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Organ on chip: building a roadmap towards standardisation

Putting Science into Standards

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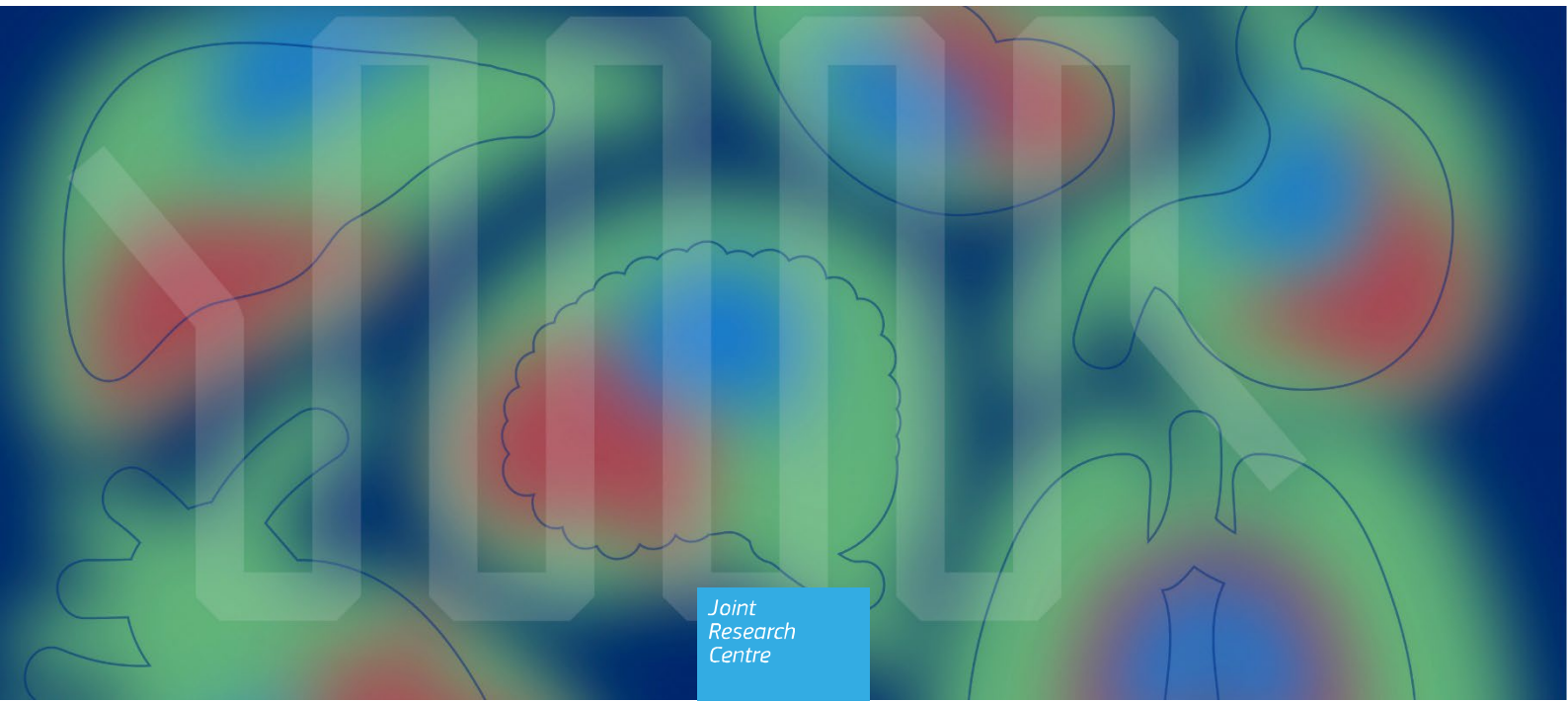

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Contents

Abstract

For Organ on Chip (OoC) there is a widespread opinion, that standardisation is an important enabler for innovation, supporting the development and application of devices through performance assessment and benchmarking, interoperability, and qualification for different contexts of use. In a two days "Putting Science into Standards" workshop the initial steps towards a standardisation roadmap were discussed and analysed, resulting in the recommendation to the European standardisation organisations to establish a dedicated platform for OoC technologies, with the aim of formulating a standardisation roadmap. The example serves for the European Commission's Research and Innovation policy makers and European Health and Digital Executive Agency to recognise the importance of standards in the valorisation of research results.

Foreword

More than eight years ago, the European Committee for Standardization, the European Committee for Electrotechnical Standardization and the Joint Research Centre of the European Commission initiated the Putting-Science-Into-Standards annual workshop series, bringing the scientific, industrial, and standardisation communities together. These workshops aim at facilitating the identification of emerging science and technology areas that could benefit from standardisation activities to enable innovation and promote industrial competitiveness. Seven workshops have been held since 2013 in different fields of science.

This year's Putting-Science-Into-Standards Workshop on Organ-on-Chip (OoC) anticipated future standardisation needs and kick-started a forum for the discussion of priorities, particular technologies and the drafting of a potential standardisation roadmap.

The European Society of Organ-on-Chip (EUROoCS) and its sponsor European Commission's Directorate-General Research and Innovation profited from the Joint Research Centre's unique position of being on the one side integrated in the science community, and on the other side active in technical committees of European and International Standardisation Organisations and other standardisation bodies.

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The workshop would not have been a success without the contribution of JRC colleagues Angel Alvarez Martinez, Samira Nik, Ana Maria Martin and Els Somers.

Executive summary

Organ-on-Chip (OoC) devices or tissue chips, which are part of the family of Microphysiological Systems (MPS), have received considerable attention in recent years because of their potential in various scientific fields. An OoC refers to a fit-for-purpose microfluidic device, containing living engineered organ substructures in a controlled microenvironment. The aim of an OoC is to replicate one or more aspects of the organ's dynamics, functionality and (patho) physiological response *in vivo*.

On 28 April 2021 more than 250 experts from 33 countries out of 21 EU Member States working on the OoC technology gathered at the 7th 'Putting Science into Standards' Workshop to complete the pathway of innovation by bringing scientific findings and innovations to the market.

Policy context

In different generations of the Framework Programmes for Research and Technological Development, valorisation of the research results have been followed in some case actively, in others passively. Standardisation is one of the pathways to leverage valorisation.

The Future and Emerging Technologies (FET) Flagship Organ-on-Chip in Development (ORCHID) involved 75 stakeholders aimed to promote the technology and elaborate a research and development roadmap. The outcome was the establishment of the European Organ-on-Chip Society (EUROoCS). The society recognised that tackling standardisation could be instrumental in building the necessary trust of the end-user community and leverage the research results and applications towards an accelerated marked uptake.

This report demonstrates the importance of linking standardisation with investments in research and development, providing a relevant case study in the field of technological innovation for chemical safety, drug development and biomedical research.

Key findings

The two-day workshop demonstrated the vast potential and timeliness that standardisation can contribute to valorise research output from European research projects. In the OoC community there is widespread agreement that standardisation is an important enabler for innovation, supporting the development and application of devices in several ways. These include performance assessment and benchmarking, interoperability, and qualification for different contexts of use. Standards can also improve communication among stakeholders, for example by providing agreed terminology and reporting methods.

There is also a high willingness to create collaborative platforms between the research community and end users of OoC applications, including industry and small and medium size enterprises. The workshop resulted in the recommendation to the European Standardisation Organisations to create within their structures such a dedicated platform with the task to elaborate a standardisation roadmap.

The JRC is actively involved in working groups of the European Organ-on-Chip Society and collaborates closely with the European standardisation organisations CEN and CENELEC. The JRC pursues the follow up of the recommendations to promote the setting up of a dedicated platform as provided in this report.

CEN and CENELEC is preparing the set-up of a platform, potentially a CEN CENELEC Focus Group to map and coordinate standardisation efforts relevant to the field of OoC as a direct outcome of the workshop.

1 Introduction

A microphysiological system (MPS)[1] uses microscale cell culture platforms for *in vitro* modelling of functional features of a specific tissue or organ of human or animal origin. Among MPS, organ-on-a-chip (OoC) is a miniaturized physiological environment engineered to yield and/or analyse functional tissue units capable of modelling specified/targeted organ-level responses (Figure 1).

The development of OoC, bringing technology and biology together, started in universities about 15 years ago, but in the past few years the field has rapidly expanded, thanks to an increasing need for better model systems in pharmaceutical and other industry, as well as an increasing pressure to reduce animal experiments.

OoC includes a wide range of different technologies of varying complexity and their range of applicability typically varies based on the organ function that is mimicked. The development of OoC requires a wide range of different technologies of varying complexity and the application domains goes from toxicity testing, drug discovery and development (including biokinetics), to personalised medicine. The use of these technologies is also relevant for biomedical research and disease modelling, enabling the study of the mechanisms of specific pathologies, such as cancer and neurodegenerative disorders, and as a basis for new therapies.

