contained in the syringe.

The electrospining technique (which can be difficult to master technically) offers the advantage of being extremely versatile. Indeed, each of the bricks of the system (A, B, C, D) can be considered as a variable on which to play to modify the final characteristics of the biomaterial obtained. Thus, the system input parameters can be adjusted: type, molecular weight, viscosity, conductivity, surface tension of the polymer(s), voltage, flow rate at the syringe outlet, distance between the collector and the syringe, environmental parameters of the process (humidity, temperature). Adjusting these parameters makes researchers control the morphology of the obtained material, such as the orientation, the diameter of the fibers obtained and the porosity (Zhao et al., 2021; Wang et al., 2020). Faced with such possibilities, electrospining is clearly considered as one of the gold standard to produce material that can faithfully mimic an extracellular matrix for applications in Regenerative Medicine (Phang et al., 2022).

Building on the interest of electrospinning for the production of material used in the composition of medical devices, our preclinical and clinical research teams (Inserm UMR 1098 and Inserm CIC 1431) have been working together for several years on R&D phases, which have now resulted in the production of an innovative biomaterial. We currently characterize *in vitro* the scaffold that seems to reproduce the architecture, composition and physical properties of human skin. Grafted on the patient, should boost tissue regeneration. Thanks to its particular properties, this biomaterial could also be used as artificial skin for in vitro tests and thus replace animal models. This biomaterial is called TissYou. It is also the name of the European project which was financed (Eurostars, 2021-2024) and which allows the continuation of work on a European scale. Indeed, to allow future patients to benefit from the results of this research, pre-clinical and clinical studies will still have to validate the safety and efficacy of this innovation in Regenerative Medicine. The state of progress of the project leads us today to have in our hands a functional prototype on the way to becoming a finished product (Figure 2).

The objective of the work presented here was first of all to describe the context of the progress of the project and the short-term objectives from a regulatory point of view. Indeed, and to ensure the transition of this product from R&D to a possible medical device, it is necessary to prepare as much as possible a precise regulatory roadmap that drives the future product development. Consequently, and relying on the European regulation and its annexes, the main objective of this paper was to demonstrate that the product meets the definition of a biomaterial, a medical device, to precisely define the class to which it belongs, and to start a risk analysis process. In order to stabilize the perimeter of the future indication of the product and feed the future risk analysis, we also worked on a questionnaire deployed among professionals in order to collect their user needs.

Table 1: Justification for medical device classification.

Article - UE 2017/745	Justification
Article 2 Section 1 *Medical device*	The biomaterial is a material, intended for use in humans, with the aim of treating traumatic wounds with extensive loss of substance, by replacing by replacing or modifying the physiological process of healing. The biomaterial meets the definition of a "medical device".
Article 2 Section 2 *Accessory*	The biomaterial is a "medical device" and is therefore not a "accessory".
Article 2 Section 3 *Custom-made device*	The device is not expressly manufactured according to a prescription and intended for a single patient. It is not a "custom-made device"
Article 2 Section 4 *Active device*	The operation of the device does not depend on a source of energy other than that generated by the human body for this purpose or by gravity. It is not an "active device".
Article 2 Section 5 *Implantable device*	The device aims to replace the skin on an injured surface. It is an "implantable device".
Article 2 Section 6 *Invasive device*	The device is applied to the surface of a wound or damaged skin and penetrates the body through its surface. It is an "invasive device".
Annexe VIII 2,2 – *Invasive device, surgical type*	The device is an invasive device but is not an "invasive surgical-type device".

2 METHODOLOGY

In order to position the TissYou product in the right regulatory context, and to place our object on the regulatory roadmap that awaits it in its regulatory journey as a medical device, we will rely in particular on the European regulation and its annexes to demonstrate that the product meets the definition of a biomaterial, and that of a medical device. Then we will precisely define the class to which it belongs, and will start a process of defining the standards that will be appropriate to apply in the continuation of the qualification of the product. In order to stabilize the perimeter of the future indication of the device, we will also present a questionnaire deployed among professionals in order to collect their user needs and the results that we have already been able to obtain.

3 ANALYSIS

3.1 Regulatory Position

3.1.1 Is our Product a Biomaterial?

According to the definition of the European Society for Biomaterials (European Society for Biomaterials), a biomaterial is defined as a : *"Material intended to be in interaction with a biological system with the aim of evaluating, treating, increasing or replace a tissue, organ or function of the human body"*. TissYou is a material intended to interact with the human body, the skin in particular, with the aim of supplementing skin healing. The notions of interaction, replacement and supplementation of a function of the organism are very present. The TissYou product can therefore be qualified as a biomaterial.

3.1.2 Is our Biomaterial a Medical Device?

According to European regulation MDR 2017/745/EU which entered into force on May 26, 2021, a medical device meets the following definition. Is considered as a "medical device":

Any instrument, device, equipment, software, implant, reagent, material or other article, intended by the manufacturer to be used, alone or in combination, in humans for one or more of the following specific medical purposes:

- Diagnosis, prevention, control, prediction, prognosis, treatment or alleviation of a disease,
- Diagnosis, control, treatment, mitigation of injury or disability or compensation thereof,
- Investigation, replacement or modification of an anatomical structure or function or of a physiological or pathological process or state,
- Communication of information by means of in vitro examination of samples from the human

body, including organ, blood and tissue donations,

and whose principal intended action in or on the human body is not obtained by pharmacological or immunological means or by metabolism, but whose function can be assisted by such means.»

