Organ on Chip in Development (ORCHID)

EU – H2020 project grant agreement no 766884 (AMD-766884-3)

Website: www.H2020-ORCHID.eu

Deliverable Number	2.5
Deliverable Title	Report on strategy workshop
Short Title	Strategy_workshop
Lead beneficiary	7-TUD
Del. Date (Annex 1)	31/03/2019
Achieved Date	30/03/2019
Nature	Report
Dissemination Level	PU
Document Filename	D25-Strategy_workshop-PU-v1.0.pdf

Date	Authors/Reviewers	Remarks	Version
04/03/2019	Thomassen	Provided format report	0.1
29/03/2018	J. vd Eijnden-v Raaij, M, Mastrangeli, S. Millet, All consortium partners	Final version, review by consortium partners	0.2
30/03/2019	Thomassen	Final Version submitted to EC	1.0

Contents

Building blocks for a European Organ-on-Chip roadmap

Massimo Mastrangeli[1], Sylvie Millet[2], Dries Braeken[3], Madalena Cipriano[4], Wolfgang Eberle[3], Luis Fernandez[5], Mart Graef[1], Xavier Gidrol[2], Nathalie Picollet-D'Hahan[2], Peter Loskill[4], Berend van Meer[6], Christine Mummery[6], Ignacio Ochoa[5], Mieke Schutte[7] and Janny van den Eijnden-van Raaij[7]

[1]Delft University of Technology (Delft, the Netherlands); [2]CEA (Grenoble, France); [3]imec (Leuven, Belgium); [4]Fraunhofer IGB (Stuttgart, Germany); [5]University of Zaragoza (Zaragoza, Spain); [6]Leiden University Medical Center (Leiden, the Netherlands); [7]hDMT (Eindhoven, the Netherlands)

Abstract

This report summarizes the outcome of expert discussions, conclusions and recommendations for the European Organ-on-Chip (OoC) roadmap that were advanced during the *ORCHID Strategy workshop*, held on 17 January 2019 in Leiden, the Netherlands. The workshop identified six specific building blocks for the OoC roadmap – namely, (1) application, (2) specification, (3) qualification, (4) standardization, (5) production and upscaling, and (6) adoption – and general complementary aspects relating to ethics and communication. Priorities, methods and targets along the roadmap were proposed for each building block. A general consensus was reserved to the newborn European Organ-on-Chip Society (EUROoCS), which is expected to play a key coordination role in the deployment of each block. EUROoCS should initiate and catalyze the necessary and early dialogue between OoC developers, end users and regulators. The dialogue should address qualification, open technology platforms, standardization and implementation of OoC technology, as well as ethical aspects, training of the next generation of OoC researchers, dissemination and communication.

1 - Introduction

1.1 The current landscape of Organ-on-Chip technology

Born out of the confluence of tissue engineering and microfluidics, Organ-on-Chip (OoC) technology is widely postulated as a promising approach to providing better model systems in healthcare research. OoC models aim to recapitulate aspects of human physiology and pathology with view to deployment in drug discovery, efficacy and toxicology testing and personalized medicine to improve upon existing bioassays and provide insights into the mechanisms underlying the development and progression of diseases. In addition, OoCs are considered as relevant to reduce the need, cost and ethical burden of animal studies.

Though the OoC field is still in its infancy, several showcases of OoC models are already being used to gain insight into disease aetiology and identify drug target pathways. These showcases include detection of thrombotic risk in vessels-on-chip (Barrile et al, 2018), discovery of targets for metastases in cancer-on-chip (Song et al., 2018), test for kidney toxicity in kidney-on-chip (Vormann et al., 2018), drug effects on neurons and glia cells-on-chip (Wevers et al., 2016), prediction of toxicity of nanoparticles in lung-on-chip (Zhang et al., 2018) and drug discovery in a disease model for ALS (Osaki et al., 2018). These and multiple other examples are at the stage of validation/qualification, to prove that compounds and drugs that have already been shown to be toxic or effective in treating disease in animals or in

patients show similar effects in OoC models. This is expected to encourage their adoption by industry, acceptance by regulatory bodies and their development as animal alternatives. However, this has not yet become a wide reality.

A comprehensive survey of the current OoC landscape in research, development, applications and market opportunities was recently performed in the context of the Horizon 2020 FET-Open project *Organ-on-Chip In Development* (ORCHID[1]). The goal of ORCHID is to create a roadmap for OoC technology, identifying potential roadblocks and corresponding solutions, raise awareness and build an ecosystem conducive to the wide implementation and use of OoCs in science, R&D and society in Europe and the rest of the world. ORCHID recently published a report (Mastrangeli et al., 2019) based on a bibliometric study, a market analysis, interviews and panel discussions with 31 experts during the ORCHID Vision workshop (Stuttgart, 23 May 2018). The report describes the unmet needs, key challenges, barriers and perspectives of this technology, as well as recommendations towards the definition of a European OoC roadmap.

1.2 The future strategy for Organ-on-Chip technology

Following up on the ORCHID Vision workshop, the ORCHID Strategy workshop was held in Leiden on 17 January 2019. 32 experts from academia, innovation hubs, pharmaceutical and cosmetic industry, patient organizations, ethics school, biotech companies and regulatory agencies attended the workshop. They represented developers, end users and regulators in the OoC field in Europe. The aim of this workshop was to define the concrete goals and milestones of the OoC roadmap, and the strategy to reach them. During two brainstorm sessions, expert groups focused on four specific application domains: personalized medicine, drug efficacy, drug toxicity and disease mechanisms. The groups addressed domain-specific issues from the perspective of both developers and of end users and regulators.

This report summarizes the results, expert discussions, conclusions and recommendations that emerged from the workshop. Six specific building blocks of the OoC roadmap were identified: (1) application, (2) specification, (3) qualification, (4) standardization, (5) production and upscaling, and (6) adoption. General and additional aspects that need to pertain to any such roadmap, such as ethical concerns, training of the next generation OoC researchers, dissemination and communication, were also discussed, and they are presented upfront to set the context for the core building blocks. We start by pointing out the eminent role that the OoC community will have to play in the endeavor.

[1] ORCHID partners are: Leiden University Medical Center (coordinator; The Netherlands), Institute for Human Organ and Disease Model Technologies (hDMT) and Delft University of Technology (Delft, The Netherlands), CEA (France), imec (Belgium), Fraunhofer Institute for Interfacial Engineering and Biotechnology (Fraunhofer IGB, Germany), and University of Zaragoza (Spain).

2 - The European Organ-on-Chip Society (EUROoCS[2])

2.1 The role of EUROoCS in community building

As articulated in the Strategy workshop and detailed below, collaboration is the key to further acceptance, development and implementation of OoC technology and to bring benefit to all stakeholders. In Europe, an OoC network of more than 28 partners in 17 European countries has recently been formed. Many countries, including the United Kingdom, the Scandinavian countries, Belgium and Israel are inspired by the Dutch OoC consortium hDMT[3] and are starting to connect OoC players in their country. This approach paves the way for a European Center of Excellence on human OoC by creating strong research collaborations throughout Europe and beyond. The European Organ-on-Chip Society (EUROoCS), an outcome of ORCHID, will facilitate and stimulate the further grow and strengthening of the OoC network.

EUROoCS was launched during the International OoC Symposium (IOOCS18) at the Eindhoven University of Technology in the Netherlands on 8 November 2018. The purpose of EUROoCS is to encourage and develop OoC research, and to provide opportunities to share and advance the knowledge and expertise in this field towards a better health for everyone. Membership is open to individual researchers worldwide and others with an interest in OoC technology. Benefits include access to the digital OoC platform, where members can present themselves, their expertise and research projects, interact with other people in the OoC field, and find new collaborators and tailored information (see section 3.2). In addition, members can benefit from discounted registration for the annual EUROoCS conference and up-to-date information on advances and activities in the field. EUROoCS will stimulate and coordinate the necessary dialogue and interaction between all parties involved in the implementation of the OoC roadmap strategy (Fig. 1).

During the workshop the logo of EUROoCS was presented (Fig. 1), which symbolizes both technology and community building in Europe and beyond. EUROoCS is expected to become an initiator and catalyst for the necessary dialogue between end users, developers and regulators towards qualification, open technology platforms, standardization and implementation of OoC technology.

[2] www.euroocs.eu
[3] www.hdmt.technology

Figure 1: Key roles of the European Organ-on-Chip Society (EUROoCS) in the OoC roadmap.

3 - General aspects of an Organ-on-Chip roadmap

3.1 Ethics

An ethics roadmap is important for identifying emerging ethical issues and addressing them timely as the technology progresses. Such a roadmap is a sensible way to balance short-term issues related to the present work in the laboratory and longer-term discussions about future visions such as 'human-on-chip'.

Communication to the public warrants a careful approach

The ethics roadmap will help the discussion of ethical and societal issues with the general public, as well as the conversation about potential future societal impacts and controversies. To avoid misunderstanding, communication about OoC technology should consider the language used and how it is understood by the public and by different stakeholder groups. There is a discrepancy between expansive ambitions (*e.g.*, 'human-on-chip') and the actual work in the laboratory. A discussion overtly focusing on the ambitions may create unjustified expectations and ensuing disappointment (*i.e.*, a hype cycle), or lead to controversy over issues not related to the research actually undertaken. Cautious language use is all the more essential with regards to patients potentially waiting for these technological developments to become a healthcare reality. It is therefore recommended to carefully plan a fine-tuned dissemination strategy that might also manage eventual associated risks.