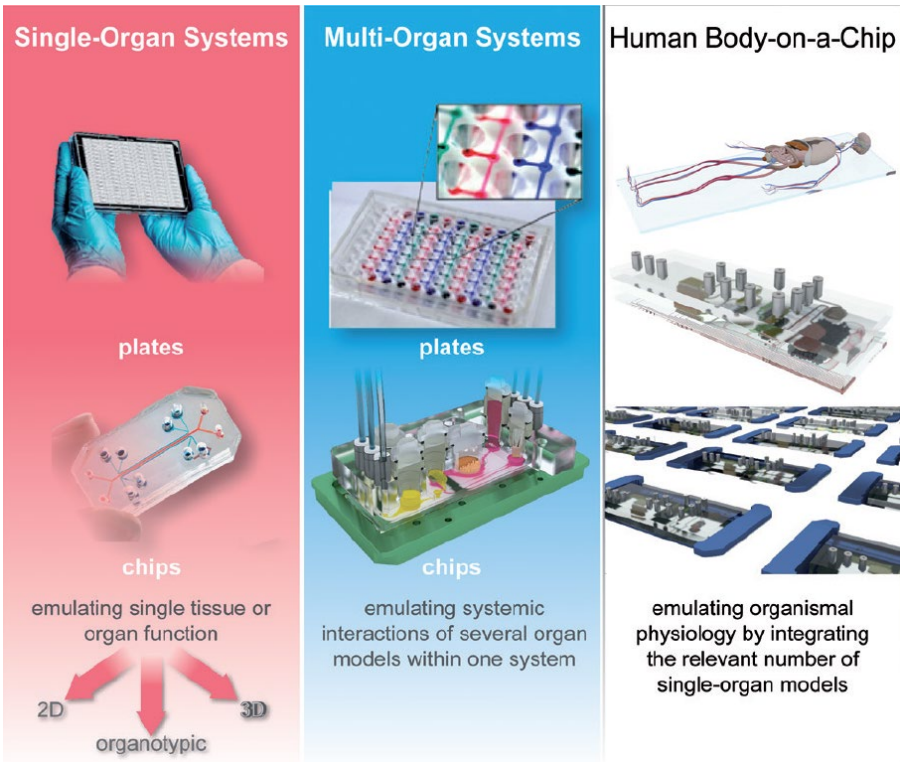

Figure 1. OoC types with focus on single organs, multiple organs with relevant interaction and full body emulation. Source: (Marx, et al., 2016).

OoC is ranked in several foresight exercises among the top emerging technologies (World Economic Forum's Meta-Council on Emerging Te, 2016), with the expectation that OoC will lead to:

- More human-relevant approaches in biomedical research;
- Faster, cheaper and more effective pre-clinical evaluation of new drugs;
- Better ways to assess the potential health effects and toxicity of drugs, chemicals, food products and cosmetics;
- Acceleration of drug repurposing;
- Refinement, reduction and replacement of animal testing.

The rapid progress in this field has revealed new challenges and opportunities, and expertise from several technological fields is required to realize the market uptake of translational applications (Low, Mummery,

[1] Advancing Alternative Methods at the United States of America Food and Drug Administration definition (FDA)

Berridge, Austin, & Tagle, 2021). Considerable international interest and funding in OoC has resulted in some companies being already able to offer products at high Technological Readiness Level (TRL 7/8) for specific applications. However, the majority of the devices are still being developed and tested in research laboratories and start-ups (TRL 3/4).

Pre-normative work performed by European and international consortia indicates that standardisation should be a cornerstone for the advancement of OoC technology and its efficient transfer into promising areas of application (Piergiovanni, Leite, Corvi, & Whelan, 2021). It is expected that standardisation activities will:

- Increase implementation of OoC in current and future regulatory frameworks.
- Allow OoC to be used in emergency situations for rapid development and testing of drugs and vaccines.
- Strengthen Europe's position as the leader in finding better alternatives to the use of animals for scientific purposes.
- Facilitate production and upscaling of OoC and reduce the costs.
- Support European OoC start-ups to bridge the 'valley of death' in shorter timeframes and with lower costs, reaching commercialisation and increasing their market share.

The European Commission's Joint Research Centre (JRC) and the European standardisation organisations, the European Committee for Standardization (CEN) and the European Committee for Electrotechnical Standardization (CENELEC), carry out an annual 'foresight on standardisation' action with the aim of Putting (more) Science into Standards (PSIS). This initiative is a unique opportunity to gather stakeholders from different fields to identify the issues and priorities, share views on future developments and stakeholder needs, and to provide recommendations to CEN and CENELEC on possible next steps.

The topic for the 2021 workshop was Organ-on-Chip, taking place online on 28 and 29 April (Piergiovanni, et al., 2021). After a first day of setting the scene to bring all stakeholders on the same ground, the workshop was organised in three tracks representing the main pillars of OoC: life science, engineering, and regulatory and data reporting. Through a panel discussion and interaction with the participants, gaps and needs in terms of timing and specific classes of standards were discussed. A final panel discussion was focused on proposing ways forward in standardisation.

1.1 The present and future of Organ on Chip

There is lack of qualified models for human organs and tissues and the majority of the models do not include aspects like mature cells, vascular flow, immune cells, physiological tissue elasticity and mechanical stimuli. To advance in this direction, OoC technology integrates a set of key enabling technologies ranging from microfluidics, surface technology, materials, sensors, mechanics and (human) stem cell technologies, and also manufacturing technology for production and upscaling purposes. There are many types of OoC, each of them with very specific features tailored on the context of use they address: single organ and multi organ (connecting two or more organs to allow for systemic interaction) systems, with studies ongoing towards the human body-on-chip.

In order to overcome technical and biomedical challenges and to reach consensus for vocabulary, metrology, experimental methods, and interoperability solutions, a unique blend of expertise is required, particularly from the domains of life sciences, engineering and ICT. The different stakeholders in the OoC field, including end users, developers and regulators, have expressed their vision on the future of OoC, provided recommendations for standardisation and qualification for a specific context of use, defined technical and biomedical challenges and offered solutions (Mastrangeli, Millet, The ORCHID partners, & Van den Eijnden-van Raaij, 2019a) (Marx, et al., 2020) (Fabre, et al., 2020). Among these initiatives, the ORCHID (Organ-on-Chip In Development) project resulted in the development of the European Organ-on-Chip Roadmap and the establishment in 2018 of the European Organ-on-Chip Society (EUROoCS), an independent, non-for-profit organisation aiming to encourage and develop OoC research and provide opportunities to share and advance knowledge and expertise in the field towards better health for all (Mastrangeli, et al., 2019b). EUROoCS is recognised as the organisation that can facilitate and stimulate the dialogue between developers, regulators and end users in the standardisation and qualification process in a community effort towards adoption of OoC.

In the field of standardisation, ongoing initiatives include a 'smart' multiwell plate[2], an autonomous system containing micropumps and microfluidic infrastructure that is fully compatible with biological and pharmaceutical workflows and can contain different chips within a modular framework. A translational OoC platform (TOP)[3] provides an infrastructure for automated microfluidic chip control and enables academic and commercial chip developers to transform their OoC to 'plug and play' formats. From the biological perspective, the Comprehensive in-vitro ProArrhythmia assay (CiPA)[4] initiative on methods improves the accuracy in predicting cardiotoxicity of drugs. Moreover, the International Society for Stem Cell Research (ISSCR)[5] is involved in standardisation, in particular in drafting guidelines for 'clinical translation of stem cells'.

1.2 What are standards and what are they good for?

A standard is a uniform and workable solution to a recurring problem. They are often developed in a consensus-based manner from science, with the aim of improving quality, safety and reliability. There are different types of standards: product, process and management standards. Standards can also cover requirements, terminology, symbols, materials, test methods and many more. While they can be developed on national, European, and international[6] levels by Standards Developing Organisations, agreements exist to ensure collaboration (the Vienna agreement on technical cooperation between ISO and CEN, for example), as well as to provide a system for new proposal, revision and publication of documents.

> Standards are documents that provide requirements, specifications, guidelines or characteristics that can be used to ensure that materials, products, processes and services are consistently fit for purpose. European Standards are established by consensus and formally approved by European Standards Organisations. These standards serve to make the EU and us safer, stronger, and more secure.

In the life science area, standardisation creates benefits by enabling comparable research, complying with legislation (as in the *in vitro* diagnostics regulation and medical device regulation), increasing patient safety and safe data sharing, fostering innovation and showing best practices. The international committees for standardisation in biotechnology[7] and in health genomics informatics[8] are noted as particularly relevant committees for OoC.

1.3 Standardisation in the pharmaceutical sector

Pharmaceutical R&D processes typically starts with target characterisation followed by drug discovery, through lead optimisation, subsequently succeeded by preclinical and clinical development. Biological assays serve different purposes based on where they fit in the R&D process. New technologies often enter the pipeline as exploratory tools in the research process. For instance, exploratory *in vitro* safety assays are used for early (human specific) hazard identification. These assays, which may include OoC, are not formally validated and their use is typically driven by in-house experiences to guide internal decision-making. For this reason, they are currently rarely used in the context of regulatory submissions. On the contrary, regulatory assays are mandatory for safety risk assessment and regulatory decision-making. These assays always require full Good Laboratory Practice (GLP) compliance.

OoC is a promising technology which pharmaceutical industry is starting to adopt to elucidate specific questions. For instance, OoC could be used to deal with conflicting results obtained from *in vitro* and animal *in vivo* assays, identifying species specificity (Steger-Hartmann & Raschke, 2020). However, due to a lack of qualified assays with scientifically proven robustness, unclear applicability domains and poor experience with the technology, pharmaceutical industry is adopting OoC only slowly.

