Organ-on-Chip In Development
ORCHID Final Report

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Organ-on-Chip In Development
ORCHID Final Report

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Photo: Paul ter Braak/Marinke van der Helm; BIOS Lab on a Chip group, UTwente.
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Healthcare challenges from 2020 and beyond

Conventional animal models and cell cultures used widely in research are increasingly documented as failing to fully capture human (patho)physiology. As a result, understanding disease mechanisms and predicting responses to medical treatments in humans is falling short of need and expectation. This is a major contributor to late and costly drug failures in clinical trials and is one important reason why drugs in general are expensive and there are no curative treatments for many medical conditions. Aside from having increasingly recognized limited predictivity, animal experiments raise ethical issues, increasing societal and political pressure to reduce their number. This requires new ways to improve drug development and identify effective, personalized treatments. Patient-specific stem cell-based systems are now making inroads in this area but in some cases it is becoming evident that only in combination with Organ-on-Chip (OoC) technology, which can effectively control biophysical conditions in tissues, human (patho)physiology is fully captured. OoCs are thus potential game changers that offer cutting-edge, multidisciplinary solutions contributing to new drugs and affordable healthcare.

Organ-on-Chip In Development (ORCHID) has been a 2-yr H2020 FET-Open project, that aimed to build an ecosystem that will move OoCs from the laboratory into real-life medical care for citizens of Europe and beyond, supported by the creation of a roadmap for OoC such that there is acceptance of the technology by end users and regulators.

The following objectives were addressed:
- Assess the status of OoC technology in Europe;
- Identify ethical issues, drive standardization and take steps towards regulatory acceptance;
- Analyse the impact of OoC technology on the economy, society, training and education;
- Establish the OoC technology roadmap;
- Raise awareness and build an ecosystem for OoC technology.

ORCHID has laid the foundations of a European ecosystem on OoC technology. ORCHID achieved this by bringing together many key European players in this field and strengthening this community by establishing the European Organ-on-Chip Society (EUROoCS). EUROoCS is meant to be a sustainable forum for information exchange among experts, development of end user guidelines and the formation of training networks. ORCHID has provided insights into the state-of-the-art, needs and challenges of the OoC technology, which formed the basis for the development of the European OoC roadmap. As a follow-up to ORCHID, EUROoCS will facilitate implementation of the roadmap in an ongoing dialogue between developers, end users and regulators.

Development of the European OoC Roadmap

During the ORCHID project, two workshops were held in which experts from academia, pharmaceutical and cosmetic industries, patient organizations, ethics panels, biotech companies and regulatory agencies took part. The bibliographical, bibliometric and market analyses and expert interviews, combined with the outcome of the workshops, identified current unmet needs, key challenges, barriers

and perspectives of this technology as the basis for developing an OoC roadmap (21). Six specific building blocks for the roadmap were defined, including priorities, methods and targets for each block (22). EUROoCS has initiated and will continue to catalyse the dialogue between developers, end users and regulators during roadmap implementation.

European Organ-on-Chip Society

A major outcome of ORCHID has been the establishment on 5 November 2018 of the European Organ-on-Chip Society (EUROoCS) (www.euroocs.eu) as an international independent not-for-profit organization aimed at encouraging OoC research and development and providing opportunities to share and advance knowledge and expertise in the field towards better health for all. EUROoCS will continue to stimulate dissemination and provide a platform for dialogue and interaction between all parties in the OoC field. With the support of EUROoCS, the OoC community will be well positioned to accelerate adoption of the OoC technology.

Societal and economic impact, training and education

A budget impact analysis of OoC technology was performed over a 5 yr period (30). Relative change in costs was assessed through a survey among 17 experts, based on an R&D productivity framework that considered each phase of the drug development process and corresponding main cost drivers. A reduction in total R&D costs of up to 26%, is expected through OoC technology. Savings will be achieved by improving the success rates of drugs moving to clinical trials with most benefits expected in lead optimization and preclinical research phases.

The current and future business models and their strengths and weaknesses were identified. Additional customer market segments, including the veterinary industry, military, and chemical industry, allow the development of new business cases and models for OoC technology, thus extending the impact of the technology beyond the current scope of drug discovery and development.

The training needs for promoting the development, utility, adoption and qualification of OoC systems have been identified using an online stakeholder questionnaire. The main target populations in need of training are technicians and end users in both industry and academia, and early career researchers, including those in applied science studies.

Ecosystem development and digital platform

A digital platform (called ‘OoC for all’) has been developed within ORCHID that has been integrated in the EUROoCS website. This platform stimulates exchange and collaboration between academic and industrial partners or other stakeholders including regulators and patient associations. The digital platform is a reserved area for EUROoCS members, and provides detailed information posted by members, including contact information of experts, project descriptions and forum discussions. The aim is to encourage researchers and others to become a member and join the community with view to accelerating implementation of OoC technology.

Regulation, standardization and ethics

For standardization, regulation and ethics a landscape analysis was performed based on scientific and business sources, followed by a SWOT analysis with respect to the development of an innovation roadmap. At present, no OoC systems are used in any regulatory approval path, there are no golden standards defined and the ethics impact of a personal OoC model is still largely unaddressed. Implementation will ultimately require regulatory authorities to state their acceptance of an OoC assay for a particular purpose based on robust evidence of reliability and reproducibility. Several primers and guidelines have been developed addressing this as well as ethical aspects of research, regulatory issues and standardization (22-29). These documents are designed to reach out to policymakers, researchers and the general public and thus align the debate on these topics with the technological advances.

Dissemination and communication

The ORCHID logo, website, brochure and LinkedIn group were created, and ORCHID was presented to the scientific community and companies during conferences and workshops worldwide. This provided considerable visibility for the OoC field. The ORCHID Vision and Strategy workshops delivered two brochures, later turned into citable journal papers (21,22,35,36), on the European OoC roadmap that were disseminated to over 2000 people, mostly researchers, but also many policymakers. Dissemination to the general public was achieved by Twitter or during global events and special meetings with children and high school students, whom ORCHID approached as the next generation of OoC researchers. The final report on dissemination and communication contains the future roadmap for outreach activities, that will be covered by EUROoCS.

Beyond the European roadmap on OoC

During the final ORCHID meeting, the European OoC roadmap was presented to a broad audience of end users, regulators, clinicians, developers, policymakers and patient representatives. There is consensus on the central role that EUROoCS could and should play in the deployment and actualization of each building block. Since qualification and standardization will accelerate OoC technology implementation, activities in this direction will have the highest priority. Among the former are the design and implementation of a European OoC infrastructure with testing, training and data centers, resulting in independently qualified and characterized models, and the development of open technology platforms to enable customized solutions for specific applications. This will guide end users in selecting the technology best suited to their purpose and provide the training needed to create success. EUROoCS will initiate and catalyse these challenging processes.

1. Healthcare challenges from 2020 onwards

Conventional animal models and cell cultures used widely in research are increasingly documented as failing to fully capture human (patho)physiology. As a result, understanding disease mechanisms and predicting responses to medical treatments in humans is falling short of need and expectation. This is a major contributor to late and costly drug failures in clinical trials and is one important reason why drugs in general are expensive and there are no curative treatments for many medical conditions. Aside from having increasingly recognized limited predictivity, animal experiments raise ethical issues, increasing societal and political pressure to reduce their number. This requires new ways to improve drug development and identify effective, personalized treatments. Patient-specific stem cell-based systems are now making inroads in this area but in some cases it is becoming evident that only in combination with Organ-on-Chip (OoC) technology, which can effectively control biophysical conditions in tissues, human (patho)physiology is fully captured. OoCs are thus potential game changers that offer cutting-edge, multidisciplinary solutions contributing to new drugs and affordable healthcare.