Privacy and ownership issues ask for clear management

There is a strong awareness of bioethics issues among researchers, and experience in how to manage these issues properly. However, privacy and informed consent procedures may have to be revisited to manage issues related to personalized medicine, especially if rare diseases with only few patients are targeted.

In addition, standardization of technology platforms raise issues related to the ownership of results. There is an underlying dilemma between the ambition to contribute to societal goals (*e.g.*, new therapies, 3Rs for animal testing) and the need for economic viability of the solutions. Though there is no best solution, these questions should be addressed further.

Interdisciplinary research and global dialogue raise awareness

OoC research requires interdisciplinary collaboration between physicists, biologists, engineers, chemists and researchers from other disciplines. Researchers active across disciplines may be incorrectly presumed to have correspondingly adequate skills, whereas different laboratories often require different or specific training. Care therefore must be taken so that all personnel is offered appropriate trainings, including safety.

Another dilemma that should be addressed relates to the organization of collaborative research communities on complex high-tech platform technologies. By lowering entry point threshold, new entrants may bring in new innovative ideas, though they may also be less aware of safety issues.

The European OoC strategy explicitly addresses ethical issues; however, this may per se not prevent the emergence of new products or systems in other parts of the world which conflict with European values. Therefore, a role for EUROoCS might be to engage in a global dialogue on ethical issues and common understanding of how these can be addressed.

Tailored training programmes for next generation OoC professionals

The interdisciplinary character of the OoC technology provides a challenge for future training programmes, as it requires experts with a broad skillset covering various aspects of bioengineering and other disciplines. Specialized training and expertise is of utmost importance for anyone involved in the development and utilization of OoC systems as well as in the assessment of the systems and of the results obtained through them. The training programmes will prepare scientists and technicians for new types of employment that will arise while, on the other hand, provide industry and academia with professionals able to keep up with innovation in the field. Therefore, those programmes will need to cover a wide range of topics – including *e.g.* biomaterials, microfabrication techniques and manufacturability, microfluidic principles, cell culture and stem cell technology, biobanking, data management and protection, monitoring and analysing (molecular biology/omics; sensors, imaging), PKPD modelling, pharmacology and toxicology principles, quality assurance, science communication, ‘regulatory affairs, ethics – with differing degree of relevance. Specifically tailored training programmes will be necessary for scientists as developers, as end users (academia or industry), as decision-makers (regulators, grant evaluators or peer reviewers), as well as for technicians and clinicians.

The level of complexity and depth of the respective training can range from introductory knowledge (awareness) to basic competence (theoretical or practical skills) up to deep knowledge (theoretical and practical skills). The programmes might be implemented at various stages of education (bachelor's, master's, doctorate studies or postdoctoral training) and could include either specific postgraduate courses (1 to 2 years), seminars/courses integrated in a broader training programme (1 semester), or only individual training sessions (theoretical or practical). Besides specific training programmes, it might make sense to include seminars/courses/sessions focused on aspects of OoC into traditional educational programmes such as engineering (mechanic, materials, chemical), bioengineering (biotechnology, biomedical), physics, chemistry, biochemistry/biology, medicine, and pharmacology/ toxicology.

In the process of developing the European roadmap for OoC, a comprehensive stakeholder consultation is currently being conducted to assess the respective training needs and skillsets and to provide recommendations for specific training programmes[4].

3.2 Dissemination & Communication

The EUROoCS digital platform as a market place: *Organ-on-Chip for all*

A dissemination and communication strategy for OoC research and activities is essential for the development of the EU's scientific knowledge base and to foster innovation, economic growth and jobs. EUROoCS and its support website, including a digital platform for members, will serve as the central coordination point to ensure higher visibility to European research teams and to position those as key leaders in the OoC field. The EUROoCS platform will gather all information and boost the recognition of the OoC domain at European and international levels: it will bring together players and let them interact, creating an interdisciplinary OoC community by targeting a broad audience (Organ-on-Chip *For All,* Fig. 2) that will accelerate the growth of the OoC ecosystem. EUROoCS is expected to move across sector-specific cultures and language barriers to facilitate effective dialogue and collaboration between the scientific community, regulators, industries, clinicians and patient groups since the early stages of development, and catalyze OoC adoption by end-users. Working together as a community and being visible through the EUROoCS website/digital platform could also help establish standards in the field. As a standardization catalyst, the EUROoCS digital platform will also collect experts' insights from different stakeholder groups to provide an indirect roadmap through building guidelines for OoC implementation.

[4] https://ec.europa.eu/eusurvey/runner/Orchid_Questionnaire_Training_needs_Organ-on-a-chip

Figure 2: The EUROoCS website/digital platform as a market place for all.

The EUROoCS website was conceived by ORCHID members and validated by a test group of selected OoC experts to efficiently reach key information. The majority of tabs (library, latest news and recent events, announcements of trainings, workshops, OoC timeline, reports and reviews) are available with a free subscription to allow the users to get a better understanding of OoC and keep informed about new scientific and technological developments. Specific links to general brochures are included. Moreover, the website was designed to be attractive for students to find jobs and funding opportunities, subscribe to newsletters, and access social networks where EUROoCS will also host different groups interested in OoC technology. Information regarding key publications, patents and discoveries will thus be distributed to the dissemination target groups besides being accessible directly from the website. The EUROoCS website will evolve over time through the addition of publications, latest news, event announcements, collaborative projects and various member-supplied contents. Finally, by giving the opportunity to industrials to be exposed and by being attractive for investors and funding agencies to support the development of prototypes, the EUROoCS website will also contribute to increase innovation and competitiveness of European health-related industries and services.

The ORCHID expert community unanimously perceived the EUROoCS digital platform as a means to build a network, to realize integrative programs and collaborative projects or consortia, to find new academic/industrial partners or people more involved in regulation and patient associations. In this respect, a reserved area, specific for EUROoCS members, opens up detailed expert contacts, project descriptions and mapping. This detailed information as well as the opportunity to debate specific topics through a discussion forum aim at encouraging people to become a member and to join the community. This member-restricted area of the digital platform is expected to be a market place for OoC-stakeholders,

with people from a wide range of backgrounds who can benefit from OoC and can share thoughts, ideas, expertise, initiate specific working groups or discuss updated topics on OoC.

Building dedicated communication tools to continuously raise awareness

Having established a communication strategy, it is important to determine whether the expected impact is achieved. To this end, online dissemination tools (*e.g.,* website, newsletters, social media) will be regularly monitored, and some key performance indicators (number of visitors, statistics on the impact of the newsletter, number of articles viewed, user feedback on the newsletter's content) will be periodically checked for quantitative and qualitative evaluation (Fig. 3). Qualitative evaluation will also be conducted on the basis of questionnaires following special events. Finally, the impact, strengths and weaknesses of the dissemination strategy on target groups will be examined regularly as well as the quality of communication about OoC.

Figure 3: Tools of dissemination.

Participating in conferences and organizing trainings and dedicated workshops on OoC will raise awareness of the community and capture young researcher's attention on OoC activities. To that end, EUROoCS members are encouraged to establish connections with press, media, politicians, general public and schools, to act as focal points for local dissemination of information, to use connections to other academics working on related domains at local and international levels, and to generate active social media content to introduce European citizens to the OoC technology. A visual identity of OoC in Europe was developed to ensure consistency and higher visibility of the OoC field. Communication tools (*e.g.*, social media, leaflets, newsletters, press releases) will be adjusted to the type of information and to the specific targeted group.

4 - Specific building blocks of the Organ-on-Chip roadmap

4.1 Application

Priority for disease mechanisms, drug efficacy and toxicity, and personalized medicine

The privileged domain to be addressed by OoCs is the drug screening and development process[5], which ranges from fundamental research to personalized medicine aspects and targets users such as biomedical researchers, hospitals and pharmaceutical industries. According to OoC experts, four main contexts of use need to be taken into account:

- improving understanding of human disease mechanisms and aetiology;
- predicting drug efficacy in humans;
- predicting drug toxicity in humans;
- paving the way to personalized medicine.

The associated priority (patho)physiological areas are driven by the need for new therapeutics discovery, including the emerging new drug modalities (large molecules like monoclonal antibodies, antibody-drug conjugates, protein therapeutics), especially for diseases for which there are little or no efficient drugs available, due to a poor pathophysiological mechanism knowledge combined to a lack of predictive disease models (see table 1). Among the most cited as public health priorities are cancer, neurodegenerative diseases like Alzheimer disease, cardiometabolic disorders, autoimmune diseases, fibrosis and also rare diseases, such as hemophilia. Each of them requires its own panel of tissue models, from single to multi-OoCs, for studies of disease mechanisms and response/resistance dynamics. Toxicity testing and safety assessment show a strong preference for OoCs mimicking ADME pathways (Absorption, Distribution, Metabolism, Excretion) including metabolic organs (liver, kidney) and barrier/digestive systems (blood-brain barrier for physiological absorption) and the presence of the immune component. OoCs can be also personalized with patients' samples to mimic key aspects of a (patho)physiological state, including specific disease-related parameters. By capturing a higher level of physiological complexity from a particular individual, OoCs might be used as companion diagnostic tools to differentiate responders from non-responders to medication, to refine dose for a dedicated patient (exposure-response relationships by pharmacokinetic/pharmacodynamics (PK/PD) modeling), to define combination therapies and personalized drug delivery, or evaluate disease progression, and predict specific adverse events (patients at risk) thereby tailoring treatment strategies to improve the benefit-risk ratio. OoCs might also contribute to patients' pre-stratification for clinical trials, leading to protocol

[5] Other relevant applications include toxicity screening of compounds for cosmetic and chemical industries and for environmental agencies, and counter-measures against chemical and biological warfare – for a comprehensive overview, see the ORCHID Vision workshop report (Mastrangeli *et al.* 2019).

optimization and supporting clinical decision-making processes. In the future, the implementation of health-related data in OoCs (lifestyle, epigenetics) may lead to even more predictive personalized devices, to position OoCs as promising physical avatars for individuals.

