# Organ on Chip in Development (ORCHID)

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# Contents

# Executive Summary

Organ-on-chip (OoC) technology is a fast-growing research field and also several companies are commercializing the technology already (for a detailed overview, see ORCHID report D3.1[1]). The roadmap for OoC technologies presents both opportunities and challenges. This document re-iterates on ethical, regulatory and standardization hurdles and opportunities and presents policy options, their consequences and finally recommendations for the policymaker to increase the impact of OoC on society and economy in Europe and beyond.

# Introduction and Overview

## Organ-on-Chip: an emerging technology

Organ-on-Chip (OoC) is a young but fast-growing field. In early stage technology fields, challenges and opportunities arise everywhere. Policymakers can have a distinct influence on early development and their decisions and directions are critical to the long-term success of a new technology. Here we are discussing the aspects of ethics and communication, regulatory pathways, and standardization efforts.

What are the policy recommendations related to ethics when we start implementing OoC in the drug discovery pathway? How do we communicate about OoC to all stakeholders, including the general public and patient representatives? How can OoC technology make an impact thereby making use of existing or creating new regulatory pathways? Are standardization efforts required and what are the advantages and disadvantages of implementing them for OoC. How will it be done? How can we shape a future for OoC?

This document will take key messages from previous efforts in the ORCHID project and bring forward options for policymaking and finally define recommendations for the policymaker.

## Policy options

Policy recommendations for the three categories discussed in this document will be assessed within a range of policy options. We chose evaluation criteria for those options according to standards defined for policymaking in literature[2]. There are many different criteria that can be used to evaluate policies, and there is often a significant debate about them. To avoid overcomplicating things, we included criteria that are of general importance, such as legality, but also those that have economic (cost effectiveness, impact) and societal (inclusiveness, impact) value.

Legality means that the specific policy is implemented in the law at this point – a negative answer here means a considerable effort in bringing the policy into place. Cost effectiveness means that the policy can be implemented at the lowest possible cost – this is important information for the policy maker. Inclusiveness means that a community has access to the result of the policy, and impact measures the

[1] D3.1 Societal and economic impact
[2] https://politicalscienceguide.com/home/policy-paper/

overall effect (economic/societal) of implementing the policy. After evaluation of the policy using these criteria, we elaborate on the different policy options and their meaning for OoC technology.

## Reach out to the general public & ethical concerns

| **Policy question: How does OoC technology need to be communicated in the future to the general public?** | **Policy choice A: no communication** | **Policy choice B: leave (academic) community to take the lead** | **Policy choice C: active EU or national programs to disseminate OoC** |
|---|---|---|---|
| **Criteria 1: legality** | Yes | Yes | Yes |
| **Criteria 2: cost effectiveness** | Yes | Neutral | No |
| **Criteria 3: inclusiveness** | Probably not | Yes, but less probable | Yes |
| **Criteria 4: impact** | No | Yes, but less probable | Yes |

Since OoC technology is still in its infancy, there is a good opportunity to communicate effectively to the general public. It is not a secret that the general public, for example, is sensitive to the use of animals for drug discovery and even research purposes. OoC technology promises to replace and reduce animal use. This is a strong point for a positive acceptance path. Besides, the concrete need in the ethical context for a new technology is a good starting point to achieve a comprehensive level of acceptance by the public. The purpose and gain for society might be central in that communication. A pitfall of the latter is that key information about OoC concepts gets lost or is misinterpreted. Expectations can become unrealistic due to the long time needed to develop OoC's and bring them to the market, so that they can impact daily lives. Setting realistic expectations is important. Further, communication to the public might have to be adapted to address different cultural and geographical backgrounds.

In the ORCHID project consensus was reached about the definition of an OoC. Now, it can be debated whether this definition is appropriate for the general public, as it contains several technical terms and might be too complex to understand. As already mentioned, OoC technology aims to replace or at least drastically reduce animal use. Bio-ethically it thus tells a more positive story. On the other hand, the use of patient material bears some risks in the privacy and consent space, which needs to be addressed accordingly.