1.1 Showcases

Though the OoC field is still in its infancy, there are several examples of OoC models that showcase the potential of the technology and have already provided insights into disease aetiology to identify drug target pathways. These examples include detection of thrombotic risk in Vessels-on-Chip (1), discovery of targets for metastases in Cancer-on-Chip (2), test for kidney toxicity in Kidney-on-Chip (3), drug effects on Neurons and Glia Cells-on-Chip (4), prediction of toxicity of nanoparticles in Lung-on-Chip (5) and drug discovery in a disease model for ALS (6). More recently, a gene therapy approach was tested for the cardiac arrhythmia condition 'Catecholaminergic Polymorphic Ventricular Tachycardia' (CPVT) (7). Inhibition of abnormal calcium waves that cause arrhythmias in patients was observed very rapidly following genetic inhibition of the Ca/calmodulin-dependent kinase II on 'strips' of patient-derived human induced pluripotent stem cell (hiPSC)-derived cardiomyocytes in a Heart-on-Chip model. Similar experiments took 3 months in mice and did not provide evidence that the approach would work in humans where cardiac physiology differs from rodents. The evidence provided by the human Heart-on-Chip data was sufficient for the researchers at Harvard to approach the regulators for permission to use the gene construct in CPVT patients. There is no other therapy for these individuals.

In another recent example (8,9), a common antibiotic was identified that could be 'repurposed' to protect against the development of schizophrenia, in particular in vulnerable families. Here, in a Blood-Brain Barrier (BBB)-on-Chip model under conditions of microfluidic flow which mimicked the neurovascular unit of the brain, it was shown that when microglia in the model were treated with minocycline, a drug for treatment of acne in adolescence, synaptic 'pruning' was inhibited. Abnormal synaptic pruning is characteristic of schizophrenia. Using the electronic data records of more than 20,000 individuals who had received either minocycline or another antibiotic in adolescence, the study was able to demonstrate a clear protective effect from minocycline treatment in relation to schizophrenia onset. It is unlikely this would have been discovered without the BBB-on-Chip model.

The last example concerns unpublished work from the Mummery group (ORCHID coordinator) regarding a disease called hereditary hemorrhagic telangiectasia (HHT). HHT patients have weak blood vessels and suffer from severe hemorrhages particular of the nose which causes extreme anaemia and poor quality of life. Mutant mice with the HHT gene defect only show mild symptoms though and are only suitable for testing drugs when the gene is deleted entirely, not as heterozygotes as in the case of patients (10). The coordinator's lab generated hiPSC from HHT patients but unexpectedly found no phenotype showing defective endothelial cells in 2D models of the vasculature. However, using 3D models of the HHT hiPSC endothelial cells under fluid flow (enabled by AIMBIOTECH chips), features of the disease as observed in patients were clearly evident. These included reduced endothelial cell proliferation and poor interaction of the hiPSC-derived vascular smooth muscle cells with the endothelial cells. This would be sufficient to cause weak vessel walls in patients. Using this model, two candidate drugs for repurposing were identified, and a grant was obtained for a clinical trial (Orlova, Lebrin, Mager and Mummery, unpublished).

These and multiple other examples (11-13) are at the stage of validation/qualification, which in general means that compounds and drugs, already demonstrated as toxic or effective in treating disease in animals or patients, show similar effects in OoC models. A reflective review on OoC technology is presently under review at Nature Reviews Drug Discovery.

One perceived shortcoming of in vitro models, including OoC, is the inability to measure pharmacokinetic/pharmacodynamic (PK/PD) relationships. However, there are multiple examples in the literature (14-18) wherein this was proven possible, and the expectation is that, as the field develops, this will be explored in more depth. Together with training courses and increased commercial availability of standard OoC modalities, these showcases are expected to encourage adoption of OoCs by industry, acceptance by regulatory bodies, and further development as animal alternatives. However, this outcome is still pending growth in confidence on OoC predictivity and utility. The showcases were presented to and discussed in depth with participants at the final ORCHID meeting. All participants agreed they reflected how the field has moved forward from promise towards real examples of utility.

2. ORCHID: organization and aims

Organ-on-Chip In Development (ORCHID; www.h2020-orchid.eu) has been a 2-yr H2020 FET-Open project, that ran from 1 October 2017 to 30 September 2019 and was funded by the European Union's Horizon 2020 Research and Innovation program under grant agreement No. 766884.

2.1 Organization

ORCHID was led by a consortium of seven partner organizations from five European countries: Leiden University Medical Center (coordinator, the Netherlands), Institute for human Organ and Disease Model Technologies (hDMT, the Netherlands), Delft University of Technology (TU Delft, the Netherlands), Commissariat à l'Energie Atomique et aux Energies Alternatives (CEA, France), imec (Belgium), Fraunhofer Institute for Interfacial Engineering and Biotechnology (Fraunhofer IGB, Germany) and University of Zaragoza (Spain). The ORCHID partners sought in a systematic way input and feedback, and received advice, from many international experts over the whole spectrum of (potential) stakeholders who contributed to interviews, questionnaires and workshops. Among them were members of the ORCHID Advisory Board consisting of multidisciplinary world-renowned experts in the OoC field, who attended the ORCHID meetings in person.

2.2 Aims

ORCHID aimed to build an ecosystem of academic, research, industrial and regulatory institutions that will move OoCs from the laboratory into real-life medical care for citizens of Europe and beyond, supported by the creation of a roadmap for OoC such that there is acceptance of the technology by end users and regulators.
The following objectives were defined in the original proposal and addressed:
- Assess the status, needs and challenges of OoC technology in Europe;
- Identify ethical issues, drive standardization and take steps towards regulatory acceptance;
- Analyse the impact of OoC technology on the economy, society, training and education;
- Establish the OoC technology roadmap;
- Raise awareness and build an ecosystem for OoC technology.

3. Organ-on-Chip definition and key features

The experts involved in ORCHID proposed a working definition for OoCs that was later ratified during the ORCHID workshops. According to this definition, an OoC is '*a fit-for-purpose microfluidic device, containing living engineered organ substructures in a controlled microenvironment, that recapitulates one or more aspects of the organ's dynamics, functionality and (patho)physiological response* in vivo *under real-time monitoring'*.

The synergistic convergence of microfabrication technologies and tissue engineering renders OoCs as promising tools for the realistic modelling of human physiology and pathology. The aim of an OoC is not to replicate the whole organ, but rather to mimic a minimal functional (sub)unit of an organ or tissue that can controllably recapitulate relevant aspects of human physiology. For this purpose the main and desired features of an OoC were proposed by the ORCHID consortium as being divided into three categories:

Tissue architecture	Conditions	Functions
Integrated long-term cell culture in defined spatial organization	Controlled microenvironment (topology, biochemistry, physics)	Physio- and pathological relevance
Tissue-tissue interfaces/cell-cell contacts/cellular heterogeneity recapitulating real organ tissue	Controled dynamics (fluid flow, electro-mechanical stimuli)	Recapitulation of organ structure and function
Miniaturization	Continuous automated perfusion	Recapitulation of dynamic mechano-biological properties and stimuli response of organs
	Real-time monitoring of multiple physical, bio- and electro-chemical parameters	
	Automated reproducible multi-sample analysis, comparable or compatible with R&D robotics	
	Large-scale manufacturability	

Table 1: OoCs key features proposed by the ORCHID Consortium

OoCs can be classified into two types with complementary goals and distinct complexity: (i) *single-organ systems*, emulating key functions of single tissues or organs, and (ii) *multi-organ platforms*, combining multiple OoCs to reproduce the systemic interaction and response of several organ models within a single system. Multi-OoCs link individual OoCs through tubing or microfluidic channels, often coated with endothelial cells, or with functional coupling provided by transfer of effluent from one organ's effluent reservoir to another's input reservoir. In either case, the coupling mimics *in vivo* physiological coupling and provides appropriate cell-to-fluid volume ratios and flow distributions to create realistic *in vitro* models of subsystems of the human body. Human(-body)-on-Chip (HoC) systems go beyond this and aim to emulate whole organismal physiology by integrating many relevant single-organ models.

As implied by these definitions, OoC technology is poised at the convergence of advances in tissue engineering, semiconductor and polymer microfabrication with human (stem) cell culture. This highlights the need for multidisciplinary approaches and expertise to implement human OoCs and for facilitating dialogue between academic and industrial developers as well as other stakeholders such as clinicians, patients, regulators and different end users. All of these disciplines were represented in the ORCHID Consortium.