CONTEXT OF USE	DISEASE AREA	KEY TISSUE MODEL	END-USER
Diseases' mechanisms	Cancer	Tumor models	Biomedical researchers Clinicians Pharmaceutical industry
	Neurodegenerative diseases	Brain, BBB, neurons, retina	
	Cardiometabolic disorders	Heart, lung, liver, pancreas, vessels, adipose	
	Autoimmune diseases	Immune system, gut, pancreas, neurons, skin …	
	Fibrosis	Connective tissues, lung, liver, kidney	
Drug efficacy	Cancer	All types	Industries: pharmaceutical, cosmetics Biomedical researchers
	Neurodegenerative diseases	Brain, BBB, neurons	
	Cardiometabolic disorders	Heart, lung, liver, pancreas, vessels	
	Autoimmune diseases	Immune system, gut	
	Fibrosis	Connective tissues, lung, liver, kidney	
Drug toxicity	All types	ADME pathway (liver, kidney), barrier systems (gut, lung, BBB), heart, brain Immune system	Industries: pharmaceutical, cosmetics Biomedical researchers
Personalized medicine: ▪ **patients' stratification** (adverse effects, dynamics/ resistance, identification of vulnerable population) ▪ **Companion diagnostic** (responders, disease progression)	Cancer	All types	Pharmaceutical industry Hospitals/clinicians
	Rare diseases	All types	
	Systemic diseases	Multi-organs	
	Autoimmune diseases	Immune system, gut	

Table 1: Overview of the applications and associated models discussed during the ORCHID Strategy workshop. ADME: Absorption, Distribution, Metabolism, Excretion; BBB: Blood Brain Barrier.

4.2 Specification

Customizable platforms for fit for purpose modular OoCs

The group and collective discussions of the Strategy workshop highlighted the following technical and functional criteria for the development of OoC models:

a) *Modularity*. It is unlikely that a single OoC device will be able to satisfy the requirements to serve all conceivable functions or applications within the reach of the OoC technology. For instance, a comprehensive list of disease mechanisms is hardly feasible if at all. Besides, the requirements may be mutually incompatible; and such single device may easily turn out to be overwhelmingly complex, economically not viable and ultimately not effective for potential end users. Instead, a reductionist, LEGO®-like approach is suggested whereby OoC devices are assembled over

platforms out of sets of basic and standardized modules according to user needs. Standardized interfaces and well-defined assembly of modules are essential for the success of such modular approach. Both technical and biological modules are considered:

1. *Technical modules*: mechanical actuators and stimuli (forces, stresses, strains), electrical stimuli, perfusion (microfluidics, pumps, valves), reporter systems and sensors (for *e.g.* oxygen, carbon dioxide, pH, glucose, metabolites, flow rates, impedance);
2. *Biological modules ('functions')*: 3D scaffolds, cell-cell interactions, neuron/neurite outgrowth, barrier mechanisms, vascularization, air/liquid interface.

The modular composition of OoCs within standard platforms shortcuts the issue of defining *a priori* the end use of the devices, leaving it open instead and suitable to a variety of different users and applications. This approach is envisioned to afford or be compatible with:

- simplicity and ease of use;
- possibility to stack levels of complexity in 4 dimensions (space + time);
- customization and user-defined fit-for-purpose
- standardization of modules (see also Section 4.4).

b) *High throughput,* at least higher than currently possible, to reduce cost-per-data point and extend the range of OoC use in pre-clinical screening.

c) *Automation* to limit errors and improve reproducibility, repeatability and cost-effectiveness.

d) *Multi-parametric assays* to benefit from various data points in a single test system, thereby improving efficiency and limiting heterogeneity. The selected parameters should provide sufficient data to support study conclusions, and they should be linked to clinical expectations to prove the added value of the technology.

e) *Use of genetically & phenotypically characterized human cells* to mimic human (patho)physiology, with eventual dedicated benchmarking (not based on animal use).

f) Sustain *long-term measurements* to evaluate compounds, as preferred to short kinetic and metabolic measurements.

g) Generic and standardized *open technology platforms*, both in hardware and software, for full public availability and compatibility across platforms (see Section 4.4).

Consequently, OoCs should be conceived and proposed as mere robust tools tailored to fit a purpose by the end users, who should be provided with customizable platforms rather than with pre-determined devices. The modular approach aligns with the belief that the ultimate purpose of the devices may only emerge from the end users themselves once the devices are in their hands, so that defining beforehand what the application of the devices should be may turn out to be a misconception.

4.3 Qualification

Qualification processes for context of use need independent testing centers

The Vision workshop highlighted the need to focus on the qualification or characterization of the OoCs rather than on the validation *per se*. The latter is considered by experts neither an appropriate nor a meaningful concept, because it implies the existence of an accepted standard or reference to measure validity. The Strategy workshop confirmed moreover that regulatory acceptance should not be the ultimate goal of OoC development. Regulatory acceptance covers a relatively very small fraction of the interests of end users: industry needs confidence in the devices, whereas regulators typically require a case-by-case analysis. Therefore, while still considered necessary, the qualification of a device does not necessarily prelude to its regulatory acceptance nor to its user adoption.

For drug screening and development processes, OoCs should recapitulate human tissue physiology but also disease-related parameters to be used as better predictive model for assessing safety and efficacy of promising therapies than current cell and animal models. 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. This aspect will help determining the biological relevance of the device and will allow qualification of its performance.

iii. Implementing quality control assays ensuring the functional characterization of cell cultures to fit with the (patho)physiological responses but also expressed in the form of material qualification (drug-biomaterial interaction), manufacturability and availability of devices.

iv. Evaluating effectiveness of OoC compared to current *in vivo* profiles, through the analysis of the corresponding data derived from conventional drug development models, and correlation with clinical data or manifestations.

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

The latter aspects should be considered as iterative approaches, supported by running pharmaceutical projects to bring added value, aiming at investigating the correlation between OoCs and the *in vivo* situation, 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 (Fig. 4).

Towards a centralized database to share information and promote OoC development

To achieve optimal results from the qualification studies, a key challenge consists in establishing an evolutive database clustering all available data about a reference set of the most appropriate compounds and biomarkers, together with the results about the performance and accuracy of the tested OoC systems, specific for each context of use and targeted tissue(s). The aim of this centralized and publicly accessible database is to provide the scientific community with in-depth information (including raw data and also 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. In this way, providing relative data from reference compounds/biomarkers and allowing the overall 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.

However, the quest for qualification of OoC devices entails the availability of abundant human data as well as multi-parameter readouts without bias (achievable with the help of proper statistical automated data analysis). In addition, a relevant list of testing compounds/biomarkers is not readily available or in the making at best thanks to several initiatives (the NIH in the US and the Crack it! European program) and are in many cases not easily accessible to academic research groups since they are companies-proprietary. A solution would be to work closely with structures like the IQ Consortium, 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. The NCATS is also currently working with well-known pharmaceutical companies like AstraZeneca, GSK, Pfizer, Roche or Sanofi, and has already established to that purpose a material transfer agreement to ensure that compounds/biomarkers provided for the characterization are cleared for inclusion in academic work (Ewart *et al*., 2017).

EUROoCs may play a catalyzing role in collecting the information with a necessary infrastructure, data management and statistical capabilities to ensure an extended dissemination among the OoC community and beyond (Fig. 4). 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 dialogue of a EUROoCS- supported database with other international existing ones should reinforce multi-partners task forces and contribute to international harmonization.

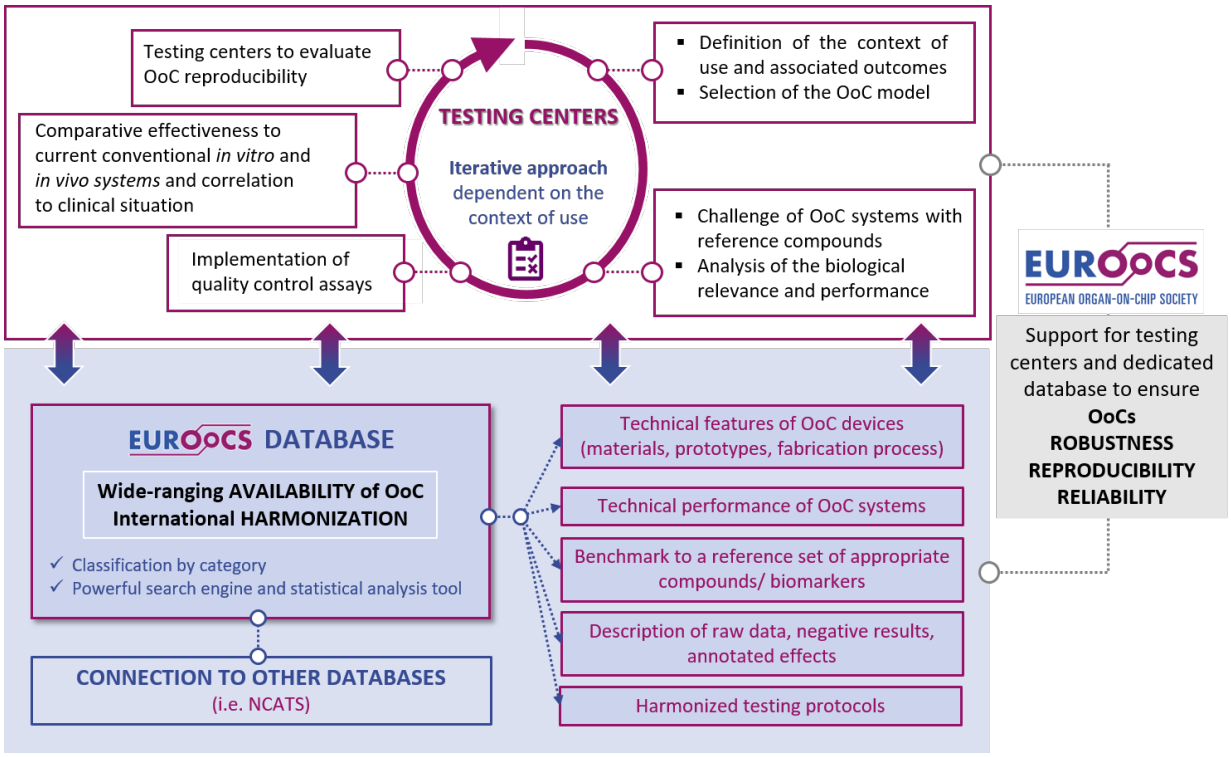

Figure 4: Synopsis of OoCs qualification processes and interfacing with a centralized database.

