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SusFE

D1.8 Ethics report by external advisor

Deliverable No.	D1.8	**Due Date**	31/12/2022
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Work Package No.	WP1	**Work Package Title**	Eco-design and specification of R2R processes and novel functional electronics components and systems
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Abstract

The wound monitoring use case of the project SusFE is expected to generate prototypes. They will be first evaluated according to a series of tests, in the laboratory, e.g., testing the performance of the different sensors and the wireless exchange of the sensor data. Prototypes should avoid the use of chemicals / materials with unknown biological / toxicological effect. If passing all the bench tests, selected prototypes may then enter animal studies, 1st in small rodents to test the biocompatibility and toxicity during the intended duration for wound monitoring (max 2 weeks) and 2nd in farm pigs to monitor the healing of full thickness skin incisions. Before starting these studies, study protocols will be submitted in order to verify, notably, the ethical requirements.

Statement of originality

This deliverable contains original unpublished work except where clearly indicated otherwise. Acknowledgement of previously published material and of the work of others has been made through appropriate citation, quotation, or both.

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About this deliverable

This document lists the prerequisites of evaluation studies in animals, according to ethical conduct and European legislation.

Deliverable context

Table 1. Deliverable context

PROJECT ITEM IN THE DOA	RELATIONSHIP
Project Objectives	This deliverable does not directly contribute to the project objectives, but it gives requirements to conduct animal studies in compliance with ethics and EU legislation
Exploitable results	There is no specific contribution to any exploitable results. Instead, this document is the basis defining the ethical basis of animal studies.
Workplan	D1.8 is attributed to the tasks of WP1 Eco-design and specification of R2R processes and novel functional electronics components and systems. It is a pre-requisite of the Task 5.5: Transfer to roll-to-roll (R2R) processing and testing of WP5 Integration of components in R2R for production, testing, validation and LCA/LCCA
Milestones	D1.8 is a key deliverable for the ethical management of animal studies to test wound monitoring prototypes of the project.
Deliverables	D1.8 defines the pre-requirements of animal studies to be compliant with ethics & the EU legislation.
Risks	D1.8 reduces the risk of conducting animal studies that do not comply with fundamental principles of animal ethics.

1 Introduction

SusFE project aims at developing a sensor system for the monitoring of wounds, Prototypes should be generated as patches or bandages and include a series of sensors, among them, pH, pO_2 and temperature sensors. They should integrate the use of the FlexIC for the analog and digital circuitry. Moreover, the sensor elements should preferably be fabricated using R2R processes.

The use case testing will be carried out a dermal wound animal model, rats or farm pigs, up to 1 week, to monitor the progress of healing over the time. Consideration will be given for selecting the correct animal model for dermal wound-healing studies.

The goal of the testing is to start showing the biocompatibility of the sensor system and to evaluate the performance of the sensors at measuring selected parameters (eg. pH, pO_2, temperature…) over the time, in conditions mimicking the clinical settings.

Above all, it is important to remember the ethical rules with which preclinical animal studies must comply. An expert report was therefore requested from Samuel Vidal, DVM, MBM (VetAgro Sup, Marcy l'Etoile, France).

2 Purpose of the animal models-based study in SusFE

The animal study should document the biocompatibility and the performance of the sensor system. It will come after a series of laboratory tests to evaluate the physical characteristics, the sterility, the stability, and the risk of potential chemical contamination during the production of the prototypes. The study should be done on finished prototypes, except if new chemicals with unknown effects are included in some parts of the sensor system. But, in first intention, this should be avoided.

The study will include 2 steps. A first study in small animals will assess the biocompatibility and the toxicity of the prototype. If generating satisfying results, a second study, in pigs, will evaluate the performance of the sensors to monitor selected parameters in a wound model, i.e., measuring the parameters and wireless transfer of the associated data.

3 Pre-clinical study: overview

The 1st animal study will be done in small rodents such as rats to evaluate the biocompatibility and the toxicity of the sensor system. The endpoint will be 1 or 2 weeks, defined according to the planned in life duration of the 2nd animal study, the performance one, in farm pigs.

The biocompatibility and the toxicity of the sensor system will be evaluated from macro-observations and anatomopathological analyses from a selection of histology staining.

The study will be performed by an accredited CRO.

The 2nd animal study will be carried out in farm pigs, in a skin wound model. The sensor systems will be placed over the wound during 1 or 2 weeks. The data measured by the sensors and communicated wireless by the electronic board will be collected and analyzed.

This study will be performed as well by an accredited CRO and will be planned, only if the 1st study gives satisfying results.

The sponsor of both studies will be Sofradim Production (SOF).