4. European Organ-on-Chip Society (EUROoCS)

ORCHID has laid the foundations of a European ecosystem on OoC technology by bringing together many key European players in the OoC field and strengthening this community by establishing the European Organ-on-Chip Society (EUROoCS) as a sustainable forum for information exchange among experts, development of end user guidelines and the formation of training networks. EUROoCS (www.euroocs.eu) was established as a legal entity with bylaws, management structure and website in 2018. This international independent, not-for-profit organization aims to encourage OoC research and development and to provide opportunities to share and advance knowledge and expertise in the field towards better health for all. Membership is currently open to individual researchers and others with an interest in OoC technology worldwide. The goal is to encourage researchers and others to join the growing community of already more than 200 members with view to accelerating implementation of OoC technology. With the support of EUROoCS, the OoC community will be well positioned to realize fast adoption of the OoC technology.

A digital platform (called 'OoC for all') has been developed within ORCHID that is now integrated into the EUROoCS website. This platform stimulates exchange and collaboration between academic and industrial partners or other stakeholders including regulators and patient associations. The digital platform is a reserved area for EUROoCS members, and provides detailed information posted by members, including contact information of experts, project descriptions and forum discussions. This member-restricted area is expected to be a marketplace for OoC-stakeholders, with individuals from a wide range of backgrounds benefitting from availability of OoC ideas and expertise, initiating specific working groups or discussing updated topics on OoC. Timely and up-to-date information regarding key publications, news, events and discoveries in the field of OoC as well as jobs and funding opportunities for research and innovation are now accessible from the EUROoCS website. Via the website and its activities, EUROoCS will contribute to the fundamental objectives of EU policies, including strengthening research, technological development and innovation, and well-being of the citizens.

5. Development of the European OoC Roadmap

ORCHID has provided insight into the state-of-the-art, needs and challenges of the OoC technology, which formed the basis for the development of the European OoC roadmap. During the ORCHID project, two workshops were held in which experts from academia, the pharmaceutical and cosmetic industries, patient organizations, ethics panels, biotech companies and regulatory agencies took part. Based on bibliographical, bibliometric and market analyses, expert interviews, and panel discussions with 31 experts (see Acknowledgements) during the ORCHID Vision workshop held in Stuttgart (Germany) on 23 May 2018, the current unmet needs (including evidence of added value, methods for automation and robustness), key challenges (structural materials, cell sourcing and culture media, long-term cell viability, real-time characterization, increasing complexity, qualification), barriers and perspectives (industrial acceptance, appropriate and timely dialogue among players) of the OoC technology, as well as recommendations were identified as the basis for developing an OoC roadmap (21,35).

During the ORCHID Strategy workshop held in Leiden on 17 January 2019, 32 experts (see Acknowledgements) sketched the landscape for future development of the OoC technology by defining concrete goals, milestones and recommendations that would form the roadmap strategy for moving forward. Specific issues from four application domains, including personalized medicine, drug efficacy, drug toxicity and disease mechanisms, were addressed from the perspective of both developers and end users/regulators. Six specific building blocks for the roadmap were defined, including priorities, methods and targets for each block: 1) application, 2) specification, 3) qualification, 4) standardization, 5) production and upscaling, and 6) adoption (Fig. 1). Potential ethical issues were also considered, as well as training of the next generation OoC researchers and dissemination and communication of the technology (22,36). EUROoCS is expected to play a role in the deployment and actualization of each building block and as initiator and catalyst for the dialogue between developers, end users and regulators during roadmap implementation. Since qualification, standardization, and production and upscaling will accelerate OoC technology implementation, activities in this direction will have the highest priority and have already been started. For this reason, these building blocks are discussed in more detail on page 16.

European Organ-on-Chip Roadmap

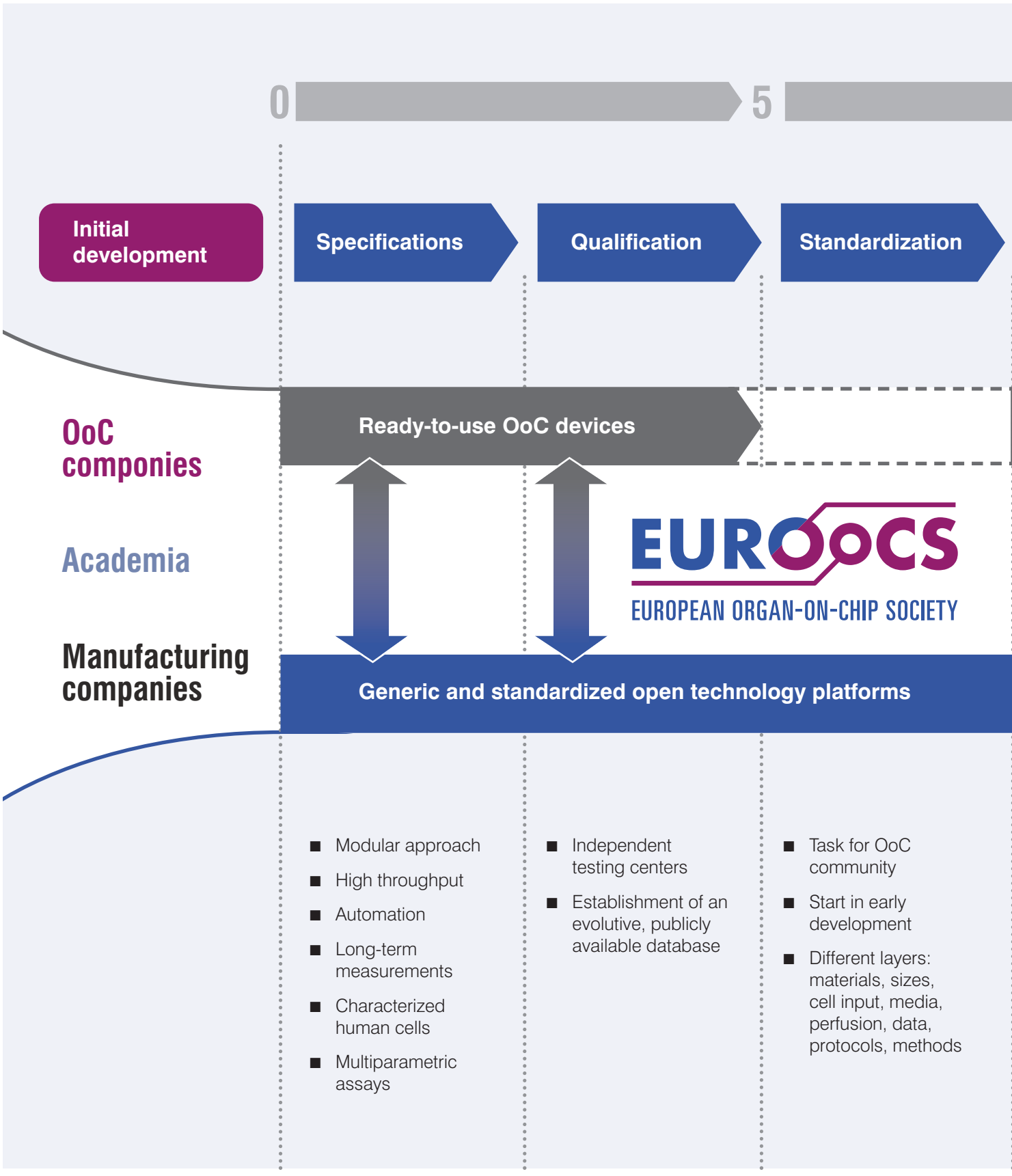
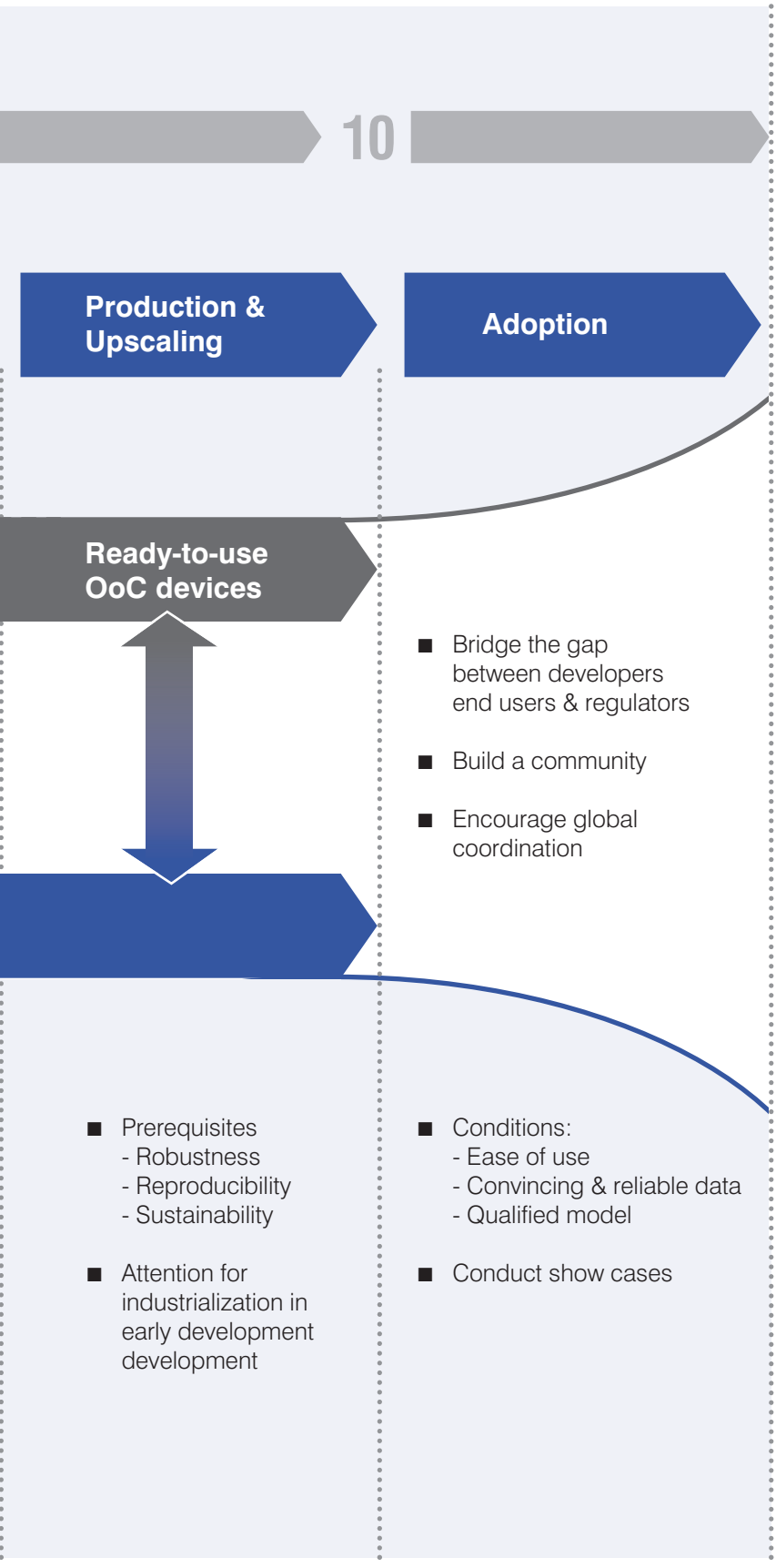