4.4 Standardization

A task for the OoC community that should be internationally harmonized

Standardization is a loaded and somewhat mystifying concept, differently interpreted and practiced across sectors and markets. Standardization of OoCs is very challenging since OoC is an interdisciplinary field gathering many players and stakeholders from various horizons. 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. While the former appear to be the current case in US, where several large players are trying to dictate OoC standards, the latter approach is expected to prevail for OoCs, with standardization emerging from a collective dialogue among developers and end users and from ensuing cross-constraints. 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, the lab-on-chip's lack of standardization may be responsible for the problems encountered today in getting into the market.

Also to avoid this risk, OoC standardization should be addressed very early in the 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 very small companies in no financial condition 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 is foremostly to enable 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 should be identified

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.*, multiwell 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.

Towards open technology platforms for OoC

One way recommended to encourage the OoC community to converge towards standardization is the realization of open technology platforms. These can be seen as shared technology platforms for the gathering of 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. 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. The whitepaper on standardization (Appendix A) discusses the benefits and pitfalls of standardization in the field of OoC devices and systems and identifies already running standardization efforts which address certain aspects of technology and operational processes in the OoC field.

4.5 Production and upscaling

Industrialization requires choices in early development of OoC devices

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 implies mass production of chips or microfluidic devices and generation of large batches of differentiated cells, respectively. As demonstrated by the success of microelectronics, high volume production of chips typically coincides with decreased manufacturing variability and leads to highly reproducible devices. However, a catch is in place here. On the one hand, such device-level reproducibility would be required especially in early stage OoC development and qualification (see Section 4.3) since the inherently variable biology introduces another layer of variability and cannot otherwise be properly assessed. On the other hand, setting up mass production of devices requires large investments which are not likely for non-qualified devices. Breaking out of this catch might require specific, public-private funding calls.

Depending on applications (see Table 1), 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 (Probst et al., 2018);

2) *Personalized medicine*, possibly in a hospital setting or dedicated SMEs. This will entail robust and reproducible OoCs with patient-derived cells, and a required upscaling to test tens (*i.e.*, 10 to 50) potential drugs and find the right concentration of the right drug for specific patients;
3) On a longer term, *clinical trials*. To date there is no clinical trial on *e.g.* children, pregnant women, or on specific or unique ethnic groups. OoC could enable a better representation of human phenotypic diversity in clinical trials. The upscaling requirement to perform clinical-trial-on-chip in CRO's will be dependent on the trial.

An industrial-level fabrication volume puts some severe 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.

4.6 Adoption

Adoption of OoC technology requires well-documented showcases

The OoC technology may be accepted and thus adopted if it provides simpler, cheaper and relevant alternatives to established models while reproducing at least the same results supported by convincing and reliable metrics, or if it affords models for which no alternatives currently exist (such as rare diseases) (see ORCHID Vision workshop report (Mastrangeli et al, 2019)). In addition, OoC adoption implies the satisfaction of many other conditions including ease of use, back-compatibility with established laboratory processes, cross-laboratory reliability, together with a supporting and organized user's community (Figure 5).

In this respect, the identification and stratification of end users, stakeholders and sectors is deemed to be critical. It should be part of a primary action conducted by dedicated methodologies and teams, and a prerequisite to organize a global community centered around the open technology attitude and allowing a frictionless transfer of expertise among disciplines and domains (*e.g.* including regulatory bodies). To build confidence in the value of OoCs and facilitate engagement of all players, structuration of (a) neutral organization(s) capable of testing and qualifying such devices has been proposed, in line with the OECD guidance. The adoption process will emerge from collective end users of OoC and rely on the data obtained with OoC included in a regulatory approval and perceived by regulatory bodies as complementary data to standard benchmark. But a key challenge remains the applicability of these guidelines to rapidly developing technologies like OoCs. A convincing way to circumvent those issues would be to encourage multi-partner task forces to conduct show cases capable of fostering end user

adoption. Such show cases may be represented by case studies, such as the CRACK-it challenges[3], even not optimized nor finalized, involving end users along with regulators and developers to start and sustain a fruitful and timely dialogue. Also, as pointed out by regulatory experts, the final decision will be up to developers since today there are no restrictions nor requirements from regulatory bodies for the use of specific cells.

Finally, community organization and subsequent adoption of OoCs by end users will need sustained dialogue and collaboration to move across the limitations of sector-specific cultures and languages: EUROoCS is thereby expected to play a leading and catalyzing role in that respect.

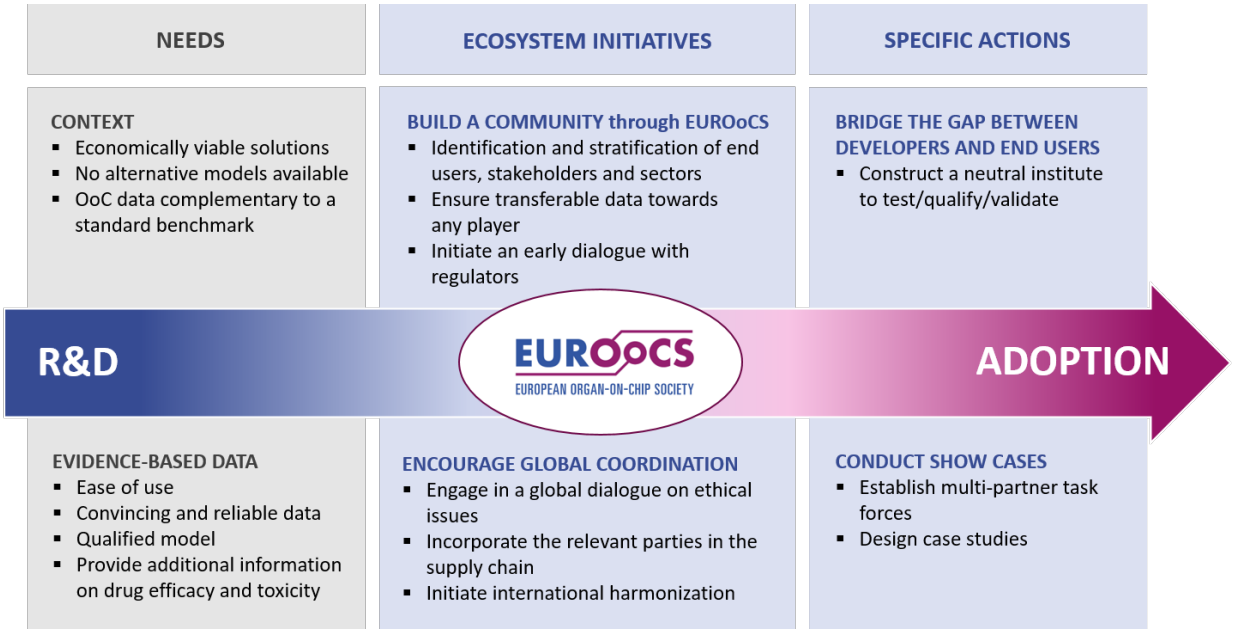

Figure 5: Overview of the context needs, initiatives and specific actions to promote OoCs adoption.

5 - Discussion and recommendations

The ORCHID Strategy workshop converged on the proposition of the roadmap for OoC development represented in Fig. 6. As described in the previous sections, to lead from the current status to applications of OoCs the roadmap is envisioned to make use of a set of main building blocks. Some building blocks are specific to the present instance, whereas others correspond to common development stages for which prior experience in collateral roadmaps can be capitalized. Along with the conception of the OoC roadmap, the gathered experts agreed on the pivotal coordination and communication role that EUROoCS should play in the deployment and actualization of each building block.

It should be reminded that the entries in Table 1 are not exhaustive but rather priority lists. This holds in particular for known disease mechanisms, whose list is hardly conceivable, and OoC applications, whereby the long-term list may even turn out to be different from the one proposed depending on the future needs of actual end users. Whereas the application domains were chosen mainly to guide the discussions, the roadmap and its building blocks are expected to apply irrespective of the directed versus emergent nature of the final applications.