When discussing standardisation needs, it is important to remember that the pharmaceutical industry is heterogeneous: different qualification needs may apply to different contexts of use. As reported by a major pharmaceutical company, OoC are mainly used for internal portfolio decision-making but there has been a recent example of an OoC study performed to respond to a specific request by US Federal Drug Administration (FDA). The activities are mainly performed in collaboration with platform providers, using pre-qualified models

[2] https://moore4medical.eu/
[3] Translational OoC platform (TOP) https://top.hdmt.technology/
[4] Comprehensive in-vitro ProArrhythmia assay (CiPA) https://cipaproject.org/
[5] International Society for Stem Cell Research (ISSCR) https://www.isscr.org/
[6] International Standardization Organisation (ISO) https://www.iso.org/ and International Electrotechnical Commission (IEC) https://www.iec.ch/
[7] Technical Committee 276 (ISO/TC 276) Biotechnology
[8] Technical Subcommittee 215/SC1 (ISO/TC 215/SC 1) Health informatics: Genomics informatics

that can be adapted to fit customer's need. Apart from the characterization of the model and assay to answer a specific scientific question, a fit-for-purpose qualification also includes external aspects, *e.g.* to secure a proper legal frame, the availability of the laboratory infrastructure, including staff and maintenance of equipment, and typically includes the testing of relevant reference compounds.

1.4 Standardisation for regulatory frameworks

The European Commission acts as the policy and regulatory body for Europe's single market and thus for its goods, finances, and workers.

CEN and CENELEC are recognized by the EU and European Free Trade Association (EFTA) as European Standardization Organizations responsible for developing standards at European level[9] through a process of collaboration among experts nominated by business and industry, consumer and environmental organizations, trade unions and other stakeholders.

CEN and CENELEC also work to promote the international alignment of standards in the framework of technical cooperation agreements with ISO and IEC.

The European Standardization System provides an invaluable contribution to the economic and social well-being of Europe and to the well-functioning of the Single Market. With more than 60,000 technical experts, predominantly from industry, CEN and CENELEC are focused on supporting industry partners to develop the standards they need for their long-term success.

Europe's standardization system is founded on a unique private/public partnership, with the European Standardisation Organisations allowing stakeholders to develop standards for the Commission. Harmonised European Standards are developed to support part of EU law and they are used by manufacturers to demonstrate that they comply with relevant regulations (*i.e.* medical devices, toys, machinery, energy efficiency…) and have immediate access to the 27 European markets. Developing these standards will ensure human safety, but also environmental protection and, most importantly, it will guarantee that the product actually works. The EU standardisation system also grants companies an easy access to the Single Market and acts as a leverage for international activities.

[9] EU Regulation 1025/2012

2 Mapping standardisation opportunities for OoC

For OoC devices, the use and development of standards can support multiple activities, ultimately leading to the demonstration of their technological and biological relevance. Firstly, standardisation should support characterisation. There is a common need for clear descriptions of the OoC system, with all its technical and biological components. This includes recommended operating conditions, protocols and Standard Operating Procedures (SOPs), which guarantee a proper functioning of the device. Moreover, the expected performance should also be assessed in terms of both technical parameters (*e.g.* fluid flow, pressure …) and biological parameters. And finally, there is a need for suitable test methods to verify that those expected performances are actually met. Secondly, standards are tools to compare. Comparison should be performed in an organised and open source way, making sure that the same parameters are measured with the same units of measure. Last but not least, standards enable a correct and efficient communication with the stakeholders. Even if sometimes underestimated, structured reporting of results is a crucial point in the communication effort, especially in the scientific and regulatory community. For an assessment of the results, it is important not only to report results, but also give a description of the test method and details on how the study was performed. Uniformity of terminology, classification criteria and performance indicators, for instance, facilitate the understanding between different stakeholders and increase at the same time confidence in the OoC technologies.

To steer formal standardization activities, the aim of the OoC PSIS Workshop was to map the standardization needs for OoC, in order to identify specific aspects of technology to be tackled and determine the best standardization option.

During the parallel sessions, a matrix (Figure 2, left panel) was used to classify specific aspects of technology that would need standardisation based on the "what" and the "how", using an approach published in the literature to map standardisation activities in innovation (Ho & O'Sullivan, 2018). Depending on the developmental stages of the technology, standards will have different roles. The Y-axis is divided in three main categories, going from idea to realisation to market. Starting from the bottom, technology related standards mainly tackle issues related to basic science and basic technology. At a more advanced stage in the innovation development process, production related standards cover aspects of manufacturing, product and other technologies. Finally, market enabling standards cover the last part of innovation, when the technology finally reaches the market. These standards are needed to define the business case, the related policy and regulation, the customer needs and so on. The X-axis categorises the "how", meaning the type of standard that is needed. The most common ones are terminology, metrology and measurement, performance characterisation, interface and compatibility and quality standards.

The final dimension that is important to completely map the standardisation panorama is time. A prioritisation graph (Figure 2, right panel) was used to tackle the "when, by discussing the importance of having a standard and the feasibility of its development. The three areas (high, medium and low priority) give an indication on which standards need to be addressed sooner rather than later.

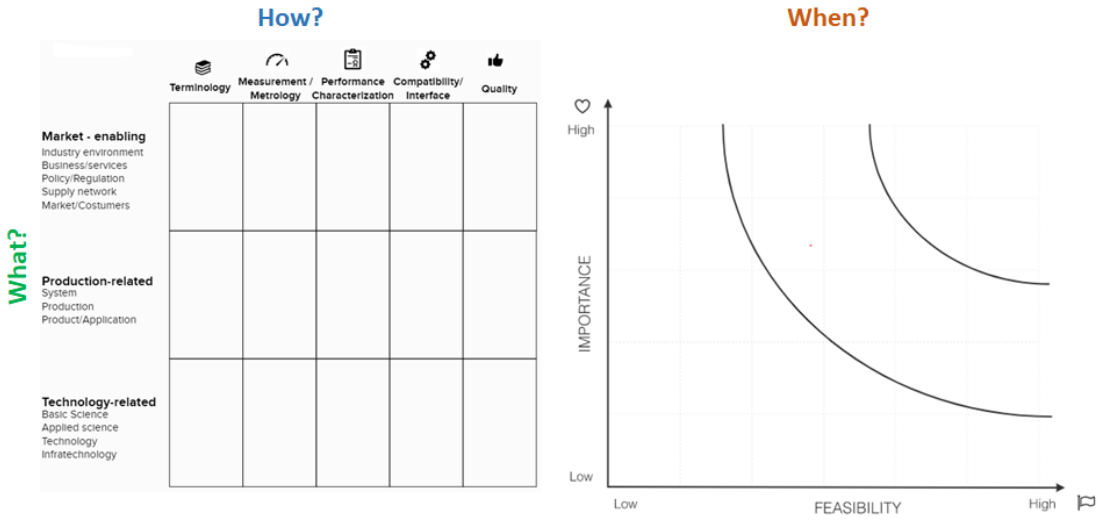

Figure 2 Standardisation mapping tools used during the workshop parallel sessions. Left panel: Classification matrix. Right panel: Prioritisation graph. The heart symbols increased importance and the flag increased feasibility.

2.1 Life science

In order to identify standardisation needs throughout the technology development chain of OoC, we fragmented the technology into biosciences, engineering, data and regulatory related topics. Within the field of bio science-related aspects of OoC, we focused on three main topics: cells and tissues, biomaterials and biomarkers and assays. Although those fields are merged in the conclusions, in the following we present the details where standards could be of benefit for the advancement of the technology.

2.1.1 Cells and tissues

The cells and tissue sector needs to find ways to overcome challenges in reproducibility of laboratory results. OoC often use human primary cells (*i.e.* from tissue biopsies or surgical waste) that closely resemble the tissue of origin but have several characteristics that affect batch to batch and over time reproducibility. Alternatively, there are cell lines and adult or pluripotent stem cells. But also in these cases, the lack of standardization can be source of undesirable variability, *i.e.* cell lines, with cancer origin are genetically instable while stem cells might show line-to-line variability and arrive to a non-adult stage. At the level of cells and tissues, standards can be implemented at different levels from cell sources, SOPs, cryopreservation and cell production, performance, reference compounds, functionality assessment, quality management and reproducibility (Table 1).

In terms of good cell performance, it is important to have standards that can check batch-to-batch reproducibility and stability over time. For that, cells need to be well characterised, with readouts that correlate cell performance with organ/body function (ideally clinical readouts). The OoC environment is very particular and different from other cell culture systems and because of that, should be characterised separately. Cell characterisation can be fished out of clinical assays and data and implemented in the form of a check list or a quality sheet, per tissue. Such characterisation should always put upfront the functionality of the cells that reflect the organ of origin (Figure 3).

Table 1. Classification matrix – cells and tissues.