Figure 1: Overview of the ORCHID roadmap for OoC development



PHARMA

FOOD

COSMETICS

ENVIRONMENT

CLINIC

ACADEMIA

5.1 Qualification and standardization

Among the first activities for qualification and standardization of OoCs are 1) the design and implementation of a European OoC infrastructure with testing, training and data centers, resulting in independently qualified and characterized models, and 2) the development of open technology platforms to enable customized solutions for specific applications. This will guide end users in selecting the technology best suited to their purpose and provide the training needed to create success. EUROoCS will initiate and catalyse these challenging processes.

5.1.1 Qualification

- Independent testing centers.

The ORCHID Vision workshop highlighted the urgent need to focus on the qualification or characterization of the OoCs rather than on the validation *per se* if the technology is to be widely accepted and used. The ORCHID Strategy workshop confirmed that while regulatory acceptance is beneficial for the commercialization of OoC devices, this acceptance should not hinder the development process. Indeed, regulatory agencies should be considered as key players involved in the early stages of OoC development, along with end users, in order to better understand the potential of the technology and its applications. Industry needs confidence in the robustness of the data retrieved through the devices, whereas regulators typically require a case-by-case analysis. Therefore, while considered necessary, the qualification of a device does not necessarily prelude to its regulatory acceptance nor to user adoption.

For drug screening and development, the characterization and qualification of such devices should be based on a generic study design including the following key aspects:

i. Defining the context of use and its associated outcomes, to select the most relevant OoC model;

ii. Challenging OoC systems with reference compounds insofar as they are classified regarding context of use and specific parameters.

iii. Implementing quality control assays ensuring the functional characterization of cell cultures, material qualification (drug-biomaterial interaction), manufacturability and availability of devices.

iv. Evaluating effectiveness of OoC compared to current *in vivo* profiles.

v. Performing intra- and inter-laboratory assays to assess the reproducibility and accuracy of OoC devices as well as monitoring technological performances (stability and robustness).

These last aspects should be considered as iterative approaches, supported by ongoing pharmaceutical projects to bring added value, aiming at investigating the correlation between OoCs and *in vivo* data, if relevant, and to make the critical link with the clinical expectations. Ideally, all qualification studies should be performed by a third party, as proposed by the testing center initiatives in the US funded by NCATS, to ensure an independent analytical characterization.

As a direct result of ORCHID, a design for a multi-center European OoC Infrastructure is currently being developed, which has the support of agencies like EURL ECVAM (EU Reference Laboratory for alternatives to animal testing). This is intended to meet the need of independent testing and qualification, and training of the next generation researchers. EUROoCS, pharma and regulatory bodies are playing a crucial role in this infrastructure which will be aligned with other large European Research Infrastructures

- Centralised database.

To achieve optimal results from the qualification studies, a key challenge is establishing an evolving database clustering all available data on a reference set of the most appropriate compounds and biomarkers, together with the results on the performance and accuracy of the specific OoC systems under test and the context of use for the target tissue(s). The aim of this centralized and publicly accessible database would be to provide the scientific community with in-depth information (including raw data and negative results) on well-characterized pharmacological and toxic compounds to demonstrate *in vivo*-like responses in OoC devices and to go beyond a simple and linear annotation of the compounds' effects. Providing relative data from reference compounds/biomarkers and allowing the community to use it wisely (including stakeholders and regulators) may help both developers and end users to challenge OoC systems and may influence the decision-making process. The coordinator's team have recently published this type of list to qualify models claiming to predict cardiac safety (20): not only are these compounds diagnostic for the system under test (in this case hiPSC-derived cardiomyocytes), but the document also indicates how they act to cause cardiotoxicity. Industrial participants in the ORCHID expert meeting indicated that similar lists were already in preparation for kidney, liver, skin and lung (see below).

Beyond having a list of compounds upon whose outcome and mechanisms of action there is agreement, the compounds may not necessarily be available to academic research groups since they are proprietary or may no longer be synthesized. A solution would be to work closely with structures like the IQ Consortium (https://iqconsortium.org), a not-for-profit organization of pharmaceutical and biotechnology companies, which is compiling a list of reference compounds that might be shared for qualification purposes.

EUROoCs may play a catalyzing role in collecting the information with the necessary infrastructure, data management and statistical capabilities to ensure an extended dissemination among the OoC community and beyond. Vice versa, this publicly accessible database could also be a promising tool to promote OoCs' adoption supported by early engagement of academic, industrial and regulatory players. Finally, the coordination of a EUROoCS-supported database with other international existing ones should reinforce multi-partner task forces and contribute to international harmonization.

5.1.2 Standardization

- International harmonization.