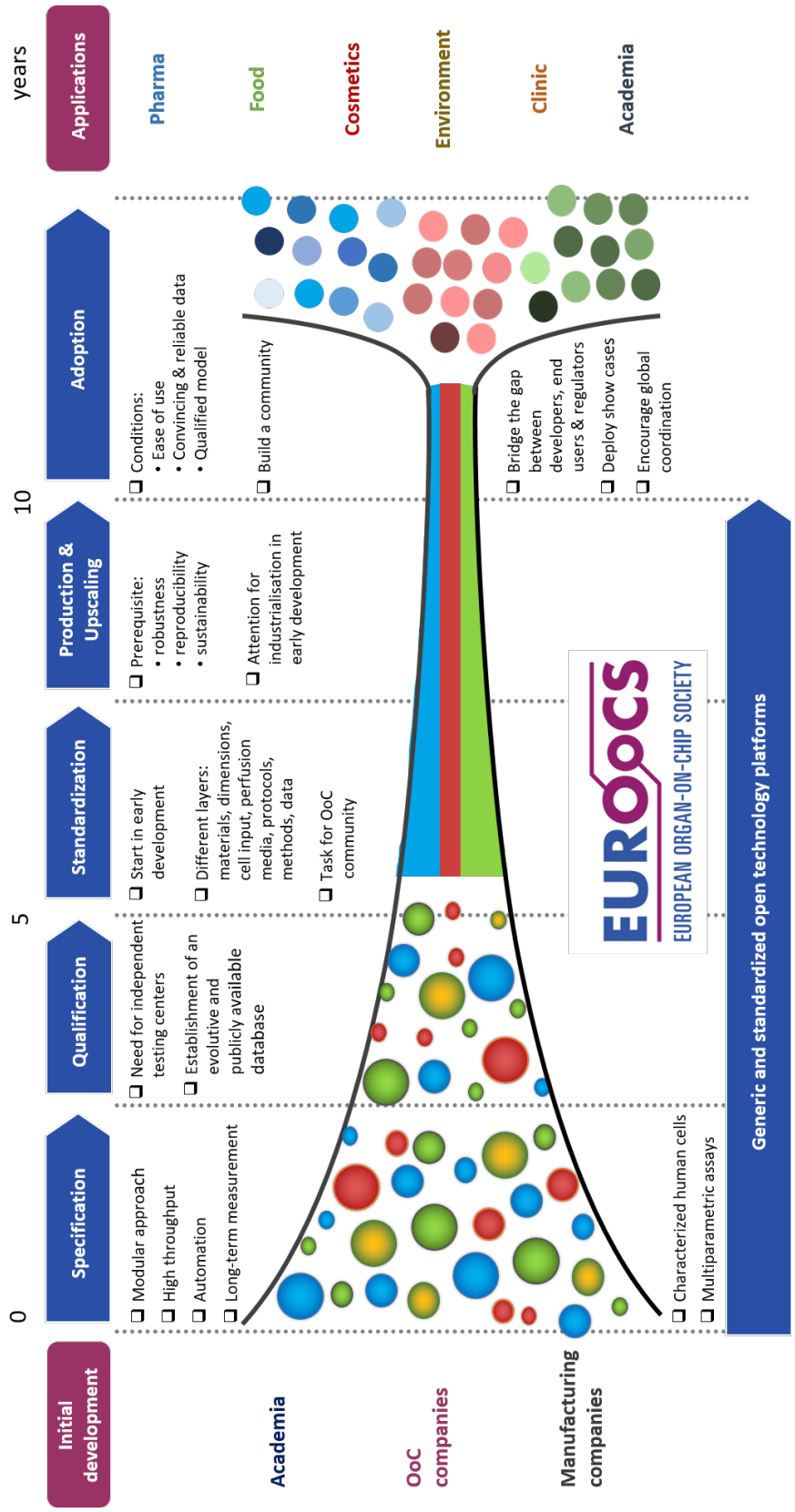

Figure 6. The ORCHID roadmap for OoC development.

The modular approach to OoCs based on customizable platforms was consequently recommended as the best 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. Device qualification, per se not corresponding to device adoption nor regulation, should pass through independent testing centers, to be established in Europe following the US lead. A single worldwide database, eventually emerging from the harmonization and interconnection of local databases, would be ideal to collect and share all related data, also following the example of shared compounds lists by *e.g.* the IQ consortium. Standardization should address multiple levels of the OoC technology and should start from forming task forces of expert groups and learning from existing standards (see also Appendix A). It is worth stressing once again the advantages of open technology platforms, along with the need to manage the coexistence of, and at times divergent needs related to intellectual property and technology sharing. Successful handling of these aspects additionally highlights the key role of a wide, open and interconnected OoC community, not lastly for its role in innovation. In this respect, while supporting the roadmap the experts at the same time acknowledged the possible dualism and coexistence of a more directed and linear approach to OoC development, as indeed embodied in a roadmap, and of an emergent and more non-linear approach building upon crowdsourcing and user-generated targets and solutions. Both approaches can find earlier examples in recent history, and can certainly interact to gain mutual benefits. It is irrespectively clear that to achieve the prefixed long-term goals of globally improved healthcare and personalized medicine for everyone, OoCs will need to be suitable for large-scale production, an aspect that should involve the choice of materials and of manufacturing technologies from early development stages. Along this line, back-compatibility of the devices with established laboratory practice and standards as well as successful showcases of complete OoC platforms and applications should favor OoC penetration and speed up worldwide adoption.

Finally, the envisioned roadmap that this report has introduced – and of which the final structure will be released in October 2019 – necessarily addresses related ethical questions, cautiously optimistic communication strategies, and information of laypeople as well as in-depth training and education of next generation experts. For all of the above tasks, EUROoCS, supported by its digital platform, publications and recurrent meetings, should be ready to play a cardinal role.

Recommendations

1. Focus on selected pathophysiological areas in the context of OoC models for disease mechanisms, drug efficacy and toxicity, and personalized medicine: cancer, neurodegenerative diseases, cardiometabolic disorders, autoimmune diseases, fibrosis and rare diseases.
2. Provide end users with customizable platforms for fit-for-purpose OoC models.

3. Apply a modular approach for the OoC models, using technical and biological modules that are assembled within standard open technology platforms.
4. Converge towards standardization of components, methods and data by a collective dialogue among experts, facilitated by EUROoCS, and starting very early in the development.
5. Establish independent testing centers for the qualification and characterization of OoC models for a specific context of use.
6. Develop a publicly accessible evolutive database, supported by EUROoCS, that clusters all available data from reference compounds and OoC test data, and interfaces with other databases to contribute to international harmonization.
7. Resolve issues related to the co-existence of private profit and public availability of technology in the OoC field.
8. Address upscaling requirements and constraints on design, dimension and structural materials as early as possible in device development to make the right choices for industrial-level fabrication.
9. Encourage multi-partner task forces to come up with well-documented showcases, based on case studies, to stimulate adoption of the OoC technology. EUROoCs should play a leading and catalyzing role in this process.
10. Engage as EUROoCS in a global dialogue on ethical issues and address them timely as the technology progresses.
11. Develop tailored training programs for the next generation OoC researchers.
12. Build the OoC community further and bridge the gap between end users, developers and regulators with the support of EUROoCS.
13. Stimulate information, communication and interaction via the digital platform and targeted meetings of EUROoCS and measure the impact on OoC ecosystem development.
14. Plan a careful dissemination strategy for the general public based on realistic expectations and ambitions.

Acknowledgements

The authors would like to thank the 32 experts that took part in the ORCHID Strategy Workshop. This work was funded by the European Union's Horizon 2020 Research and Innovation program under grant agreement No. 766884.

References

Barrile R., van der Meer A.D., Park H., Fraser J.P., Simic D., Teng F., Conegliano D., Nguyen J., Jain A., Zhou M., Karalis K., Ingber D.E., Hamilton G.A., Otieno M.A. (2018), "Organ-on-chip recapitulates thrombosis induced by an anti-CD154 antibody: translational potential of advanced microengineered systems", *Clin. Pharmacol. Ther. 104, 1240-1248.*

Ewart L, Fabre K, Chakilam A, Dragan Y, Duignan DB, Eswaraka J, Gan J, Guzzie-Peck P, Otieno M, Jeong CG, Keller DA, de Morais SM, Phillips JA, Proctor W, Sura R, Van Vleet T, Watson D, Will Y, Tagle D, Berridge B. (2017), "Navigating tissue chips from development to dissemination: A pharmaceutical industry perspective", *Exp. Biol. & Med. 242, 1579-1585*.

Mastrangeli, M.; Millet, S.; partners, T.O.; van den Eijnden-van Raaij, J. (2019), "Organ-on-Chip In Development: Towards a roadmap for Organs-on-Chip". *Preprints* 2019, 2019030031. DOI: 10.20944/preprints201903.0031.v1.

Osaki T., Uzel S.G.M., Kamm R.D. (2018), "Microphysiological 3D model of amyotrophic lateral sclerosis (ALS) from human iPS-derived muscle cells and optogenetic motor neurons", *Sci Adv. 4, eaat5847*.

Probst C., Schneider S., Loskill P. (2018), "High-throughput organ-on-a-chip systems: Current status and remaining challenges", *Curr. Op. Biomed. Eng. 6, 33-41*

Song J, Miermont A, Lim CT, Kamm RD., "A 3D microvascular network model to study the impact of hypoxia on the extravasation potential of breast cell lines", *Sci Rep.* 2018, 8(1):17949. DOI:10.1038/s41598-018-36381-5.