	Terminology	**Measurement/ Metrology**	**Performance characterisation**	**Compatibility/ Interface**	**Quality**
Market enabling • *Industry environment* • *Business/services* • *Policy/Regulation* • *Supply network* • *Market/Customers*	• Qualified assay for Weight Of Evidence • Acceptable tissue/cell type • Ethical considerations • Description of tissue origin	• Detection threshold • Guidance on x-system to be assessed	• Criteria for qualified assay • Controls to differentiate variability from abnormal • In Vitro to In Vivo Extrapolation • Time for cryopreservation • Cryopreservation conditions	• Mutual acceptance of data (MAD) • Criteria for imp/export of biological material • Mutual acceptance of data interpretation • Patents • Disseminate paradigm shift and on-board stakeholders	• GLP • Documentation Standard • Qualification Standard • Ring trials • SOPs • Biological variability (ethnic, sex...) (Standard)
Production related • *System* • *Production* • *Product/application*	• TRL characterization according to OECD • Alignment of exposure scenario (SCCS for cosmetics) • Alignment of required quality standards	• Acceptance criteria for variability of detection thresholds and sensitivity • Dimensions of sensors (some endpoints)	• QC check criteria • Genetic stability • Model/cell related benchmarks • Batch-to batch consistency • Human biological standard (performance) • Functional stability (in different culture platforms) • Metabolic signature of cells • Bio analytics to validate cells readiness	• Standard for dimension and scaling • Characterization and compatibility of materials • Distribute application tips via new media options	• ISO- / DIN Standard • GCCP; GMP (cell production)
Technology related • *Basic science* • *Applied science* • *Technology* • *Infra technology*	• Definitions on types of tissues • Reporting units • Standard normalization of measurements • GIVIMP terminology	• Sensors for aligned endpoints Measurement standards for comparability • S/N,Z' • Mass balance analysis parameters • Standard sensor for cells • Standard assays for cell perform • Standard sensors for constant environment	• Performance characterization (per cell source) • Maturation and production • SOPs • Functionality criteria Reproducibility • Functional maturity • Disease reproducibility • Reference compounds	• Scaling and dimension • MPS and PBPK - • Compatibility • Education and Training (ITN for MPS) • Cell-matrix chip compatibility	• C.E (for systems) • Replicates and statistics • Documentation • GIVIMP • GCCP 2.0 • Organ related QC

Source: PSIS workshop on standards for Organ on Chip, 28-29 April 2021.

In the chip, uncertainty can be decreased by standard online sensors and characterisation of cell-material interaction. In general terms, on technology related aspects in basic science, there is a need to define or harmonise definitions, normalisation of measurements and reporting units. A consensus is needed regarding SOPs, as well as higher adoption of guidance documents to ensure cell quality such as Good *In vitro* Method Practices (GIVIMP) (Organisation for Economic Co-operation and Develop, 2018) and Good Cell Culture Practice (CGGP) (Coecke, et al., 2005). Cell therapy area can be taken as example, where FDA and the European Medicines Agency (EMA) approval for certain therapies and transplantations has been achieved. Standards of acceptability have been built only for cell types therapeutically relevant.

Despite the need of reproducible systems, human variability should not be ignored. Although cell culture standards should work towards a reflection of the biological variability (i.e. sex, age, ethnicity), in the OoC this is not feasible at the moment.

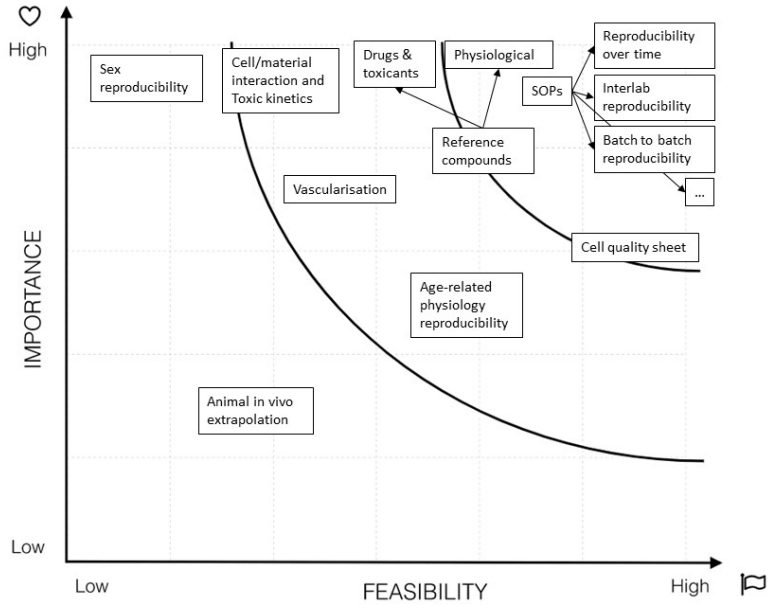

Figure 3 Prioritisation graph – cells and tissues (Source: PSIS workshop on standards for Organ on Chip, 28-29 April 2021).

2.1.2 Biomaterials

In the OoC there are two types of biomaterials, the chip material and the extracellular matrix (ECM) substitute, which is an integral part of tissues and organs. Several criteria in performance characterisation and interoperability were identified, such as, transparency, permeability, porosity and stiffness. Biomaterials still require overcoming challenges in reproducibility and scalability in production, calling for reference standards.

The key requirements for the biochip material comprise long-term stability, non-interference with cells or assay and optical transparency. In terms of characteristics, it is beneficial that the material is easy to manufacture, scale up and use, as well as having a production compatible with automation. Moreover, it would be beneficial to have low amount of material composition variables and the right quality controls. It should exist a list of materials and their characteristics allowing the user to choose or prioritise based on the context of use (Table 2). In what regards characterisation there are three key aspects:

i) absorption (for toxicokinetics characterisation),

ii) interference with cell performance (affecting either viability or cell function) and

iii) gas permeability of the material.

iv) characterisation of the entire structure of the chip (*i.e.,* tubbing connections…).

In the case of ECM, standardisation is more challenging as this type of material is actually aimed to introduce the variability observed *in vivo*. One way of standardisation, when using natural ECM, is to respect the specie and organ of origin. Nevertheless, the retention of the organ ECM is potentially more important, despite the low

feasibility at the moment. Standardisation also includes the insurance of low batch-to-batch ECM variability. A standard list with relevant quality criteria (QC) for the different ECMs, including acceptable cell-ECM (Figure 4) helps to facilitate the characterisation and scale levels applicable both for natural and synthetic ECMs.

Table 2. Classification Matrix - biomaterials.

	Terminology	**Measurement/ Metrology**	**Performance characterisation**	**Compatibility/ Interface**	**Quality**
Market enabling • *Industry environment* • *Business/services* • *Policy/Regulation* • *Supply network* • *Market/Customers*					• Human based ECM for human based OoC
Production related • *System* • *Production* • *Product/application*			• Easy of manufacturing • Robustness • Approved materials • Scalability	• Compatible with automation • Scalability	• Well defined ECM • Reproducibility (low variability) • Quality Control •
Technology related • *Basic science* • *Applied science* • *Technology* • *Infratechnology*		• Acceptance criteria • Standard units for rigidity • Material characterization	• Drug interaction characterization • Interference with cell performance • Transparency • Permeability • Reference standards • Porosity • Stiffness	• Low ECM variability • Assay compatible • Comparable material • Low interference (inert) material • Inter-species comparability	• High IPQ • Biological relevance • Biological variability

Source: PSIS workshop on standards for Organ on Chip, 28-29 April 2021.

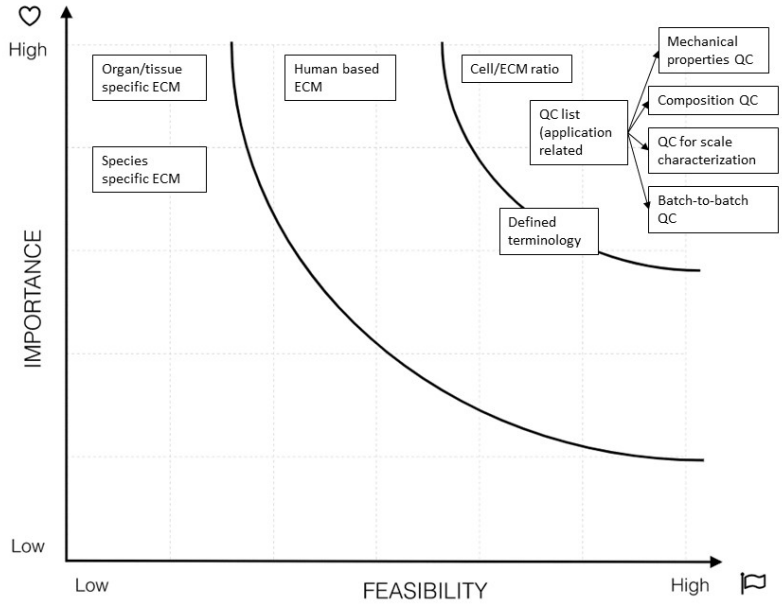

Figure 4 Prioritisation graph - biomaterials (Source: PSIS workshop on standards for Organ on Chip, 28-29 April 2021).

2.1.3 Assays and biomarkers

When deciding the biomarkers and endpoints relevant for a human situation, the benchmark should ideally include the ones used in clinics. It is advised to use several complementary assays and measurement methods that confirm the results of each other. To reinforce assays reproducibility, it is important to have good and well documented SOPs, strong application protocols and good technical support, all described in detail. Standards should also work to measure and ensure robustness of the data over time. That is possible with continuous measurements, statistics and reference data (Figure 5). Endpoints are typically independent of models and OoC can use the same endpoints as other cell culture models (Table 3). Nevertheless, advantage should be taken from the evolution of the complexity of the systems to have more physiological endpoints.