Standardization is an overused concept with multiple interpretations across different sectors and markets. Standardization of OoCs is very challenging since OoCs are inherently developed through interdisciplinary interactions. In recent history, technological standards have usually arisen either from dominant commercial players or from collective entities such as regulatory authorities or roadmaps jointly established among field competitors. However, standardization emerging from a collective dialogue among developers and end users and from ensuing cross-constraints is ultimately expected to prevail. Alongside flexible ready-to-use devices, a modular approach to OoCs based on customizable platforms was recommended within ORCHID as a solution to enable both user-defined and specific fit-for-purpose applications and at the same time align or facilitate qualification, standardization and large-scale production of OoCs. Successful examples of standardizations in electronics (*e.g.,* data communication protocols, interfaces, and peripheral cross-compatibility) can be capitalized as important learning experiences. In particular, lack of standardization for lab-on-chip approaches may be responsible for the problems it currently encounters in getting into the market.

To avoid this risk, OoC standardization should also be addressed very early in development to enhance the prospect of being competitive with alternatives. On the other hand, standardization cannot be promoted by most of the current stakeholders, as these are mostly small (biotech or start-up) companies without sufficient financial resources to support a standardization strategy. OoC standardization is therefore considered a task for the OoC community. The role of the community is in fact central, because the purpose of standards lies foremostly in enabling the OoC community itself to work together towards developing prototypes. Community-driven standardization may also ensure that standardization addresses sufficiently common issues, benefitting a set of users and thus becoming a means to accelerate innovation. EUROoCS can play an important role in bringing developers, stakeholders, regulators and end users together into a community, as well as in serving as a collective expert group to advise on OoC standards, protocols, methods and guidelines, similarly to prior experiences in *e.g.,* stem cell research and toxicology, whereby protocols were defined by panels of experts.

- Different standardization layers.

Layers of standardization can be envisioned, ranging across multiple levels of abstraction and user experience. They include: materials, dimensions, cell input and content, perfusion media, flow rates, interconnections and interfaces, optical access, platforms, cross-compatibility among modules, back-compatibility with existing substrate standards (*e.g.,* multi-well plates, microscope slides, multi-electrode arrays) and laboratory instrumentation, cell sources and lines, cell phenotypic and genotypic characterization and protocols for cell differentiation, cell handling, use of devices and quality control. Additional layers should be further considered. Standards for commercialization could eventually emerge from research prototypes, though this should not be the primary aim of the community. Commercial standardization should be internationally harmonized, avoiding competing groups particularly between US and Europe.

- Open technology platforms.

One way that experts recommended to encourage the OoC community to converge towards standardization was the realization of open technology platforms in addition to the existing. These can be seen as shared technology platforms to gather knowledge and expertise into a centralized database, in which potential users could contribute by developing and sharing building blocks of modular systems to enable customized solutions for specific applications. The open technology platform concept is in line with the modular approach suggested for the development of OoCs. It will stimulate further innovation, rather than restrain it. These platforms would reduce barriers to expensive manufacturing of devices, because they could generate the production volumes needed for sustained technology development.

A recent initiative in this direction is the Translational Organ-on-Chip Platform (TOP; https://top.hdmt.technology), a platform providing infrastructure for automated microfluidic chip control and open for both academic and commercial chip developers. The freedom to develop demonstrators in parallel may moreover lead to quick learning cycles and broad uptake of the successful innovations in the community. However, the implementation of an open technology platform rises crucial questions concerning the co-existence of, on the one hand, open interfaces, open standards, and the freedom to exploit together open source content with, on the other, patenting and licensing of intellectual property as sources of commercial drive and market penetration. These and similar issues related to the co-existence of private profit and public availability are well-known from prior standardization attempts in other fields, and they represent evidently an important aspect of the proposed roadmap that needs to be resolved.

5.2 Production and upscaling

5.2.1 Early choices for industrialization

OoC production perspectives will be determined by the type and scale of use of OoCs – whether for *e.g.,* drug screening or replacement of animal tests or personalized medicine – such that a 96-well plate format or similar may need to be developed for applications requiring high throughput, whereas in other cases a 2-well plate or single-chip format may be sufficient. Clear and standard guidelines for quality control of technology and biology should be introduced in all cases to get and maintain robustness. The type of use will also determine the allocation of resources. In this respect, drug development prioritizes rate of success and time-to-market, and hence time saving rather than cost saving.

It is important to remark that upscaling of OoCs inherently involves both technological and biological components. This respectively implies mass production of chips or microfluidic devices and generation of large batches of differentiated cells that are quality controlled prior to use in OoCs. As demonstrated by the success of microelectronics, high-volume production of chips typically coincides with decreased manufacturing costs and variability and leads to highly reproducible devices. On the other hand, setting up mass production of devices requires large investments which are not likely for non-qualified devices. Solving this issue might require specific, public-private funding calls.

5.2.2 Upscaling strategies

Depending on applications, at least three different upscaling strategies could be envisioned:

1. *Drug efficacy and toxicity* in pharmaceutical industry. In this case the SBS well-plate format will likely be the preferred and target format, with highly characterized, robust and reproducible OoC enabling relative comparison of hundreds of drugs;
2. *Personalized medicine*, possibly in a hospital setting or dedicated SMEs. This will entail robust and reproducible OoCs with (patient-derived or genetically modified disease bearing) cells, and upscaling to test tens (*i.e.*, 10 to 50) of potential drugs and find the right concentration of the right drug for specific patients or disease states;
3. In the longer term, *clinical trials*. To date, there are no clinical trials on *e.g.,* children, pregnant women, or on specific or unique ethnic groups. OoC could enable better representation of human phenotypic diversity in clinical trials.

An industrial-level fabrication volume puts manufacturing constraints on the design, dimension and structural materials of the devices. These choices should be considered as early as possible in device development along with back-compatibility with established laboratory tools and cross-compatibility among platforms. At the same time, the use of standard cell lines might not match such extended device request, though standard cell handling protocols could still be helpful, and banks hosting cells for different population subgroups might need to be established.

6. Guidance for regulation, standardization and ethics

For regulation, standardization and ethics a landscape analysis was performed based on scientific and business sources, followed by a SWOT analysis with respect to the development of an innovation roadmap (23). At present, no OoC systems are used in any regulatory approval path, there are no golden standards defined and the ethical impact of a personal OoC model is still largely unaddressed. Implementation will ultimately require regulatory authorities to state their acceptance of an OoC assay for a particular purpose based on robust evidence of reliability and reproducibility. Several primers and guidelines have been developed to address these topics as well as ethical aspects of research and regulatory issues designed to reach out to policymakers, researchers and the general public, thus aligning the debate on these topics with the technological advances (23-29). In addition, the ORCHID partners published a whitepaper on standardization (22).

6.1 Regulation

OoC represents potential solutions for strongly regulated application fields involving development of pharmaceuticals, advanced medical products, diagnostics and therapies. A regulatory framework that would make this possible has not yet been established and requires defining common ground, understanding and methodologies on how to implement OoC and products and safeguard outcomes based on their use. Differences in regulatory processes in an international context were considered in ORCHID. An outlook on how this challenge can be taken up in a collaborative way was developed within ORCHID for this reason (24). For OoC devices to be integrated into regulatory pathways, the R&D OoC community needs to organize itself and seek guidance from all stakeholders involved. Qualification of OoC devices needs to be performed in the context of use, and in the presence of industry and regulatory bodies. Regulatory acceptance pathways of related technologies or example programs such as reproductive toxicity can be used as a guideline for OoCs. Finally, ORCHID advised that EUROoCS plays a major role as mediator and promoter to drive this technology forward in the future.

Applications of OoC technology for drug discovery were unanimously identified as a figurehead market, having the largest potential to be the first application with impact on industry and society. The opportunities for OoC systems in drug discovery, today and in the future, were discussed extensively within ORCHID, both at stakeholder and partner meetings (25). Steps proposed were those that could be immediately applied to current R&D. It was advised that first OoC focus could be replacement and/or refinement of drug safety assessments. First steps would need to address on further qualification and engagement with regulators to create common ground and understanding on the value of OoC technology, thus paving the way to inclusion in the pathway to regulatory approval. In addition, a view was given on how EUROoCS can play a role in facilitating adoption of OoC in drug discovery, and what the expected impact in the future can be.