Vormann M.K., Gijzen L., Hutter S., Boot L., Nicolas A., van den Heuvel A., Vriend J., Ng C.P., Nieskens T.T.G., van Duinen V., de Wagenaar B., Masereeuw R., Suter-Dick L., Trietsch S.J., Wilmer M., Joore J., Vulto P., Lanz H.L. (2018), "Nephrotoxicity and Kidney Transport Assessment on 3D Perfused Proximal Tubules", *AAPS J. 20, 90.*

Wevers N.R., van Vught R., Wilschut K.J., Nicolas A., Chiang C., Lanz H.L., Trietsch S.J., Joore J., Vulto P. (2016), "High-throughput compound evaluation on 3D networks of neurons and glia in a microfluidic platform", *Sci. Rep. 6, 38856.*

Zhang B., Korolj A., Lai B.F.L., Radisic M. (2018), "Advances in organ-on-a-chip engineering", *Nat. Rev. Mater. 3, 257-278.*

Appendix A: White paper on Standardization

Executive Summary

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 Organ-on-Chip (OoC) community can find a basis for standardization in standards already developed in areas of individual components such as sensors, microfluidics and cell cultures. This document aims to introduce the theoretical framework of the process of standardization, its functionality, and a current and future view of standardization efforts related or of importance to the OoC field.

Introduction and Overview

Standardization is the process of developing and implementing specifications based on the consensus of the views of firms, users, interest groups and governments. This process then ensures an optimum degree of order of the rules, guidelines or specifications. In this document, the definition and impact of standardization are introduced, the functions of standardization, and the methodologies to create new standards. Finally, the benefits and pitfalls of standardization in the field of OoC devices and systems are discussed. Further, already running standardization efforts are identified which address certain aspects of technology and operational processes in the OoC field.

1. Definition and impact of standardization on innovation

Standardization is the process of developing and implementing specifications based on the consensus of the views of firms, users, interest groups and governments (Sherif, 2001; Xie, Hall, McCarthy, Skitmore, & Shen, 2016). The resulting standards are intended to promote compatibility, interoperability and quality. Standards can be developed by standard development organizations, such as the International Organization for Standardization (ISO), or independently by companies who have a dominant position in the market (Utterback & Suarez, 1993). The economic cost of inadequate or non-existing standardization in a particular industry can be very high. For example, in the automobile industry in the US, about US$ 1 billion per year is lost due to interoperability problems associated with sharing product and engineering data (Tassey, Brunnermeier, & Martin, 1999).

To understand the functional aspects of technology standards, it is helpful to consider the differences between the supply and demand side. On the supply side, a technology standard represents the synthesis of proven concepts on the design logics to organize the hierarchy and functional parameters of a particular type of product (Narayanan & Chen, 2012; Tassey, 2000; Tushman & Anderson, 1986). On the demand side, it reflects the desire for a consumer or user for agreement on a uniform technological format that allows for integration and interchangeability across multiple end products (Axelrod, Mitchell, Thomas, Bennett, & Bruderer, 1995). Thus, a technology standard represents the collective choice resulting from a balance between utility, technical possibilities and the cost structure of manufacturers on the one hand, and constraints of political, social and economic institutions on the other (Garud, Jain, & Kumaraswamy, 2002; Hargadon & Sutton, 1997; Narayanan & Chen, 2012; Tassey, 2000).

Standards played an important role in the industrial revolution as they allowed companies to achieve economies of scale and enabled markets to execute transactions in an equitable and efficient manner (Tassey, 2000). The traditional economic function of standards can restrict the product choice in exchange

for the cost advantages of scale, but more advanced standards can, on the contrary, facilitate product variety and thus choice.

Although there is a large group of researchers that claims that standardization has a significant positive and accelerating effect on innovation (Hashem & Tann, 2007; Rysman & Simcoe, 2005), there are also other reports claiming that it constrains innovation by hampering creativity and delaying commercialization of inventions (Hamel, 2006; Hill & Rothaermel, 2003). As standardization affects both innovation and technology diffusion, the concern of R&D policy should be the evolutionary path by which a new technology becomes standardized. Standardization can indeed increase efficiency within a technology life cycle, but it can also prolong existing life cycles to an excessive degree by inhibiting investment in technological innovation that creates the next cycle (Tassey, 2000). In the following section, we will elaborate on the functioning of standards, and how to develop them.

2. Standards functions and development methodology

2.1 Functions of standardization

Some of the basic functions of standards can be categorized in 4 groups: *quality/reliability, information standards, compatibility/interoperability, and variety reduction*. A standard that specifies a minimum level of performance often provides the point of departure for competition, which benefits the user or consumer eventually. By reducing the transaction cost between buyer and seller drastically, a range of measurement and test method standards provides information in advanced industries. For R&D processes, an efficient way of working can be obtained by standardizing the scientific and engineering data, and by using standardized equipment calibration techniques. Besides this, real-time monitoring and control of certain processes can eliminate wasted material and increase product mix flexibility (Tassey, 2000).

Standards specify properties that a product must have in order to work with complementary products within a product or service system. Compatibility or interoperability is typically manifested in the form of a standardized interface between components of a larger system. Most commonly, interface standards provide 'open' systems that allows proprietary component designs to coexist. So, they enable innovation at the component level by being competitively neutral with respect to design. Competitors can innovate on either side of the interface leaving the consumer with a choice to select particular components to optimize the system. Standards do limit a product to a certain range or number of characteristics such as size or quality levels. The 4th function is thus the reduction of variety to attain economies of scale. This is achieved by most standards, but not only by treating particular physical dimensions of a product, but also data formats and combined physical and functional attributes.

Standardization is not an all-or-nothing proposition; it typically proceeds in an evolutionary manner. Its patterns are determined by the pace of the technology development and changes in market structure. Government can play an important role in establishing and demonstrating a backbone infrastructure, which in turn promotes private-sector R&D investment in standards to enable effective use of this infrastructure. Innovation in certain markets can be heavily impacted by regulatory instruments. Although regulation often comes with increased costs or restriction in freedom of action, well designed regulation may guide or even force firms to invest in innovative activities (Porter & Linde, 1995). Regulation stems primarily from a top-down approach, while formal standards are typically the result of a market-driven process, or differently put, self-regulation vs. direct governmental regulation. Moreover, regulation is mandatory, while the adoption of formal standards is voluntary. According to Blind *et al.*, in uncertain

markets, the effects of formal standards and regulation in relation to regulatory capture do not differ substantially from each other (Blind & Mangelsdorf, 2016). In uncertain markets, regulators have less access to information than the standard setters, causing an information asymmetry.

2.2 Development of standards

ISO is an independent, non-governmental organization with members being the standard organizations of the 162 member countries. It is around since 1926 and is the largest developer of international standards, with over 20,000 standards been set up. Other technology standard organizations are the Institute of Electrical and Electronics (IEEE), Internet Engineering Task Force (IETF), and 3rd Generation Partnership Project (3GPP). Like a symphony, it takes a lot of people working together to develop a new standard. The role of the standard development organization is to conduct this process, while the orchestra is made up of independent technical experts[6]. These experts form then a technical committee that is responsible for a specific subject area. They begin the process by developing a draft that meets a specific market need. This is then shared for commenting and further discussion.

The voting process in the technical committee is key to achieve consensus on the standard development. If no agreement is reached, the draft will be modified further, and voted on again. In the experience of ISO, developing a standard typically takes about 3 years. Figure 1 shows the main stages in the process of ISO.

[6] Available at: ISO (accessed: March 19, 2019).

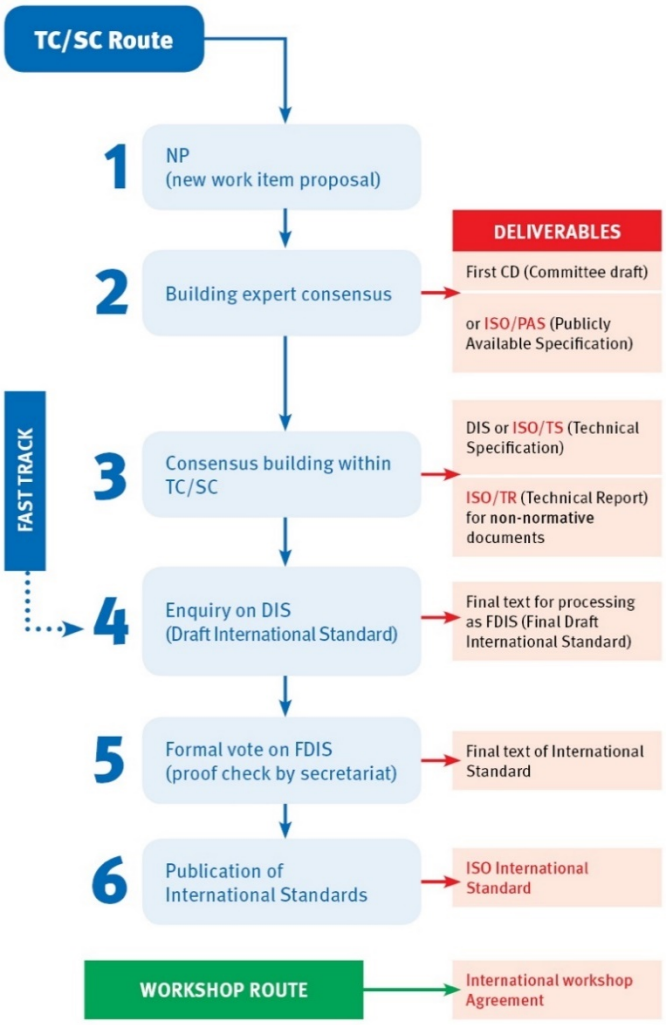

Fig. A1. ISO standards development process.
(TC): a Technical Committee, which develops standards in a certain sector or industry
(SC): a Subcommittee, which addresses a specialized area within a TC

The key principles in standard development can be summarized in the following 4 items:

1. ISO standards respond to a need in the market

The request to develop a new standard always comes from industry or other stakeholders. In the process, a member of the stakeholder group contacts the national member of ISO, who then contacts ISO.