Novel endpoints should be validated in combination with reference compounds that are well characterised both in terms of expected effects as with detailed SOPs for preparation and exposure. The availability of criteria to prioritise the selection of the compounds to test would be helpful. For chemical toxicology, the reference should be human biomonitoring data and exposure. There are platforms available such as IPCHEM[10].

The context of use is important to standardise the model, including assays and biomarkers. Success cases should be shared within packages as models to follow (*e.g.* the liver model referred before). A good example is what the IQ consortia is developing for assessment of liver OoC (Baudy, et al., 2020).

Table 3. Classification matrix – assays and biomarkers

	Terminology	**Measurement/ Metrology**	**Performance characterisation**	**Compatibility/ Interface**	**Quality**
Market enabling • *Industry environment* • *Business/services* • *Policy/Regulation* • *Supply network* • *Market/Customers*			• Extrapolation of standard assays for regulatory purposes • Clinical relevance		• Liver MPS Guidelines • Organ specific MPS guidelines
Production related • *System* • *Production* • *Product/application*	• Cell source • Omics	• Use already existing standard • Clinical endpoints • Readouts • Cell quantification • Biomarkers detection levels • Integrated tools/sensors	• Continuous measurements • Data robustness • Culture volume • Endpoint • module/set of functional assays • No standard model for a specific purpose	• Culture medium composition • Standard Dosing • Throughput • Integration of biomarkers	• Technical repeats • Threshold criteria for variability • Cell quality criteria • Criteria for assessment of cell functionality
Technology related • *Basic science* • *Applied science* • *Technology* • *Infra technology*		• Reference organ parameters • Compound Toxicokinetics • Cell composition stability • Reference compounds • Disease extrapolation • Standard reporting units	• Compound manipulation • Functionality assays (over time) • Human benchmark • Existing and emerging functional assays • Reflect biological variability (not variability due to other sources)	• Relevant benchmark • Model fitness	• SOPs of standard measurements • Continuous measurements • Data robustness overtime

Source: PSIS workshop on standards for Organ on Chip, 28-29 April 2021.

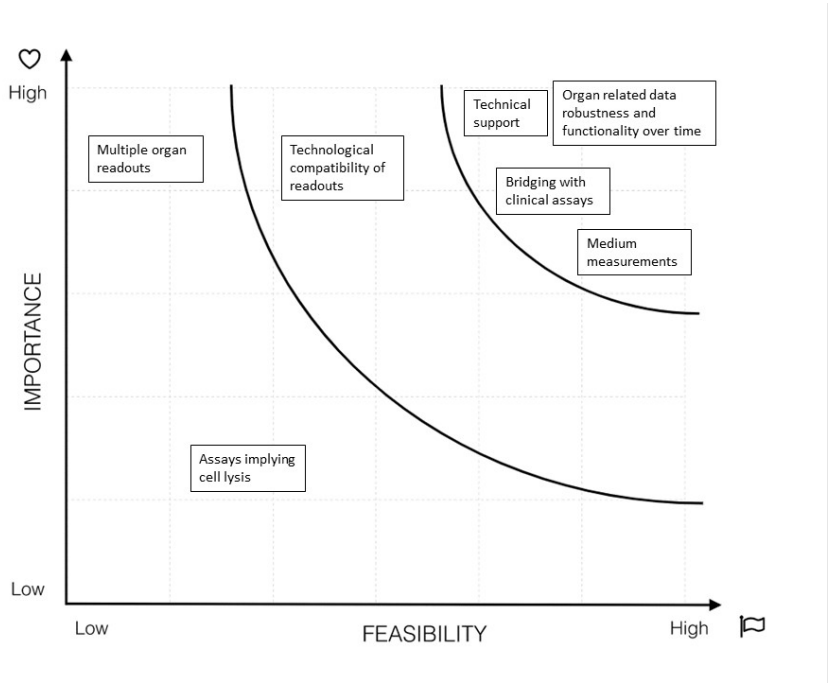

Figure 5. Prioritisation graph – assays and biomarkers (Source: PSIS workshop on standards for Organ on Chip, 28-29 April 2021).

[10] https://ec.europa.eu/jrc/en/science-update/update-information-platform-chemical-monitoring-ipchem

2.1.4 Summarising standardisation needs in life science related aspects of OoC

Standardisation aims at harmonisation and increase of reproducibility, each context of use might have a different model that would be the best fit. The best way to decide on the appropriate model is to demonstrate compelling evidence for defined use cases. This will build on the decisions on what are the best cells, materials, set-ups, assays and endpoints to be used. As humans are not standard, the models used should reflect human true human diversity and variability in data should not be due to technical immaturity. Whenever possible, multiple complementary functional endpoints should be taken from the same cells/chip and OoCs where such is possible, should be preferred. Culture media measurements, OoC integrated sensors and interoperable systems are an advantage.

Four types of standards can be identified: i) biology-relevant standards (reproducing human/animal biology) ii) standards to assess cell functionality iii) use of reference compounds (i.e. reference drugs and chemicals) iv) standards that ensure robustness and reproducibility, such as SOPs.

Having standard practice guidelines (such as CGGP and GIVIMP) and standard terminology and metrology is highly relevant. Although several standardising criteria are general to all cell culture systems, OoC shows particularities that can be advantageous in biological standardisation, such as circulating media and incorporated sensors.

2.2 Engineering related aspects

Tackling standardisation in engineering and device aspects of OoC, three fields could be differentiated: one focussing on sensing and integration, the other one on microfluidics, and thirdly interoperability and control systems. As there is no clear cut between the session fields, they partially overlap with our definition of standardisation needs. The below chapters are summarising current discussions on aspects of the OoC engineering.

2.2.1 Sensing and Integration

Sensor characteristics and testing procedures for sensors can be standardised in an application-specific way, fit for the purpose. Common sensor requirements include materials, quantity, dimension and position, quality, robustness, stability over time, sensitivity. Regarding actuators, it is crucial to establish requirements, performance criteria, calibration strategies and test methods to assess their technical functionality and reliability, which should be defined independently on the fabrication process of the specific device.

Table 4 Classification matrix – Sensing and integration.

	Terminology	**Measurement/ Metrology**	**Performance characterisation**	**Compatibility/ Interface**	**Quality**
Market enabling • *Industry environment* • *Business/services* • *Policy/Regulation* • *Supply network* • *Market/Customers*					
Production related • *System* • *Production* • *Product/application*		• Calibration • Sensor metrology		• Interoperability • Data format connectivity (Interfacing) • External connectivity to the computer	
Technology related • *Basic science* • *Applied science* • *Technology* • *Infra technology*	• Sensor specifications fit for a purpose • Materials (PDMS, glass, gold, etc...) • Quality of the sensors	• Standardize sensors for different applications		• Internal connectivity (interfacing)	

Source: PSIS workshop on standards for Organ on Chip, 28-29 April 2021.

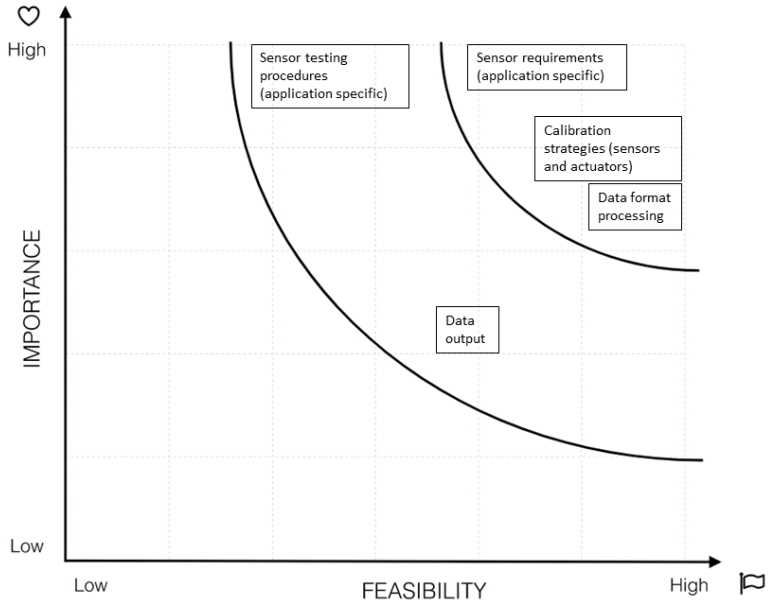

Figure 6. Prioritisation graph – Sensing and integration (Source: PSIS workshop on standards for Organ on Chip, 28-29 April 2021).

Cable connectivity and interface to the software are important questions that can be easily tackled with standardization (for instance with USB connections), but it is also essential to put those in context, accounting for the perfusion system and the incubator environmental conditions, that could influence the sensor performance (Table 4). To ensure interoperability, also among different suppliers, the output data and the processing methodologies (like sampling rates, filtering) need to be harmonised. Integration of other technologies in the same device, even if it not quite feasible at the moment, is key to achieve superior products. All future standardisation activities will need to account for and respect the IP rights of specific companies and it will be fundamental to find smart ways of collaboration, as common practice in the field of electronics (Figure 6).