6.2 Standard Benchmarking

OoC system standardization can build further on existing standards or standardization efforts for its subcomponents and sub-processes (see earlier). Although there are no golden standards defined so far, keeping in mind previous standards and guidelines and stimulating close collaboration between relevant stakeholders will determine successful introduction of OoC's in drug development pipelines. Standardization has helped many technology-driven industries in scaling up output, increasing impact while closely monitoring costs. OoC draws heavily on a set of underlying technologies, both established as well as emerging. Standardization is a method to provide guidance in a particular industry. It has a persistent and often ambiguous influence on innovation. Standardization efforts are very different for industries in different stages of development. The OoC community can find a basis for standardization in standards already developed in areas of individual components such as sensors, microfluidics and cell cultures. The specific needs for OoC and ways on how to benefit from established standardization approaches present in related technology industries have been described in the whitepaper on standardization, added as Appendix in the paper of the building blocks of the OoC roadmap (22). This whitepaper introduces a view on the theoretical framework of the standardization process, its functionality, and a current and future view of standardization efforts related or of importance to the OoC field.

6.3 Ethics

An ethics expert joined the ORCHID Strategy worskhop and provided a vision of how OoCs were viewed from that perspective. The ethical discourse on OoC development and applications, even using human stem cells, has been largely favourable, indicating OoC as a possible solution reducing cost, need, and ethical burden of animal studies, both for drug discovery and even more for toxicology studies. OoC as a broad platform technology has the benefit of being able to adapt to evolutions in biological science, *e.g.,* the replacement of controversial human embryonal cells by hiPSC, which largely silenced the ethical debate, provided supported by proper informed consent of tissue donors for hiPSC generation. OoC has also the potential to allow drug discovery and personalized treatment for small- or differentiated target groups (rare diseases, children, pregnant women, gender specific, ethnic specific). However, this also poses the question of who indicates priorities. Citizen/patient donors may expect a personal benefit of donation rather than a societal impact. There is an underlying risk that media interest and coverage on new evolutions in OoC may overpromise, possibly resulting in a hype cycle. A second risk is to underestimate aspects of informed consent, data ownership, and privacy concerns when using human-donated cell or tissue samples in combination with OoC trials. The ethics impact of a 'personal OoC model' as part of a personal avatar model, partly in silico and partly on chip, and related aspects of data ownership and privacy are still largely unaddressed.

Within ORCHID, a concise primer has been prepared (26) for separate, public distribution, addressing the fact that OoC technologies need to be discussed with non-specialists. It aims at enabling transparent communication with the general public, particularly taking into account ethical concerns. Appropriate engagement with the general public on the use and potential impact of OoC technologies is important. Timing for communication with the general public appears appropriate with the exponential increase of activities and scientific media attention on the use of OoC technology. The primer contains the appropriate terminology and scope to open the communication with the general public.

The research community needs to deal with a variety of stakeholders. This requires mutual understanding of opportunities and concerns whilst addressing them with proper communication. The research community itself is fairly interdisciplinary and hence diverse, ranging from clinics and biotech, technology labs to instrumentation builders (often SMEs) and big pharma or biotech companies. A guide for the research community (27) was developed for that purpose. Dialogue on ethical implications between the research community, driving the technology and applications roadmap and the ecosystem, and stakeholders must be targeted to specific expectations, opportunities and risks for the different stakeholders. It must be timely and should be aligned with expected evolution of the roadmap.

6.4 Decision-making

Policy makers need to embrace OoC technology but will need to understand the complex set of implications, in particular what is needed to facilitate or accelerate aspects such as regulation and standardization and to properly judge ethical concerns and societal benefits. A translational step from the more technical findings is needed to reflect this in policy choices. The outcome of a study in ORCHID describes several scenarios and policy choices, adds criteria and prepares a common ground for decision-making for policy makers and societal stakeholders (28). The roadmap for OoC technology presents both opportunities and challenges. The policy 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.

Similarly, the research and industry community face a problem of integrating non-technical aspects with the progress on OoC technology. The ORCHID roadmap gives an overall frame and trades off technical feasibility with time, placing figurehead market options first and putting out complex applications further into the future. During execution, industry and researchers usually feel at ease with technological decision-making but less comfortable with properly integrating ethical discourse, stakeholder communication, regulation and standardization, which require dealing with a more diverse audience. A primer has been provided on how to judge such aspects of desirability, safety and efficiency which are key when actual product definition is considered (29). It describes the process of decision-making along the research & innovation roadmap from science over technology to product needs reflecting the wish of end users and societal stakeholders to obtain a desirable, safe and efficient product in their hands.

Offering an expectedly ‘better’ technological solution only is not sufficient to gain impact in the complex application field that OoC technology can target. Instead, OoC technology will become adopted and gain impact only when it will enable solutions that are judged desirable, safe and efficient – three properties that draw on a matrix of ethical and regulatory oversight and standardization aspects put on top of the proposed technological solution. The primer advises the research & innovation community on how to embed these three adoption criteria in the technology and product development process and into the decision-making. The example case of OoC for drug discovery is addressed in detail as a case study for illustration purposes.

7. Impact, business models and training needs

Healthcare systems are faced with the challenge of providing innovative treatments, while shouldering high drug costs that pharmaceutical companies justify by the high costs of R&D. OoC as emergent technology could transform R&D efficiency. The technology bridges the gap between preclinical testing and human trials through better predictive models, significantly impacting R&D costs. Within ORCHID, an expert survey on the future role of OoC in drug discovery and its potential quantitative impact was conducted. It was shown that the technology has the potential to reduce R&D costs significantly, driven by changes in direct costs, success rates and the length of the R&D process.

In addition, the current and future business models and their strengths and weaknesses were identified. Additional customer market segments, including the veterinary industry, military, and chemical industry, allow the development of new business cases and models for OoC technology, thus extending the impact of the technology beyond the scope of drug discovery and development.

Also, the training needs for promoting the development, utility, adoption and qualification of OoC systems have been identified using an online stakeholder questionnaire. The main target populations in need of training are technicians and end users in both industry and academia, and early career researchers, including those in applied science studies.

7.1 Economic and societal impact

For the analysis of the economic and societal impact of OoC, a scenario-based budget impact analysis was conducted over a period of five years (30). Relative change in costs was assessed through a survey based on an R&D productivity framework that considered each phase of the drug development process and the corresponding main cost drivers. Relative efficiency change was derived by means of expert elicitation, modelling a probability distribution around likely cost estimates. 17 interviews with experts in the OoC and R&D fields were conducted. Overall, experts expect a significant reduction in the total R&D costs, reaching up to 26% reduction in costs. While all cost drivers were impacted, savings were mostly achieved by improving the success rates. The R&D phases in which experts expected the most benefits were the lead optimization and preclinical phases. From this study, the technological readiness of the R&D environment and acceptance from the regulatory agencies were mentioned as the main barriers for actual implementation.

7.2 Current and future potential business models

Based on stakeholder consultations within ORCHID, an overview of examples of commercial OoC providers was generated that are currently active in the market and their respective business models were categorized (31). The different business models that these commercial providers employ may be placed into four distinct categories:

a. **Chip Sales,** with or without training
b. **Chip & Instrument Sales:** Chip sales with companion instrument(s) needed to operate chips, with or without training, custom model development

c. **Contract Research Services:** Performing experiments with chips/instruments from in-house manufacturing or other commercial OoC providers
d. **Hybrid:** Various combinations of the abovementioned business models (a-c)

The discussions with the stakeholders identified various strengths and weaknesses of the different business models, which are obviously depending on the respective individual strategy and goals of each company. The various stakeholders differ in their specific interests in the OoC field, their impact on the field, and their responsiveness to other stakeholders. Yet, the interactions between the different players within a particular customer's company may as well determine whether a new technology is adopted or not.