4 Legal and Scientific Compliance

Animal studies will be planned and executed according to the ethical and legal requirements as listed in the Export report written by Samuel Vidal, DVM, MBM (See Appendix A), including the compliance to European Directive 2010/63 and the ARRIVE Guidelines.

5 Conclusions

As shared by Samuel Vidal, DVM, clear and transparent accountability for the animals used must be maintained throughout the duration of the SusFE project.

Appendix A shares a preliminary assessment of the ethical, legal, and scientific requirements.

Final ethical review of animal studies will be generated based on non-animal preclinical evaluations (e.g., physico-chemical analysis, sensor performance, sterility, stability, identification of chemicals with unknown biological effects) and study protocol, in a sequentially manner, starting with the 1st study to assess the biocompatibility and toxicity of the sensor system and, addressing the 2nd study, the performance study in a pig wound model, if the 1st study generates satisfactory results.

Appendix A Ethics Report by External Advisor

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Samuel Vidal, DVM, MBM

Animal Welfare Officer

Deputy Chair of the Ethics Committee n°18

Guidance on the Ethical use of animals for the Horizon Europe Project n° 101070477

"INNOVATIVE **PROCESSES AND METHODOLOGIES FOR NEXT GENERATION CLIMATE-NEUTRAL AND CIRCULAR FUNCTIONAL ELECTRONICS COMPONENTS AND SYSTEMS (SUSFE)"**

This project gathers a vast consortium around a global goal for the development several systems to which could contribute to the production of new materials, new sensors and the use of cell powered technologies.

Experiments could be necessary of the Work Package 2 **Sensor fabrication and characterization:** This WP will integrate a combination of physical sensors for temperature and strain as well as chemo/biosensors. They would be integrated in a conformal bandage for the remote timely and accurate monitoring of wound healing.

This project raises several questions which need to be studies by methodic approaches:

- The production of the bandage will introduce new materials with physical and biochemical characteristics which have not been yet tested on healing wounds.
- The conformal bandages require a reliable contact with the healing tissues in order to maintain the function of the sensors and bring the information of interest.
- The efficacy, the stability and the reliability are up to now of the device is not confirmed, in a medical context.

The members of the consortium are fully responsible of the choice of the methods and test which will be used to assess the biochemical/physical features, the efficacy and the reliability in a biological context of the device. However, in the European legal framework and ethical context, some recommendations could be given:

1- Most of the evaluation should be performed with in vitro techniques. The evaluation of physical characteristics, the evaluation of sterility, stability and potential chemical contamination during the production must be assessed in vitro.
2- The in vivo biocompatibility should be evaluated only on the finished device, except if really new compounds which have never been tested in vivo have to be introduced. In this case, a harm/benefit analysis shall be done before taking the decision of testing an isolated compound. Testing in vivo biocompatibility should only be performed after all results of in vitro investigations have been analyzed.

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3- In vivo biocompatibility should lead to studies on rodents, with representative samples of finished bandages of limited volumes. The preparation and sterilization of the samples should use a similar process as the one used for the final product
4- Efficacy studies should be performed on large animal models where the healing physiological and physical constrains are analogous with humans' skin healing. Swine could be an adequate model. Wound size should be sufficient to bring robust information and comparison with other medical devices on complex would. The number of test items used should be adapted to the size of the animal models, according to the capacity of the research organizations to manage safely and carefully the system. A statistic assessment should confirm the necessity to compare wounds with reference treatments, test item and wounds with no treatment.
5- In all in vivo testing, a regular pain management including pain prevention, assessment and treatment should be included with all state-of-the-art techniques.
6- Humane endpoints must be defined in order to avoid any suffering in case of failure or unexpected event during the procedure. In this context, as the purpose of the testing is more the compliance and reliability of the sensors than the healing speed, the interest of using non steroid anti-inflammatory drugs should be evaluated.

In general, all animal studies must be fully compliant with the national transposition of the European Directive 2010/63 of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes. Wherever they would be conducted in the EU, they must be performed in licensed institutions, with formal authorization provided by the national authorities and by competent staff.

In addition, if any scientific peer review publication was issued, it should follow the ARRIVE Guidelines 2.0 published on 14 July 2020 by Percey du Sert et al. in Plos Biology : https://dx.plos.org/10.1371/journal.pbio.3000411. Following these recommendations will bring reproducibility, robustness and avoid any repetition of these in vivo experiments.

The design of the studies must also satisfy the requirement of at least one certification and market approval organization in the EU which should be consulted if this is acceptable.

During all the life of this Horizon Europe Project n°10107047, a clear and transparent accountability of the animals used should be kept. The number of animals, the purpose of the studies and the actual severity of the procedures should be provided to contribute to the final ethical evaluation of the project.

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