With the help of the European regulation and the articles that make it up, we have chosen as a strategy for determining membership in the category of medical devices the creation of a checklist in order to answer point by point the questions that must be asked (Table I). In the light of the answers provided according to the characteristics noted, the TissYou biomaterial can be considered as a medical device. It is not an accessory of DM nor of a custom-made or active DM. On the other hand, TissYou is an implantable MD, invasive but not of the surgical type.

3.1.3 What Class of Risk for TissYou ?

MD classification, as defined by European legislation, is a risk-based system that takes into account the vulnerability of the human body and the potential risks associated with the devices.

This approach uses a set of criteria that can be combined in various ways to determine classification, such as duration of body contact, degree of invasiveness, local vs systemic effect, potential toxicity, body part affected by use of the device and whether the device depends on an energy source.

The "classification rules" set out in Annex VIII of Regulation (EU) 2017/745 relating to medical devices (MDR) were used and transcribed in the form of a checklist (Table II) in order to determine the class of membership of our medical device “TissYou”. Thus, for each of the 22 stated rules, the notion of applicability has been defined and justified with regard to our product. In accordance with the answers provided, the TissYou medical device can be classified as a class III medical device, the class with the highest level of risk. Indeed, the device is an implantable device, absorbed in whole or in large part, and is intended to undergo a physico-chemical transformation in and by the body. Furthermore, the device is composed of combinations of substances intended to be introduced into the human body by application to damaged skin and absorbed by the human body or dispersed locally therein. The substances in question, or the products of their metabolism, are systemically absorbed by the human body in accordance with the intended purpose of the Device.

3.1.4 What Intended Use for TissYou?

The skin is an essential organ for maintaining the homeostasis of the human body as a whole. However, being the first barrier against the external environment, skin tissue can be easily damaged, leading to the formation of an injury. The severity of these injuries is variable and depends on the layers of skin affected.

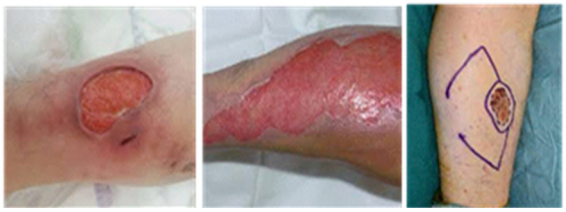

Figure 3: Example of clinical indication addressed by TissYou. From left to right: leg ulcer, burn, and skin cancer.

In response to this injury, a physiological repair process takes place: healing. Healing is an extremely complex and regulated phenomenon that can be summarized in 4 major phases: hemostasis, inflammatory phase, proliferative phase, and remodeling phase. During serious injuries, the dermis is no longer able to regenerate properly. One of the therapeutic management strategies may then consist of the use of equivalent dermis / regeneration matrix. Three main clinical indications (Figure 3) have been considered in terms of application of our future medical device TissYou: chronic wounds, burns, reconstructive surgery after surgical resection.

Depending on the intended indication, the properties of the biomaterial may not be the same. From a regulatory point of view, the risk analysis, which will have to be carried out to feed the documentation relating to our medical device in order to converge towards its CE marking, will also greatly depend on the clinical indication. In the current state of development of the TissYou biomaterial, a firm indication has not yet been chosen. Nevertheless, for the reasons mentioned above, and in order not to slow down the progress of the translational project, this choice must be made quickly.

Today the project team working around TissYou does not include a committee of clinical experts. As part of the work presented here, we then wrote and distributed a questionnaire intended for future users / endusers of our biomaterial. This questionnaire (Figure 4) aimed to achieve several objectives:

- Define the best indication for TissYou according to user needs,

Table 2: Justification of the risk class assigned to the device (for full definition: 2017/745: http://data.europa.eu/eli/reg/2017/745/oj).

Classification rules (Appendix VIII)	**Applicability**	**Justification**
1 to 4: Non-invasive device	Non applicable	The device is an invasive device.
5: Invasive devices with respect to body orifices	Non applicable	The device is unrelated to body orifices and is not a surgical type invasive device.
6 et 7: Transcient/ shor-term use	Non applicable	The device is intended for long-term use (more than 30 days) because, the scaffold will be graft on the skin and will be biodegraded by the organism over time (> degradation rate > 30 days).
8: Implantable device classification?	Applicable Classe III	The device is an implantable device, absorbed in whole or in large part and is intended to undergo chemical transformation in the body.
9 to 13: Active device	Non applicable	The device is not an active device.
14: Drug incorporation	Non applicable	The device does not incorporate any substance that could be considered a drug.
15: Contraception or STD prevention	Non applicable	The device is not used for contraception or to prevent the transmission of STDs.
16: Desinfection or sterilization	Non applicable	The device is not intended to disinfect, clean, rinse or moisturize contact lenses or Class IIa devices.
17: X-ray radiation	Non applicable	The device is not intended to record diagnostic images generated by X-ray irradiation.
18: Tissue or cell origin	Non applicable	The device is not manufactured from tissues or cells of human or animal origin or their derivatives.
19: Nanomaterial incorporation	Non applicable	The device does not incorporate nanomaterials and does not consist of them.
20: Medicinal product inhalation	Non applicable	The device is not related to the body orifices and are not intended to administer medicinal product.
21: Human body absorption	Applicable Classe III	The device is composed of combinations of substances intended to be introduced into the human body by application to damaged skin and absorbed by the human body or dispersed locally in it. The substances in question, or the products of their metabolism, are systemically absorbed by the human body in accordance with the intended purpose of the device.
22: Active device	Non applicable	The device is not an active device.