Individual roles within a customer business can be categorized as follows:

- Initiators: Suggesting the purchase of a product or service;
- Deciders: Choosing the product among all available options;
- Financers: Providing funding/budget for the purchase;
- Gatekeepers: Controlling the flow of information to and among the other stakeholders in the customer's business;
- Influencers: Helping develop specifications that a new technology has to fulfill and evaluate alternative products;
- Buyers: Selecting suppliers and negotiate the terms of purchase;
- Users: Using the product and evaluating performance;

When one applies these categories to the current OoC market, and considers pharmaceutical companies as the main customers, it becomes evident that researchers in the R&D department(s) of pharmaceutical companies have the biggest influence on the adoption and implementation of new technologies.

A number of examples for new potential customer segments were identified (31) in which the implementation of OoC technology is feasible and which might provide additional markets:

In-vitro diagnostics (IVD)

- OoC as 'humanized' version of current IVDs, *e.g.,* to evaluate the best treatment regime for specific cancers, thus enabling more personalized health care;
- OoCs as companion diagnostics;

Food industry

- Testing foods/food ingredients regarding their allergenic potential;
- Personalized model systems towards personalized food;
- Assessing the health of the animal life stock for food production, *e.g.,* use of antibiotics;

Cosmetic industry

- Testing of cosmetic products/substances without animals due to new laws, *e.g.,* the ban of cosmetic products tested on animals throughout the EU;

Chemical industry

- Testing of chemicals to assess their hazardous potential (*e.g.,* toxicity, irritation);
- Testing negative effects of the ingestion of residues of chemicals used in food production (*e.g.,* pesticides);

Veterinary industry

- Pets are increasingly being 'humanized', leading pet owners to increase their spending on pet medications and medical treatments. This market is enormous as the number of pet owners is steadily increasing worldwide (US: 55.3 million dogs, China: 27.4 million dogs) (32). Race animals (horses, camels) provide very high value and are subject to even more expensive treatments.

Military

- OoC systems for the assessment of threats related to nuclear, biological or chemical weapons, or warfare;

Government agencies

- Safety assessment of food/food ingredients, environmental compounds (*e.g.,* pseudo-hormones in water, microplastics), chemicals, and other goods;

The identification of such novel, additional customer market segments, allows the development of new business cases and models for OoC technology, thus extending the impact of OoC technology beyond the scope of drug discovery & development.

7.3 Training needs

OoC applications in basic research, pharmaceutical drug development, safety assessment of drugs, cosmetics and chemicals among others is facing an exponential rise in interest. Therefore, specific training is required on the production of such cell culture systems using advanced microfabrication techniques and adequate on-chip characterization of relevant cell functions. Within ORCHID a questionnaire has been developed (33) to gain insight into the training needs of the OoC community to promote the OoC systems qualification, usability, uptake and long-term development in a variety of fields.

This survey was directed to those who were considered to be the current and future strategic stakeholders in the advancement and use of OoCs. On the one hand, scientists and technicians should be prepared for new types of employment that will arise while, on the other hand, industry and academia should be provided with professionals able to keep up with innovation in the field. The answers to the survey contribute to designing appropriate training programs to fulfil the needs of this emerging field.

The survey aimed at evaluating the key aspects for the future of the OoC field, at identifying who to train and in which skill set, career moment as well as knowledge areas. The data showed that there is a need (i) to increase end-users familiarity with the chip development and production; (ii) to focus on technicians and end-users in both industry and academia with special emphasis on quality assurance and qualification of the models; (iii) to train early career researchers early and include OoC in applied sciences studies such as bioengineering and pharmacology/toxicology (34). This will foster education in Europe in this technology, and result in well-qualified and competent researchers and engineers, who will continue exploring OoC applications.

In summary, the development and utilization of OoC technology requires experts with a broad and interdisciplinary skillset at several levels. The identified target groups and training needs are described below:

- Technicians and end-users in both industry and academia are the main target populations in need of both practical and theoretical training covering mainly:
  - (i) *Cell culture and stem cell technology*;
  - (ii) *Monitoring and analyzing (sensors, imaging)*;
  - (iii) *Quality assurance*.
- The key aspects for the development of the field and, hence, with the largest need for specific training are:
  - (i) *The definition of specific cell culture standards – function and origin of cells*;
  - (ii) *Usability*;
  - (iii) *Qualification of the models*.
- Early career researchers should be trained at all levels of studies with particular focus on Master's and Doctorate's Studies.
- OoC specific training should be included in the curriculum of programs within applied sciences, i.e., b*ioengineering and pharmacology/toxicology*.

Additional experiences gained from a Marie-Curie Innovative Training Network on OoC (EUROoC) that started in December 2018 and is currently training 15 PhD students will be used as further input for future refinement of a training strategy in the OoC field.

8. Dissemination and communication

For dissemination of the ORCHID results the ORCHID logo, website, brochure and LinkedIn group were created, and ORCHID was presented to the scientific community and companies during conferences and workshops worldwide. This provided considerable visibility for the OoC field. The ORCHID Vision and Strategy workshops delivered two brochures on the European OoC roadmap (35,36) that were disseminated to over 2000 people, mostly researchers. The brochures were launched at the International Organ-on-Chip symposium 2018 (IOOCS18) in Eindhoven (the Netherlands) and the EUROoCS 2019 conference in Graz (Austria), respectively. The latter conference attracted many new EUROoCS members, and this is expected to continue in the 2020 conference in Uppsala (Sweden). These conferences provided many opportunities for scientific discussion and interaction and brought together young scientists with top experts in the field. Also worth mentioning is the joint OoC symposium of EUROoCS and the European Society for Artificial Organs (ESAO; Hannover, 2018) that was organized to explore how these societies can benefit from each other's expertise and networks. Dissemination to the general public was achieved by Twitter or during global events and special meetings with children and high school students, who were approached as the next generation of OoC researchers. The Netherlands public television network produced a documentary intended for children on OoC technology in the context of a popular news programme (Klokhuis; https://www.hetklokhuis.nl/tv-uitzending/4243/Mini-organen) in which the ORCHID coordinator and her department's members took part. This has been widely used in patient outreach and clinician postgraduate education programmes to convey what the technology is and can mean in the future. The final report on dissemination and communication (37) contains the future roadmap for outreach activities, which will be covered by EUROoCS.

9. Beyond ORCHID: recommendations from the field

During the final ORCHID meeting in Leiden (the Netherlands) on 23 September 2019, the European OoC roadmap and the other deliverables and milestones of ORCHID were presented to a broad audience of end users, regulators, clinicians, developers, policymakers and patient representatives (38). It is noteworthy to mention the major impact of the ORCHID project on the OoC community, not only in Europe but worldwide. To illustrate this, quotes from participants of the ORCHID final meeting are cited below, indicating that the ORCHID project has significantly contributed to the advance of the OoC field. ORCHID defined an OoC roadmap, stating which steps would be needed to transform developing technology into routine laboratory procedure in disease modelling, drug discovery and beyond, and built a multi-stakeholder OoC community, which has been formalized in a growing and ambitious society (EUROoCS) and that places Europe in a leading position in OoC technology. This is the first sustainable (not finance driven) infrastructure for OoCs established to date. In addition to the role of EUROoCS in the implementation of the specific building blocks of the roadmap, the ORCHID expert community unanimously perceived EUROoCS as a means to build a network, develop training and education programs, engage in a dialogue on ethical aspects, create awareness, realize integrative programs and collaborative projects or consortia, and find new academic/industrial partners or individuals involved in regulation, and patient associations.

Leading scientists of EUROoCS have joined forces in an attempt to create a novel experimental Open Access journal format (according to Plan S) that combines – for the first time – publishing and funding in one format. In this way the group of scientists hopes to be able to attract potential high impact manuscripts while facilitating and simplifying fund raising. The success of the new format will depend on sponsoring of the funding by research organizations, and on a high profile editorial board. Ongoing discussions are encouraging. The journal format is planned to be administered by a scientist driven non-profit foundation that is responsible for sponsor interface, technology and contingency, while the thematic Open Access journals are planned to be driven by scientific or editorial societies. The specialized journal on Microphysiological Systems/Organs-on-Chip could become the official journal of EUROoCS.