**The policy question raised here is** do governmental stakeholders need to actively promote the outreach to the public when it comes to OoC technology? We posed different policy options: A) the EU or national policy makers actively promote communication through funding schemes, pilot projects and programs to engage academic, regulatory, industrial and other stakeholders in active and effective communication about OoC; B) no active (e.g. funding schemes) promotion but possible passive support of the academic community to translate academic opinions to the general public; C) no active or passive engagement of policy makers.

## Regulatory pathways

| **Policy question: How can OoC technology be implemented in the regulatory pathway?** | **Policy choice A: Follow current guidelines for qualification, in concert with original methods (e.g., animal testing)** | **Policy choice B: Policy maker creates an instrument or framework** | **Policy choice C: Policy makes pilot lines for consortia that include relevant stakeholders and is actively involved** |
|---|---|---|---|
| **Criteria 1: legality** | Yes | Not at this moment | Not at this moment |
| **Criteria 2: cost effectiveness** | Yes | No | No |
| **Criteria 3: inclusiveness** | No | Yes, to a lesser extent | Yes |
| **Criteria 4: impact** | Yes, to a lesser extent | Yes | Yes |

Adoption of OoC technology into the drug discovery pathway can only happen through a qualification phase – where the new method is compared and evaluated against traditional methods. Validation of the technology needs to be performed in a specific context of use and needs thus to follow other regulatory pathways as is the case with for example novel biomarkers. The presence of all stakeholders (regulatory, pharmaceutical industry, academia, OoC companies) in specific programs (EU, IMI, FDA, NIH) might offer options for this qualification step.

**The policy question raised here is** how the policy maker can facilitate faster and more efficient implementation of OoC technology into existing or novel regulatory pathways. Today there are existing frameworks for regulatory approval of novel methods, as discussed extensively in D5.1 of the ORCHID project[3]. Novel technologies can be qualified even without the active inclusion of regulatory stakeholders (Policy option A). However, for example in the EU, the lack of independent testing centres or dedicated working groups will strongly hamper the roll out of OoC technology in drug discovery. Independent and comparative (side-by-side) efforts could be performed for OoC technology to enable adoption and use in the drug discovery process, for example (Policy option B). Another option is enabling early integration of

[3] D5.1: State of the art of regulation, standardization and ethics

the OoC technology in pharmaceutical programs, with an active role for the regulator, and steered by the policy maker. The latter option (Policy option C) includes all the stakeholders and is preferred but not required.

## Standardization

| **Policy question: How can standardization be implemented in OoC technologies?** | **Policy choice A: Bottom up, i.e., spontaneous and without active role of the policy maker** | **Policy choice B: Top down approach facilitated by the policy maker** | **Policy choice C: Top down approach with a strong direction of the policy maker and influenced by regulatory stakeholders** |
|---|---|---|---|
| **Criteria 1: legality** | Yes | No | No |
| **Criteria 2: cost effectiveness** | Yes | Yes | Yes |
| **Criteria 3: inclusiveness** | No | Yes | Yes |
| **Criteria 4: impact** | Uncertain | Yes | Yes |

At this point in time, the OoC technology and application field is very young and relatively small; it is mainly defined by academic efforts and small, starting companies. Standardization, as described in the report of the ORCHID project (D5.5)[4], is a process that often is triggered in a more mature industry by a need of end users or is initiated by a major player in that industry. Several aspects of OoC technology, however, are already being considered for standardization: microfluidics, cell culture and sensors. These efforts can help push standardization efforts for OoC forward.