- Collect information on user expectations vs competitiors,
- Obtain data allowing us to develop our biomaterial in order to meet closely their needs,
- Propose to clinicians to join us as an expert,
- Propose to the clinicians contacted to be those who will participate in the first clinical and usability trials,
- Obtaining other user contacts with a “close by close” strategy, with clinicians sending us the contact details of potentially interested colleagues.

To date, our questionnaire was distributed to 12 clinicians (Dermatologists and Plastic surgeons) working at the Besançon University Hospital or at the Nord Franche-Comté Hospital in Trevennans (France). It was sent in Word format as well as in Googleform to facilitate data extraction.

Among the responding clinicians, 1/3 have already used dermal substitutes and 2/3 have never experienced such device. The dermal substitutes usually used are Integra® and Matriderm®. The indications leading to the use of a dermal substitute are: preparation for thin skin grafts and resurfacing. The complications encountered were superinfection, lack of integration of the biomaterial and detachment of the basement. Regarding the manipulation of the dermal substitute, the surgeon is not the only user. Nurses and interns may also be required to handle it. The reasons that hinder practitioners from using dermal substitutes are the lack of easy availability of such medical devices, the lack of habit of use on this subject, their cost and the difficult match with the topography of deep wounds. The reasons that could lead clinicians to use more dermal substitutes are: a shortening of the healing time, better functional and aesthetic results, the management of wounds, an effective and permanent discharge of chronic wounds, the treatment of a superficial wound, the fact that the device is available, ergonomic and at a low cost. Clinicians would also prefer the device to be ready-to-use and not sutured.

4 CONCLUSION

TissYou is a bicomposite biomaterial produced by an optimized electrospinning technique. The material is said to be bicomposite because it is composed of two polymers: a natural and a synthetic one. In order to ensure the transition of this product from R&D to a possible medical device, the regulatory roadmap that awaits the future product should be prepared as much as possible.

To achieve this objective, we have shown here that our product meets the definition of a biomaterial and more specifically that of a medical device within the meaning of European Regulation 2017/745. Appendix VIII and the positioning of our product have enabled us to show that our product consists of a class III, invasive and implantable medical device. Nevertheless, there remains uncertainty about the positioning of medical devices as an invasive product and about the proposed definition of invasiveness. Interpretation of the definition may not be as clear as expected with respect to the use of the device on injured skin and the interface with the inside and outside of the body. To contribute to progress on this subject, a study of the competition has been initiated in order to compile the information available, in particular via the ANSM's documentary base to parallelize us with the devices of the same type already on the market.

Still based on the regulations, and thanks to appendix II (section 6.1 and 6.2), we will also list the verification and validation elements to be provided in the technical documentation of our future MD. Thus, the output data from appendix II will allow us to orient ourselves towards the standards that will have to be followed and respected within the framework of our work, in particular standard 10993 devoted to the biological evaluation of medical devices. Other standards have also been identified which would also be applicable to the future DM TissYou (data not shown). This non-exhaustive list will be completed, in particular in parallel with the performance of a risk analysis. This analysis may begin as soon as the indication for use of the TissYou device is fixed. Indeed, for the time being, the indication for use is not defined. Several avenues have been suggested (chronic wounds, burns, reconstructive surgery) as shown previously.

In order to converge towards a choice based on the desire to respond strongly to an unmet clinical need, we decided during this work to build and distribute a questionnaire to health professionals with several objectives: to collect information to develop our biomaterial, better meet their needs, choose the right indication, create a network of experts. The data collection is not finished but already many relevant answers and comments allow us today to validate some of our technical choices (thickness and mechanical properties), to rule out indications not favorable to the use of our product (chronic wound), to identify possible indications. The choice of an indication, and therefore of specific claims, will help define what preclinical steps will be taken and which remain ahead of us, namely the trials in small and large animals that we will have to conduct soon.

In conclusion, the work presented has triggered a regulatory switch in the way the TissYou project is viewed until today. Indeed, the available prototype, and soon to become a finished product, only has a chance of becoming a medical device with a place on the market if it meets a strong clinical need. This is the challenge of positioning our product quickly in front of a precise indication. We will thus be able to take a further step on the regulatory roadmap which will lead us to carry out work contributing to meeting the requirements of the regulations, to demonstrating

the safety and then the effectiveness of our class III medical device and to being able to file medium term a CE marking dossier.

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