2. ISO standards are based on global expert opinion

ISO standards are developed by groups of experts from all over the world as part of larger groups called technical committees. These experts negotiate all aspects of the standard, including its scope, key definitions and content.

3. ISO standards are developed through a multi-stakeholder process

The technical committees are made up of experts from the relevant industry but also from consumer associations, academia, NGOs and government.

4. ISO standards are based on a consensus

Developing ISO standards is a consensus-based task. Comments from all stakeholders are considered.

In the electronics industry, the Semiconductor Equipment and Materials International (SEMI) is an organization that provides industry stewardship and engages its members to advance the interests of the global electronics supply chain. SEMI has a standards program which is also one of their key services for the benefit of the worldwide semiconductor, photovoltaic LED, MEMS and flat panel display industries. The program started over 40 years ago in North America but was expanded in 1985 to include worldwide programs. It operates as a neutral forum for the exchange of information among suppliers and users resulting in the production of timely and technically accurate specifications and other standards of economic importance to the industry. Over 5,000 technologists representing both device manufacturers and equipment and materials suppliers participate in the program.

The SEMI standards program provides a framework and procedures for industry experts to meet, discuss, and develop essential standards and guidelines. Once the need for a standard has been identified with appropriate input from the user community, a task force is assembled to carry out the development effort. The result of this process is a draft document, which is then reworked until consensus is reached. The consensus is then reported regionally to obtain comments from other members. When that stage finishes, the worldwide balloting process is initiated to search for global consensus.

The new standard is then communicated to the industry and users are advised to cite and utilize them, although the use is entirely voluntary. Management of the program is provided by industry volunteers serving on administrative Regional Standard Committees in North America, Europe, and Japan. The international Standards Committee has the overall responsibility for the conduct of the program. It establishes the regulations governing the program procedures and maintains relationships with other standard-setting organizations worldwide[7].

3. Standardization for lab-on-chip and organ-on-chip devices

3.1 Debate and ongoing efforts

As lab-on-chip (LoC) technology matures, there is a growing debate about standardization. As previously discussed, there are advantages and disadvantages of standardization and their impact on innovation. This has led to different views on whether standards need to be developed for microfluidic devices (Klapperich, 2009; Van Heeren, 2012; Zengerle, 2007). Microfluidic technology is the heart of a LoC device, and also forms a crucial aspect of OoC devices.

One of the key points that hamper standardization efforts is the lack of vocabulary for microfluidics. Before reaching a standard for a product, testing standards have to be developed. Testing standards enable an objective comparison between the data sheets of competing products, independently of any specified technical requirement for the product. A variety of testing standards have been suggested already[8,9] based on the current need for methods to measure *e.g.* the internal dimensions of microfluidic devices, solution temperature, electroosmotic mobility, zeta potential and autofluorescence (Stavis, 2012).

[7] Available at: SEMI (accessed: March 19, 2019)
[8] iNEMI Technology Roadmap, MEMS Technology Working Chapter 2011.
[9] SEMI International Standards, Technical Committee Charter, Charter of Global MEMS/NEMS Committee.

One of the key features under discussion is the standardization of interconnects, connections made to/from microfluidic devices (Fredrickson & Fan, 2004). One of the remaining issues to be solved is what aspects of interconnects should and can be standardized. A possible solution is to make a strong link between microfluidic interconnects with existing standards already found in laboratory equipment such as (mini)Luer connections to microscope slides or microtiter plates (Harink, Le Gac, Barata, Van Blitterswijk, & Habibovic, 2014; Van Heeren, 2012). Still, following that trajectory might lead to increasing costs. The effort of attempting to publish document standards has led to the creation of a working group in ISO, CEN/TC 332 (WG 7 micro process engineering), and subsequently the publication of a document entitled *"Micro process engineering – vocabulary" (ISO 10991 2009).* Additionally, there is a DIN (Deutsches Institut für Normung) standardization group on characterization for microreactors.

Ongoing efforts exist between stakeholders from the Microfluidics Consortium[10] and consortium partners of an EU project called MFmanufacturing[11], some national groups and SEMI. A questionnaire was sent around, and responders consisted of small-medium enterprises (SMEs) for about 50% and research laboratories (a quarter). The rest of the responders consisted of large enterprises and other research organizations. The discussion has identified several implementations of connectors in microfluidic devices and it was found that, for example, connectors should be easy to plug, be removable and reusable. Another outcome identified the need to have the microfluidic connector be easily combined with other connectors such as electrical and optical. Further, because of the growing trend of miniaturization, smaller components and thus smaller pitch spacing dimensions are needed. The MFmanufacturing project defined a specific standard pitch spacing based on a 0.75mm grid using multiples of 0.75. Another outcome of discussions among stakeholders identified the need for edge connectors and reliability (van Heeren, Tantra, & Salomon, 2015). From the need of reliability in turn the need to develop suitable testing schemes arises. A common testing strategy can also speed up the process of testing and limit duplication efforts, eventually leading to harmonization on activity on a global scale.
In a simplified view, adding of cell cultures to microfluidic lab-on-chip devices has led to the development of organ-on-chip systems. Indeed, with the advent of human stem cell-based cell cultures, study and testing of human physiology and pathophysiology in a dish has become reality. A key challenge, though, is the quality control and lack of standards in cell culture in terms of *e.g.* protocols and reference cell lines. Besides the cells themselves, *in vitro* culture conditions also need standardization: culture medium, medium conditions, frequency of replenishment. Operations linked to cell culture include cell culture handling and maintenance, antibiotics use, and are also of great importance in the process of standardization.

The International Society for Stem Cell Research (ISSCR) has historically developed guidelines that address the international diversity of cultural, political, legal, and ethical perspectives related to stem cell research and its translation to medicine. The guidelines were updated in 2016 to encompass a broad and expansive scope of research and clinical endeavor, imposing rigor on all stages of the research, addressing the costs of regenerative medicine products, and highlighting the need for accurate and effective public communication[12]. However, standardization is implemented to a very limited degree so far, especially in the field of induced pluripotent stem (iPS) cells, which is strongly linked to the OoC technology.

[10] Available at: Microfluidics Consortium (accessed: March 19, 2019).
[11] Available at: Mf-manufacturing (accessed: March 19, 2019).
[12] ISSCR Guidelines for Stem Cell Research and Clinical Translation

3.2 Steps towards harmonization

For LoC devices, and more in particular microfluidic chips, a first step towards harmonization is the development of a generic classification system which is independent of the application. One potential way to do this is by classifying microfluidic devices according to certain similarities, for example according to the temperature and pressure under which they have to operate. A recent example of a path towards standardization of microfluidics was presented by Dekker *et al.*, where a modular toolbox of microfluidic components was demonstrated, and which standardization effort was backed up by the MFmanufacturing consortium (Dekker et al., 2018). A combination of microfluidic building blocks (MFBB) and fluidic circuit boards (FCB) designed and fabricated according to guidelines which have been documented in an ISO workshop agreement[13]. Interoperability is key to make this concept work. Therefore, the outside dimensions are standardized according to a grid. A library of CAD based designs is available for any designer to develop specific devices with unique physical dimensions, while decoupling this from the functional design. This approach is very similar to methods used in the electronics industry.

In the field of cell culture-based systems, harmonization was found by a group of stakeholders seeking a set of specialized standards to ensure quality in cell culture-based systems and tools. The recently approved OECD Guidance Document on Good In Vitro Method Practices (GIVIMP)[14], coordinated by the European Commission Joint Research Centre's EU Reference Laboratory for alternatives to animal testing (EURL ECVAM), provides a framework of technical and quality practices to help ensure that the overall development and implementation of in vitro methods is of scientific integrity and of the highest quality possible. While the guidance is intended for all OECD member states and encompasses a wide range of audiences including method developers, validation bodies and end users, its greatest impact may be in regions where *in vitro* methods are just beginning to take root. GIVIMP tackles the following key aspects related to in vitro work: (1) Roles and responsibilities, (2) Quality considerations, (3) Facilities (4) Apparatus, material and reagents, (5) Test systems, (6) Test and reference/control items, (7) Standard operating procedures (SOPs), (8) Performance of the method, (9) Reporting of results, (10) Storage and retention of records and materials. The document identified quality requirements for equipment, material and reagents (*e.g.*, cell line authentication, cell purity, stability and functional integrity, testing for microbial contaminations, use of serum, alternatives to the use of animal sourced serum, antibiotics, special media, certificate of analysis, stability and traceability). Within GIVIMP, there are relevant annexes such as the Good Cell Culture Practice (GCCP), established to reduce the risk of generating erroneous data as well as worker health issues and legal liabilities (Coecke et al., 2005), the Good Cell Culture Practice for stem cells and stem-cell-derived models (Pamies et al, 2017), and mentions to standardization and accreditation bodies as well as to Good Laboratory Practice (GLP).

3.3 Standardization for the OoC field

The OoC field is a young but fast developing field. The industry today is consisting mainly of start-ups and many developments are still in a research phase. However, individual technology and biology components and operational processes of the OoC systems have been around much longer, and standardization efforts can be found (see above; microfluidics). The challenge for the OoC field will be integrating these components and adapt existing standards to the more complex nature of the OoC

[13] IWA 23, Interoperability of Microfluidic Devices – Guidelines for Pitch Spacing Dimensions and Initial Device Classification, 2016

[14] *Guidance Document on Good In Vitro Method Practices (GIVIMP)*, OECD Series on Testing and Assessment, No. 286, OECD Publishing, Paris. Available at: https://doi.org/10.1787/20777876 (accessed: March 27, 2019).

technology. Ongoing harmonization in the field of microfluidics and cell culture, and existing standards in the electronics industry can represent a strong base for guidelines in the OoC field[7,8]. Moreover, efforts initiated by regulatory stakeholders, industry and academic labs by a need for novel regulation, such as novel ICH (E14, S7B) guidelines for cardiotoxicity as presented by the CIPA initiative[15], can possibly overcome the challenges that are related to an immature and uncertain market (see above), and drive standardization in the field.