2.2.2 Interoperability and control systems

Equipment interfaces and dimensions of OoC components are typical features to be standardised. Generally speaking, agreeing on external form factors, pumping systems, flow/pressure measurement, gas and temperature control factors, interfacing (tubing, connections) are areas where standardisation can play a big role (Table 1). The form factors of OoC devices are already converging towards those found commonly in biological laboratory settings, such as the microscope slide or the multiwell plate. The use of these form factors enables interfacing with existing laboratory equipment, such as microscopes. Moreover, many aspects of the multiwell plate are already defined in standards documentation by ANSI/SLAS, so there will be opportunities for OoC devices to harmonize with these standards (Figure 7).

Materials and surface modification strategies, together with interfaces for optical readouts are specifically relevant for the industrial development of OoC. devices. The whole system setup (OoC device and all equipment connected to it) should be clearly identified, calibrated and tested in a holistic way. Connectivity, both fluidic, electrical and optical, is quite advanced in the devices available from the industry and it really enables interaction with the OoC device. Standardized, structured, and high-quality data outputs from control and sensor read-out systems would warrant integration of data across different devices, as also discussed in the Data management session.

A big field for standardisation would be the description and performance characterisation of the OoC system as a whole (*i.e.* chip, pump and incubator…), rather than its individual components. This could be achieved by defining a general template to report OoC experimental protocols and data interpretation. Thus, results obtained from the system can be compared one another. Long term ambition is to automate the whole process, including a statistical interpretation of the results. To reach this goal, it is necessary to ensure that the system is thoroughly characterised and its performance assessed.

Table 5 Classification matrix – interoperability and control systems.

	Terminology	Measurement/ Metrology	Performance characterisation	Compatibility/ Interface	Quality
Market enabling • *Industry environment* • *Business/services* • *Policy/Regulation* • *Supply network* • *Market/Customers*			• Characterisation/High level protocol for your system		
Production related • *System* • *Production* • *Product/application*	• Terminology for high-level characterization (simulation)	• Methods to characterise the systems • Sensor read-out equipment quality standards	• System description and performance • Interfacing	• Pumps interfaces and tubing	
Technology related • *Basic science* • *Applied science* • *Technology* • *Infra technology*		• Pumps quality standards	• Automating equipment • interfaces, dimensions	• Chip dimensions, interfaces	

Source: PSIS workshop on standards for Organ on Chip, 28-29 April 2021.

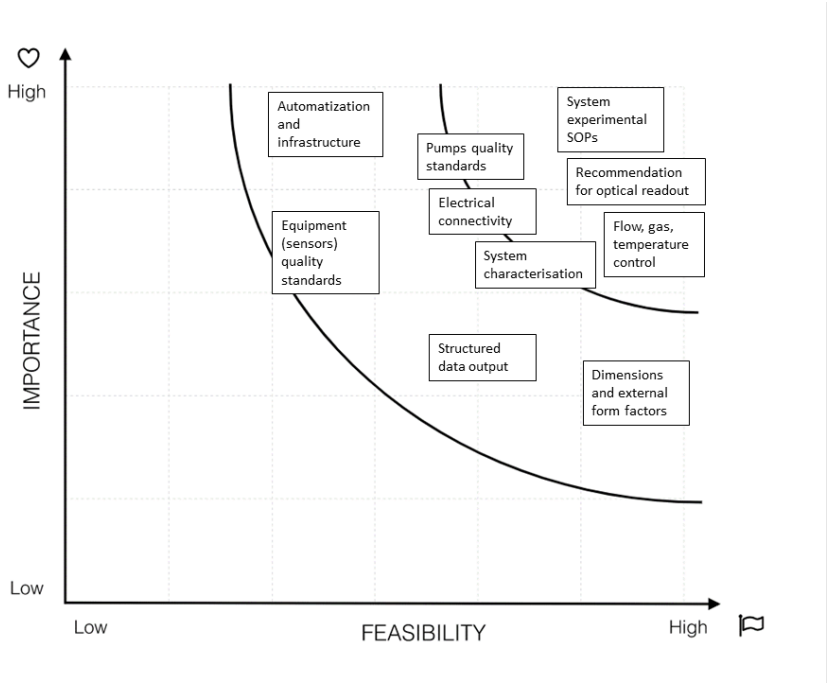

Figure 7. Prioritisation graph – interoperability and control systems (Source: PSIS workshop on standards for Organ on Chip, 28-29 April 2021).

2.2.3 Microfluidics

The most important aspects to be standardised for microfluidics are:

i. Choice of materials;

ii. ii. Metrology at device and system level;

iii. iii. Interoperability between components (chip to chip) and system (chip to the external world) (Table 6).

Standardisation activities can either produce a formal standard, but it is noted that also guidelines and/or technical specifications are useful tools to obtain the same result. Generic protocols for production and material characterization are essential, also to assess biocompatibility in the context of the specific applications, as well as detailed SOPs and specifications for assays performed in a microfluidics context (Figure 8).

Table 6 Classification matrix - microfluidics.

	Terminology	Measurement/ Metrology	Performance characterisation	Compatibility/ Interface	Quality
Market enabling • *Industry environment* • *Business/services* • *Policy/Regulation* • *Supply network* • *Market/Customers*				• Volume production issue: integrated/modular approach • Volume production issue	• Standard • SOPs • Translation • Business model /cost optimization from the beginning
Production related • *System* • *Production* • *Product/application*		• Metrology for production • Testing for biocompatibility	• Materials	• Measuring protocols for a successful scale up • Electrical and fluidic connections	• Scalability • Manufacturability • Reproducibility • throughput
Technology related • *Basic science* • *Applied science* • *Technology* • *Infra technology*			• Cell viability • Biomimetics		

Source: PSIS workshop on standards for Organ on Chip, 28-29 April 2021.

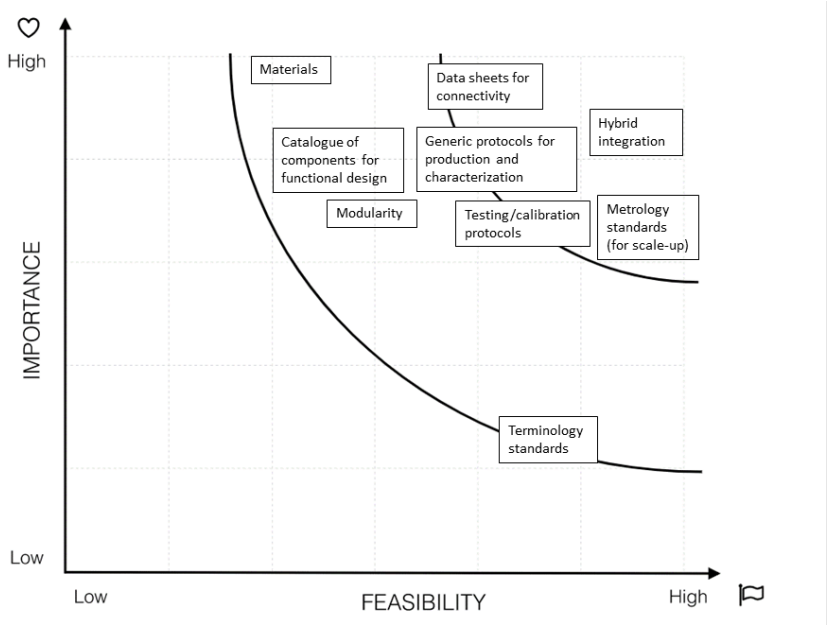

Figure 8. Prioritisation graph - microfluidics (Source: PSIS workshop on standards for Organ on Chip, 28-29 April 2021).

Testing and calibrations methods need to be standardised and properly described to enable use in different conditions. Interfacing at various levels of hybrid integration would allow the use in many other applications. Standardised high-quality data sheets and performance characterisation standards for flow parameters and fluid leakage can facilitate interoperability and eventually speed up the translation to commercial applications. Modularity is one of the promising aspects of microfluidics and standards can be great enablers to achieve this goal. Microfluidic devices can be made from off-the-shelf components from commercial sources, resulting in low-cost, easy, and flexible end products.

Microfluidics uses already specific standards for vocabulary (International Organization for Standardization, 2009), for symbols and performance communication (International Organization for Standardization, In press), for interoperability (International Organization for Standardization, In press), microfluidic components, interfaces, protocols for associated testing and protocols for microflow control, as performed by the CEN Technical Committee 332/WG7.

2.2.4 Summarising standardisation needs in engineering related aspects of OoC

When developing OoC systems and technologies, manufacturability, scalability and industrialization are essential aspects to be considered where standards can play a role.

With a proper level of characterization and description, the use of components and off-the-shelf technology would greatly facilitate the adoption of OoC devices. A standard catalogue of components, as well as standardised dimensions and geometries could help interoperability, still allowing enough design choices to guarantee the uniqueness of each device.

Metrology standards are seen as fundamental tools to support the development of a common strategy for testing and calibration of sensors and equipment. Moreover, a general standard protocol for materials characterisation could help quantify the issue of molecule adsorption on many OoC materials. Agreed protocols would ease automatisation, while modularity in development can help end-users to bridge the valley of death.