9.1 Recommendations

The ORCHID final meeting elicited the following recommendations for EUROoCS to foster further progress in the rapidly establishing OoC field:

Multidisciplinary community

1. With the support of the ORCHID stakeholders, involve investors, big pharma (including incubators such as J&J's Jlabs and GSK's Catalyst), Technical Transfer Offices (TTOs) and OoC device manufacturers for industrialization of OoCs and to bridge the 'valley of death' between academia (producing prototypes) and the end users (needing ready to use products with standard protocols for implementation). Use the pharmaceutical representatives in the ORCHID Advisory Board, and EFPIA as the board members of EUROoCS to connect to big pharma.
2. Consider the establishment of an overarching International Organ-on-Chip Society with different, more regionally focused divisions, such as EUROoCS, US OoC Society, Japanese and Chinese

OoC Society. Organize every two years a joint world conference on OoC in addition to separate annual conferences of the member Societies in order to keep up with world-wide new developments, but at the same time also enable young scientists to attend the latter smaller and less costly meetings to exchange results and ideas and find new collaborators.

Communication and dissemination

3. With the support of the ORCHID stakeholders, use conferences of societies, such as *e.g.,* the Society of Toxicology, and the Lush Prize Conference, but also the cosmetics industry, MedTech Europe and the 3R Centers (*e.g.,* Sweden, Norway, UK, the Netherlands, Switzerland and Italy) and their stakeholders to disseminate OoC technology. Several of these centers have scopes beyond OoC and might offer EUROoCS an 'agnostic' platform for discussion of *e.g.,* best practices, cell type, OoC manufacturing and sources. In addition, disseminate scientifically realistic, evidence-based and credible information about ORCHID and OoC in general via You-Tube or TV channels (BBC interview).
4. Translate the technical definition of OoC for the general public, doctors and patients. Communicate in a realistic way and manage expectations.
5. Consider informing high school children about OoC to make them aware of the technology and encourage STEM education choices among the younger generation to ensure future sustainability within Europe (*e.g.,* in the Nordic OoC network and UK OoC network).

Technological development

6. Rank the qualitative contribution of current OoC models into 'highly likely' (heart, kidney, lung), 'unlikely' (reproductive system) and 'in between' (brain) as a guide to communicate the state-of-the-art of the OoC technology.
7. Understand when complexity is needed in the OoC models, in particular regarding interaction of different cells and the dialogue between organs, the interface between kinetics and dynamics enabling compensation mechanisms and feedback loops for ADME studies, and for which application a simple system is sufficient, *e.g., a* minimal model with the correct readout for a specific purpose.
8. Initiate dialogue with pharma companies on the potential efficacy testing benefit of not only competitive but also precompetitive models (as is the case in the safety area) enabling validation of the models in cross-company consortia by sharing reference compounds and clinical data on a non-exclusive basis.
9. Clearly define (long- and short-term) goals and the right stakeholders.
10. Utilize the available lists of diagnostic reference compounds, including those negative controls, with known effects in patients and animal models to test in OoC models for heart (LUMC), reproductive organs (EMA), and kidney, liver, skin, lung and heart (IQ Consortium).

Applications

11. Come up with clear consensus statements about the role of OoC in replacement of animal experiments for the coming 20 years and place it on the EUROoCS website.

Regulation

12. Promote better dialogue between developers and companies that answer regulatory questions and improve interaction with the regulators.

Qualification

13. Make use of the qualification procedures and guidelines of the EMA for the definition of qualification criteria for a specific context of use of the OoC models. Select 'early success options' (heart, lung) and initiate open dialogue with the regulators, based on data of the models.

Standardization

14. Define the vocabulary (glossary) for standardization, consider existing standards and determine which route to follow for OoC.
15. Make use of the Guidance on Good In Vitro Method Practices (GIVIMP) of OECD with help of EURL-ECVAM as a step towards standardization and validation of OoC models.

9.2 Quotes from attendees

Patrick Boisseau Director, EU Research & Innovation Partnership Policies, MedTech Europe
'ORCHID delivered an outstanding roadmap for the development of Organ-on-Chip technologies. In order to do so, ORCHID consortium has created a multi stakeholder community, that will last as EUROoCS. ORCHID consortium has delivered fantastic achievements with a very professional quality. ORCHID will definitely become the milestone on the Organ-on-Chip development'

Andreas Lymberis, European Commission, DG Connect
I participated in the ORCHID final meeting and I'm grateful to the organisers. The area is exploding in terms of technology, publications, IPs, collaborations and there are high expectations for medicine and well-being. This puts Europe in a challenging and promising position to compete world-wide. ORCHID succeeded to bring together all key aspects of OoC, from technology to systems, applications, markets, barriers & perspectives and major European players, establishing the foundations of a European ecosystem.
An ambitious European society has been created as a result, aiming to facilitate the implementation of OoC priorities *e.g.,* application, specification, qualification, production and adoption as well as ethical, training and standardization aspects. The whole initiative is a leading example of European knowhow and mobilisation to organise and drive an emerging field.

Lissa Boxy and Stefan Ellenbroek, senior accountmanagers Innovation Quarter, Leiden
'Innovation Quarter recognizes Organ-on-Chip technology as one of the key technologies that enable the development of true ATMP's, most of which will be personalized medicines. In order to truly understand the mechanisms behind health or disease, Organ-on-Chip technology is a very useful tool. Furthermore, as a platform to develop (personalized) diagnostics and therapies, InnovationQuarter believes Organ-on-Chip technology is both ethically and scientifically to be preferred above animal testing'

Rosário Zincke, Alzheimer Portugal
On behalf of Alzheimer Portugal I had the opportunity of attending the ORCHID final workshop. As a patient representative it was very rewarding getting in touch with the work that has been done on the emerging and promising Organ-on-Chip technology.
Involving patients and knowing their perspectives is really crucial to assure that the research meets the real-world needs. Now that ORCHID project came to an end, I am looking forward to know about any further development on this issue from the European Organ-on-Chip Society.

Sandra Coecke @SandraCoecke Sep 23 EU NETVAL Coordinator
Great to share our @EU_ScienceHub #ecvam activities #EUNETVAL #GIVIMP #3Rs networks at #h2020 FET workshop #ORCHID @organonchip designing roadmaps for https://euroocs.eu/ and other global networks @OrganOnAChip bridging fields of #organoids #stemcell #MFS

Reyk Horland, head of business development, Tissuse, Berlin
The ORCHID project significantly contributed to the advancement of Organ-on-Chip research in Europe by bringing experts together for stimulating discussions and facilitating collaborations.

Jens Schwamborn, Developmental and Cellular Biology Group, University of Luxembourg
I am convinced that Organ-on-Chip has a tremendous potential and will help us to understand human physiology and pathology at a level that we have not reached so far. Particularly I see interesting applications from novel drug development approaches.

Jacqueline van Engelen, National Institute of Health and the Environment (RIVM)
The ORCHID project has been a very fruitful project, I enjoyed participating in the workshops. The dialogues were open, well structured, and effective, not in the least because of the diversity of the participants, ranging from scientists from the research community to medical doctors, representatives from patient organisations and regulators. Congratulations on the Roadmap and on the launch of the European Organ-on-Chip Society, that will definitely facilitate the future developments on Organ-on-Chip technologies!

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Ngoc Berris-Pham[6] (Transition Animal-free Innovation, the Netherlands),
Patrick Boisseau[6] (MedTech, France),
Milton Bonelli[6] (EMA, the Netherlands),
Lissa Boxy[6] (Innovation Quarter the Hague, the Netherlands),
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[1] See https://h2020-orchid.eu/summary/ for detailed reports

ORGAN ON CHIP IN DEVELOPMENT

The ORCHID project (Organ-on-Chip development) was an EU initiative, coordinated by Leiden University Medical Center and the Dutch Organ-on-Chip consortium hDMT in The Netherlands. The main goal of ORCHID was to create a roadmap for Organ-on-Chip technology and to build a network of all relevant stakeholders in this promising innovative field. In the ORCHID project ran from 1 October 2017 to 30 September 2019 in total seven leading European research institutions were involved.

More information: **https://h2020-orchid.eu**

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