The electronics industry follows strict roadmaps in terms of technology nodes, packaging, handling, etc. OoC systems can benefit from these standardization efforts by adopting those standards (see IEEE, SEMI) for the development of new sensor/actuator technology. Currently, there is a myriad of sensor implementations, few of which are based on standardized fabrication flows. Interaction with stakeholders or technical experts in the SEMI organization represents an opportunity for OoC developers to seek harmonization.

Regarding standardization of cell cultures and operations related to them, OoC systems can build readily on efforts already developed by the toxicology and stem cell research community, and which are embedded in the OECD guidance document GIVIMP, GCCP documentation and ISSCR guidelines[7]. Specific guidelines related to OoC systems are already described in the GCCP document, and challenges for the OoC field are defined as: (1) the lack of detailed understanding of some human organs and tissues, (2) complexity of protocols, (3) expensive technologies, (4) requirement of precise cellular manipulation, (5) reproducibility of the systems. Further, there are also training/education guidelines described in the GCCP document: iPSC differentiation protocols, co-culture of differentiated cells, the use of microfluidics in combination with cells are the main challenges (Pamies & Hartung, 2017).

In analogy to many existing overarching organizations in different fields of research and development driving standardization efforts, the newly founded European Organ-on-Chip Society (EUROoCS)[16] can play a role in mediating and facilitating standards in the field of OoC by bringing together stakeholders of industry, regulators, academia, clinicians and patient organizations. Thereby it will be important to keep its actions open to the international OoC community and search for international harmonization of guidelines.

To move OoC technology towards standardization, the OoC community (stakeholders, national and international societies) needs to get organized to reach a common goal. Regular meetings between Key Opinion Leaders (KOL) from industry, regulatory bodies, academia, clinics, and patient organizations should be organized to discuss standardization in detail. This working group can then disseminate the outcome of the meetings, *i.e.* report on the discussion points and if possible, formulate guidelines.

Standardization can be a step towards open technology platforms, as criteria defined in the guidelines can result in common design environments and building blocks (cfr. Microfluidics). As described above in the theoretical framework and from learnings of other industries (such as the automobile), the earlier efforts are taken up for standardization, the easier implementation will be. Further, this would also translate in a more efficient spending of available development costs, and thus have a distinct influence on the level of maturity of the field.

Within EUROoCS, a standardization workgroup/committee, consisting of KOL's of different stakeholder groups, can take up the role to drive standardization effort. The committee could meet on a regular basis to identify standardization needs and could invite relevant stakeholders from academics, industry or regulatory bodies to aid the process.

[15] CIPA
[16] EUROoCS press release, available at: EUROoCS

Conclusion

Standardization in relatively new industries can be driven by government, a changing regulatory landscape or a dominant player. The young OoC field is defined by several small companies and a growing academic crowd. Pharmaceutical industry as end users and regulatory bodies are closely involved in several initiatives. OoC technologies, however, can build upon established standardization efforts related to its subcomponents such as microfluidics and stem cell technology. Finally, a leading role in terms of standardization could be taken up by the EUROoCS consortium, considering international initiatives, so that guidelines are harmonized on a global scale.

References

Axelrod, R., Mitchell, W., Thomas, R. E., Bennett, D. S., & Bruderer, E. (1995). Coalition formation in standard-setting alliances. *Management …*. https://doi.org/10.1287/mnsc.41.9.1493

Blind, K., & Mangelsdorf, A. (2016). Motives to standardize: Empirical evidence from Germany. *Technovation*. https://doi.org/10.1016/j.technovation.2016.01.001

Coecke, S., Balls, M., Bowe, G., Davis, J., Gstraunthaler, G., Hartung, T., … Stokes, W. (2005). Guidance on good cell culture practice: A Report of the Second ECVAM Task Force on good cell culture practice. *ATLA Alternatives to Laboratory Animals*. https://doi.org/papers3://publication/uuid/9D1057FB-0497-414E-81A3-D17499D13A0F

Dekker, S., Buesink, W., Blom, M., Alessio, M., Verplanck, N., Hihoud, M., … Odijk, M. (2018). Standardized and modular microfluidic platform for fast Lab on Chip system development. *Sensors and Actuators, B: Chemical*. https://doi.org/10.1016/j.snb.2018.04.005

Fredrickson, C. K., & Fan, Z. H. (2004). Macro-to-micro interfaces for microfluidic devices. *Lab on a Chip*. https://doi.org/10.1039/b410720a

Garud, R., Jain, S., & Kumaraswamy, A. (2002). Institutional entrepreneurship in the sponsorship of common technological standards: The case of Sun Microsystems and Java. *Academy of Management Journal*. https://doi.org/10.2307/3069292

Hamel, G. (2006). The why, what, and how of management innovation. *Harvard Business Review*. https://doi.org/10.1080/09537320802557384

Hargadon, A., & Sutton, R. I. (1997). Technology Brokering and Innovation in a Product Development Firm. *Administrative Science Quarterly*. https://doi.org/10.2307/2393655

Harink, B., Le Gac, S., Barata, D., Van Blitterswijk, C., & Habibovic, P. (2014). Microtiter plate-sized standalone chip holder for microenvironmental physiological control in gas-impermeable microfluidic devices. *Lab on a Chip*. https://doi.org/10.1039/c4lc00190g

Hashem, G., & Tann, J. (2007). The adoption of ISO 9000 standards within the Egyptian context: A diffusion of innovation approach. *Total Quality Management and Business Excellence*. https://doi.org/10.1080/14783360701349435

Hill, C. W. L., & Rothaermel, F. T. (2003). The performance of incumbent firms in the face of radical technological innovation. *Academy of Management Review*. https://doi.org/10.1016/j.jala.2010.03.003

Klapperich, C. M. (2009). Microfluidic diagnostics: Time for industry standards. *Expert Review of Medical Devices*. https://doi.org/10.1586/erd.09.11

Narayanan, V. K., & Chen, T. (2012). Research on technology standards: Accomplishment and challenges. *Research Policy*. https://doi.org/10.1016/j.respol.2012.02.006

Pamies, D., & Hartung, T. (2017). 21st century cell culture for 21st century toxicology. *Chemical Research in Toxicology*. https://doi.org/10.1021/acs.chemrestox.6b00269

Pamies, D., Bal-Price, A., Simeonov, A., Tagle, D., Allen, D., Gerhold, D., Yin, D., Pistollato, F., Inutsuka, T., Sullivan, K., Stacey, G., Salem, H., Leist, M., Daneshian, M., Vemuri, M., McFarland, R., Coecke, S., Fitzpatrick, S., Lakshmipathy, U., Mack, A., Wang, W., Yamazaki, D., Sekino, Y., Kanda, Y., Smirnova, L. and Hartung, T. (2017). Good Cell Culture Practice for stem cells and stem-cell-derived models. *ALTEX - Alternatives to animal experimentation*. 34, 1 (Feb. 2017), 95-132. DOI: https://doi.org/10.14573/altex.1607121.

Porter, M. E., & Linde, C. van der. (1995). Toward a New Conception of the Environment-Competitiveness Relationship. *Journal of Economic Perspectives*. https://doi.org/10.1257/jep.9.4.97

Rysman, M., & Simcoe, T. (2005). *Patents and the Performance of Voluntary Standard Setting Organizations*. *SSRN*. https://doi.org/10.2139/ssrn.851245

Sherif, M. H. (2001). A framework for standardization in telecommunications and information technology. *IEEE Communications Magazine*. https://doi.org/10.1109/35.917510

Stavis, S. M. (2012). A glowing future for lab on a chip testing standards. *Lab on a Chip*. https://doi.org/10.1039/c2lc40511c

Tassey, G. (2000). Standardization in technology-based markets. *Research Policy*. https://doi.org/10.1016/S0048-7333(99)00091-8

Tassey, G., Brunnermeier, S. B., & Martin, S. A. (1999). Interoperability cost analysis of the US automotive supply chain. *Research Triangle Institute Final Report. RTI Project*. https://doi.org/10.1002/pro.75

Tushman, M. L., & Anderson, P. (1986). Technological Discontinuities and Organizational Environments. *Administrative Science Quarterly*. https://doi.org/10.2307/2392832

Utterback, J., & Suarez, F. (1993). Innovation, competition, and market structure. *Research Policy*.

Van Heeren, H. (2012). Standards for connecting microfluidic devices? *Lab on a Chip*. https://doi.org/10.1039/c2lc20937c

van Heeren, H., Tantra, R., & Salomon, P. (2015). Microfluidic devices: a road forward by standardization of interconnects and classification. *Microfluidics and Nanofluidics*. https://doi.org/10.1007/s10404-015-1639-4

Xie, Z., Hall, J., McCarthy, I. P., Skitmore, M., & Shen, L. (2016). Standardization efforts: The relationship between knowledge dimensions, search processes and innovation outcomes. *Technovation*. https://doi.org/10.1016/j.technovation.2015.12.002

Zengerle, R. (2007). Microfluidic platforms for lab-on-a-chip applications - Lab on a Chip (RSC Publishing) DOI:10.1039/B706364B. *Lab on a Chip*.