The OoC community needs to find ways to collaborate more efficiently to be widely adopted and integrate other technologies into more complex devices, while still respecting IP rights. A step-by-step approach in delivering standards is essential to deal with complexities, as is the case for OoC technologies. One option would be to develop best practices and guidelines, which are effective tools to bridge towards more formal standards. Last but not least, existing standards that are related to OoC should be widely communicated and promoted, especially among academics and start-ups.

2.3 Regulatory and data management aspects

Regulatory acceptance is a fundamental pillar in the advancement of OoC field that will guarantee widespread use and acceptance. Standardisation aspects are related to good experimental practices and data management, putting the basis for scientific validity and result interpretation. Reporting standards and classification criteria for OoC are fundamental to help regulators completely understand the OoC devices and the results they provide.

2.3.1 Good experimental practices

Standardisation is an important first step towards regulatory acceptance, thus towards qualification and validation of OoC devices. The same basic concepts are also applied in drug development pipelines to assess the scientific validity of a method, by using due diligence lists for internal decision-making. It is fundamental to start with a good definition of the test item, particularly in the context of use of choice. To this goal a careful definition of reference and control items, method acceptance criteria and of the endpoint is crucial, together with the basic components having a mechanistic relevance and a strong basic biological background. The GIVIMP (Organisation for Economic Co-operation and Develop, 2018) provides a comprehensive set of principles and best practices, applicable for a wide range of *in vitro* methods, to ensure that the data generated can be used in critical decision-making (Figure 9). “Start simple” is the proposed strategy for OoC regulatory acceptance, by tackling the most data rich models, preferably single organs, where *in vivo* human data are available for comparison and a routine use of OoC is already in place.

Table 7 Classification matrix – good experimental practices.

	Terminology	**Measurement/ Metrology**	**Performance characterisation**	**Compatibility/ Interface**	**Quality**
Market enabling • *Industry environment* • *Business/services* • *Policy/Regulation* • *Supply network* • *Market/Customers*			Interesting CoU where it is possible to define performance criteria: • Heart on a chip • Immunoncology • Liver metabolism		• Repeatability and relevance of the OoC test system • Use of existing good practices (GIVIMP and GCCP)
Production related • *System* • *Production* • *Product/application*					
Technology related • *Basic science* • *Applied science* • *Technology* • *Infra technology*			• Choice of reference compounds (commercially available and applied in human-relevant doses) • Mechanistic relevance of the biological model	• Database for data sharing of preclinical results • Use of reference compound lists • Comparison of results with measured plasma concentrations (human in vivo data)	

Source: PSIS workshop on standards for Organ on Chip, 28-29 April 2021.

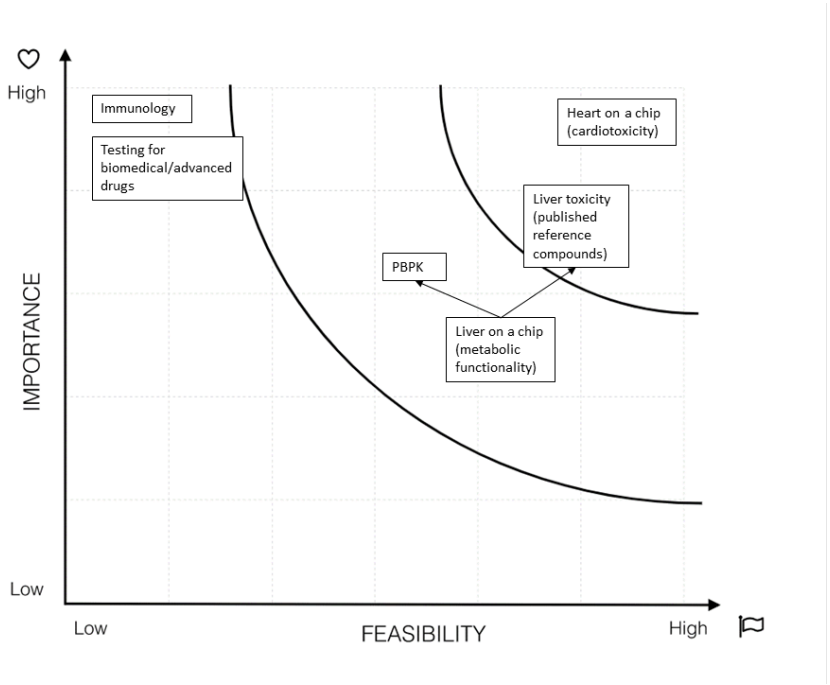

Figure 9. Prioritisation graph – good experimental practices (Source: PSIS workshop on standards for Organ on Chip, 28-29 April 2021.).

Heart on a chip is seen as potentially having a strong impact in safety testing for cardiac toxicity, as well as liver on chip. The real added value of OoC, however, can come from the immunology field, where the community lacks good preclinical models. To identify data rich contexts of use, a database to allow for data sharing and lists of reference compounds could be precious tools to boost future uptake (Table 7).

2.3.2 Data acquisition and management

A proper data management process should be based on FAIR (Findable, Accessible, Interoperable, Reusable) principles for data sharing. Concretely, this means to use rich, highly structured and interlinked metadata, stored in indexed and accessible repositories; data should be open to everybody who has the right to access, complying with GDPR and respecting IP rights and confidentiality of the data where needed. For ensuring interoperability of the data, the corresponding metadata should have multiple attributes, following relevant minimal information guidelines, to describe the content of the datasets and the context in which they were recorded, including the biological source material (Table 8).

Table 8 Classification matrix - data acquisition and management.

	Terminology	Measurement/ Metrology	Performance characterisation	Compatibility/ Interface	Quality
Market enabling • *Industry environment* • *Business/services* • *Policy/Regulation* • *Supply network* • *Market/Customers*	• Terminology and vocabulary (endpoints and biological parameters)		• Data processing standards	• Open data (for everyone who has the rights to do so) • Well defined, structured, interrelated and harmonised metadata	• Provenance standards for data and biological material
Production related • *System* • *Production* • *Product/application*	• Terminology and vocabulary (endpoints and biological parameters)			• Well defined, structured, interrelated and harmonised metadata • Data Interoperability	
Technology related • *Basic science* • *Applied science* • *Technology* • *Infra technology*	• Terminology and vocabulary (endpoints and biological parameters)		• Biological data sample	• Data Interoperability • Well defined, structured, interrelated and harmonised metadata • Biological data sample • Metadata guidance for data capturing and reporting	• Data quality standards • Standardised data formats • Provenance standards for data and biological material

Source: PSIS workshop on standards for Organ on Chip, 28-29 April 2021.

Specifically, for OoC, there is a need to better integrate experimental data with computational models (*i.e.* mechanistic models, as well as models derived from artificial Intelligence and data analytics methods), with a clear identification of the model inputs needed and the data generated, also defining the derived endpoints and used vocabulary/terminology (Brunak, et al., 2020) (Figure 10). Metadata guidance for data capturing and reporting, meaning a standard minimum information checklist of metadata that should accompany each data, should be defined for the main OoC devices and applications, with a strong link to the test method that is used.

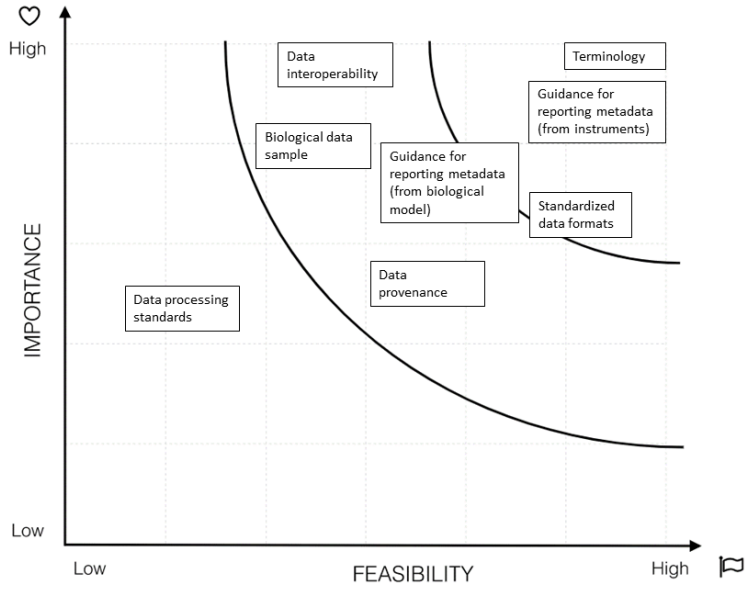

Figure 10. Prioritisation graph - data acquisition and management (Source: PSIS workshop on standards for Organ on Chip, 28-29 April 2021.).

Publicly accessible databases (with possibilities to define limited sharing rights for restricted access data) and structured data management frameworks (Wolsencroft, et al., 2015) for data sharing should be widespread for OoC technologies, also for data from scientific publications, to allow interoperability and feasible reuse of the data. Standardised guidance for data analysis to be used down the pipeline for data analysis, together with the implementation of data provenance standards for tracing the data over the processing steps, could improve the quality of the results and ensure data interoperability, by obtaining results that are independent from the data processing steps, as well as traceable back to the primary data and used biological material.