**The policy question raised here is** how standardization can be implemented for OoC technologies. The bottom-up approach, as can be learned from other industry examples, is often a spontaneous process that would take an uncertain amount of time and policy makers are not involved actively. A more active role for the policy maker is reserved in the second option we propose: the role of facilitator, i.e. policy is developed to guide stakeholders to a defined process of standardization. This effort might lead to a more efficient development of the technology and ease the uptake. A more active and directive role can also be taken by the policy maker. In this case, a strong direction is given, and regulatory stakeholders can be asked to help guide the process (see policy question regulatory aspects above).

[4] D5.5: White paper on standardization

## Projected outcomes of policy making and recommendations

The ORCHID consortium has brought together a large group of key opinion leaders representing all stakeholders and has **communicated** already extensively on OoC technology (see also public reports on https://h2020-orchid.eu/) (Franzen et al.[5], 2019; Mastrangeli[6], 2019). Through social media we have reached a broader audience. We have set up a training network and a digital platform. Finally, with the birth of EUROoCS we will strive to continue and strengthen the outreach through workshops, meetings, conferences, etc.

Recommendation: The active promotion of and communication on OoC technology seems a better choice than a wait and see policy. Active communication on the topic of OoC will strengthen the academic field and bring together stakeholders from regulatory, industry and patient organizations so that OoC technology can be adopted faster and more efficiently and can have a large impact on society. Active communication also requires and allows to bring the right message and to explain difficult, technical concepts in layman terms. Expectation management about the impact of OoC on daily life of the general public is necessary. Ethical concerns can be answered early by opening the debate, for example about informed consent. A reach out to other current ethical debates about human material is advised.

The **regulatory** aspect is challenging but policy makers can have a strong influence on facilitating this process. Creating awareness and bringing people together is a good first start. We have involved several key opinion leaders throughout the ORCHID project, as described in our Vision and Strategy workshop reports, which has proven to be crucial in the development of the OoC roadmap. Regulators have also provided valuable feedback and expressed their interest in active participation in future discussions about OoC and in the EUROoCS community.

Recommendation: Similar to efforts in the US, where independent testing centers and active contributions of the FDA are pushing OoC technology forward, OoC technology in the EU would benefit greatly from a promoting role of the policy maker.

Currently, with the support and in the context of EUROoCS a European OoC Infrastructure is being designed that will bridge the gap between Developers and End User applications and support widespread implementation and acceptance of the OoC models: from experimental model to standard product. This infrastructure will select and qualify models based on criteria defined and established jointly by Developer and End User stakeholders that include the European OoC Society (EUROoCS), the Netherlands Organ-on-Chip Consortium (hDMT), regulatory agencies such as the European Medicines Agency (EMA) and the Food and Drug Administration (FDA; USA) and representatives of pharma. Models that comply with initial requirements will be taken forward to in depth testing and qualification leading to fully characterized models with guidelines and standard operating procedures on use and applications. All results will be available in a database based on FAIR guidelines, and will help end users to choose the right model for

[5] DOI 10.1016/j.drudis.2019.06.003
[6] DOI 10.14573/altex.1905221

their applications. In addition, complex *in silico* modelling (PK/PD modelling) based on clinical data available through the regulatory agencies and pharma will support *in vitro* to *in vivo* translation.

The creation of a framework or dedicated consortia or pilot projects where all stakeholders are represented seems necessary to tackle the regulatory hurdles for OoC technology. An active role of the regulatory bodies is desired. EUROoCS s can play a coordinating role in this effort.

**Standardization** can boost innovation and increase efficiency in industry. Although OoC is a young and relatively small industry, it is worth looking at standardization efforts already taking place in related fields or subcomponents.

Recommendation: Besides the spontaneous process of searching for standards in a field without the aid of the policy maker, a more active role can help organize standards and protocols around a complex technology such as OoC. A top down approach, where the policy maker is actively giving direction might bring structure early and help define early standards. This can be achieved by a facilitating role or a more directive role of the policy makers, in order to bring academia and industry together in working groups for example. Including the link to the regulatory aspect is desired as early alignment with regulatory pathways can help shape standards.