2.3.3 Characterisation and reporting

Terminology in the OoC field was already discussed and some definitions are available in the literature (Marx, et al., 2020). In order to proper characterise OoC and thus assess their performance, a proposal is to cluster together devices with similar properties via a standardised system and thus create a classification system. The grouping could be independent of the application, but based on similar technical properties and characteristics of the biological model that the device is incorporating (2D, spheroids, and organoids) (Figure 11).

Table 9 Classification matrix - Characterisation and reporting.

	Terminology	**Measurement/ Metrology**	**Performance characterisation**	**Compatibility/ Interface**	**Quality**
Market enabling • *Industry environment* • *Business/services* • *Policy/Regulation* • *Supply network* • *Market/Customers*			• Reporting standard needed for regulatory uptake • Framework that can accommodate specific needs		• End user experience is key to guarantee performance of the OoC
Production related • *System* • *Production* • *Product/application*			• IQ, OQ, PQ standards can be applied to all devices		
Technology related • *Basic science* • *Applied science* • *Technology* • *Infra technology*	• Terminology to be strengthened • Definition of classification criteria that relate to specific application	• Qualification definition (cells, protocols, assays)	• Modular Approach • Minimum set of parameters that guarantee that the chip works • Standardisation of the method • List of compounds that are absorbed and released from OoC materials		• Quality of readouts needs to be fit for the application • Careful comparison with existing data

Source: PSIS workshop on standards for Organ on Chip, 28-29 April 2021.

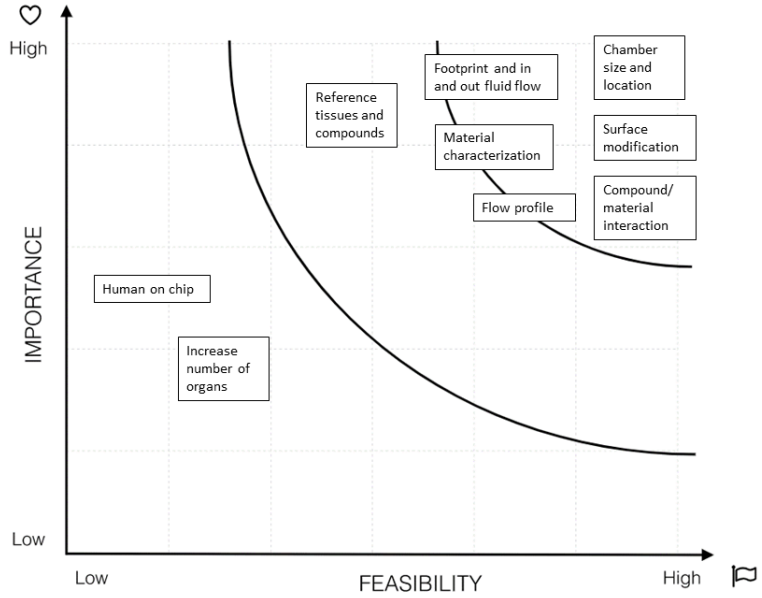

Figure 11. Prioritisation graph - Characterisation and reporting (Source: PSIS workshop on standards for Organ on Chip, 28-29 April 2021).

This classification method can also benefit the reporting of data for research and regulatory purposes, clarifying all components of the OoC device in a framework that could accommodate different applicability areas. Splitting up in modules may help to account for all applicable criteria, covering aspects such as specific cellular model, fluidic system (including pumping and connections), environmental control, type of readout, materials and their interaction with the compounds, surface modification, presence of barriers/scaffolds, compatibility with automatic pipetting and imaging systems (Table 9).

2.3.4 Summarising standardisation needs in regulatory and data management aspects

Regulators are looking favourably to the use of OoC and propose that the community focuses initially on data-rich contexts of use, such as liver metabolism and cardiotoxicity. Future activities could be focused on those areas where OoC could really make a difference, as in the immunology field where animal models give really poor predictions. The most important aspect is a precise definition of the context of use that will guide the relevant/required parameters needed to replicate (human) physiology. Building a suitable reporting standard could greatly support regulatory uptake, by creating a template specific for OoC devices, describing all technological and biological components, as well as its limitations. By defining classification criteria, it will be possible to define a minimum set of operational parameters that demonstrate reliability.

Enabling data-sharing across different repositories for multiple usage was highlighted as an important step for integration of OoC outcome with, for instance, computational models. High priority actions to be put forward include the use of highly structured and interlinked metadata, the development of guidance for accurate reporting of metadata (at least those coming from equipment and instrumentation) and the definition and use of a common vocabulary.

3 Concluding statements and the way forward

The workshop revealed a strong justification for translating scientific evidence into standards, supporting the advance of the OoC field towards wide acceptance by the stakeholders and creating a robust marketplace for human-relevant alternatives to animal testing. In this section, we reflect suggestions, initiatives and actions that are ongoing or required to identify the communities and synergies that will need to be involved to achieve market acceptance of these technologies and gain acceptance with the regulators.

Despite the initial euphoria on the potential revolutionary opportunities and the promise presented for OoC technology, the end-users remain hesitant to adopt OoC models into mainstream research and development pipelines. Some consider handling as too complicated, output uncertain and the necessary specialised training and high cost a major hurdle. Others argue that the current solutions are designed too developer-driven, often missing the mark, as opposed to a community approach, where developers and end-users define together the problem to be addressed and the best way of going about it.

So, is there a way forward? The technical complexity of many OoC devices, and the need for costly specialized equipment that may become outdated because the technology is still evolving, are perhaps the most immediate barriers for wide adoption. There is a notion to keep devices simple, and not to try to obtain one system that serves all needs. Rather, we need to recognise and embrace the fact that each technology or device that comes along will have its own utility and limitations. In order for end-users to fully engage in collaboration and co-development, fit-for-purpose OoC systems should be available off-the-shelf. There are already products on the market that support design of the biology requested by customers.

Additional immediate solutions that, when resolved, may increase the market share of OoC technologies in drug development and safety evaluation are related to the characterisation of different components along the different technology readiness levels. Thorough characterisation of the technological components, like materials or biomechanics will facilitate the technology transfer process. By describing requirements and performance of the technical components, standardisation could be an important facilitator in the adoption of the devices. However, technological issues are only some of the issues that need to be addressed since the biology of the cells or tissues in the system also comes into play. There is a need to consider donor specificity of the input tissue and the cell source.

Standardization of OoC technology has been on the agenda for a number of government-sponsored programs in the United States and Europe. The National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH) in the United States sought to catalyse OoC technologies by enhancing the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions. NCATS funds not only the research into the development of diverse OoC models, but also the activities on testing and standardization that may help the promising technologies to “go the last mile” towards market acceptance. There are a number of successful examples of public-private partnerships in collaborative OoC testing, such as the Tissue Chip Validation Center at Texas A&M University. This partnership builds on existing infrastructure and expertise and promotes the use of OoC devices by industry and regulatory bodies at the same time.

In Europe, EUROoCS was recently established as an independent, not-for-profit organisation that supports OoC research and development and provides opportunities to share and advance knowledge and expertise in the field towards better health for all. Whilst not a physical institute, the society shares specialised platforms with its community through its website, collecting white papers and grey literature, lists of experts in specific application areas, and training resources and workshops. Central to the future of OoC is making the best of existing funding, facilities and strategic partnerships. Towards this goal, EUROoCS appointed regulatory- and industry advisory boards and established a strategic collaboration with the ISSCR, which may play an important role in contributing to standardisation of biological aspects of OoC technology.

Through different generations of framework programmes, the European Commission has invested public funding into research in the health sector. Such investment into this research should also encourage standardisation as demonstrated by recent calls for proposals. The need to invest in standards is immediate because this is the only way to ensure robust translation of research and its results to the market. Commission funding could support a clearer regulatory application pathway along technology readiness levels (TRLs) for example. For preclinical research for instance, TRLs of 4-5 are usually required. Formalising TRLs as milestones along this path could lead to the generation of data that can be certified by a regulator to be eligible for Marketing Authorisation applications. In this way, standardisation can trigger further funding from public and private sources, by increasing reliability.

From a policy viewpoint, three other areas for action were suggested:

a. The validation of various OoC devices as a logical continuation from *in vitro* assay validation has become necessary and would need involvement or support from regulatory authorities. An option could be to make use of the Open Innovation TestBeds, established in Horizon 2020, as well as structures involved in the European Strategy Forum on Research Infrastructures (ESFRI)[11].

b. Information obtained from OoC testing should be made publicly available in databases as comparators in future clinical testing. In this context, the European Commission will set up dedicated sites in the European Health Data Space, covering aspects such as biomarkers, to enhance the monitoring both of health and disease. The ultimate goal is to define how OoC can accurately reflect real life clinical situations as we move towards personalised medicine. This also includes consideration of cost, simplicity, reproducibility of biology, materials and devices. OoC therefore has the potential to create models of real-life situations, that will generate evidence to define safety and efficacy profiles better both before and after drug approval.

c. As part of the Multiannual Financial Framework (MFF), the Pharmaceutical Strategy has laid out a vision to create a future proof regulatory framework and to support industry in promoting research and technologies that actually reach patients in order to fulfil their therapeutic needs while addressing market failures for the next years. As research takes off in Horizon Europe, there is an opportunity to include the opinion of the OoC community as part of this strategy. Thus, OoC can contribute to crossing of the "valley of death" from the bench-to-bedside for many new therapies, with shorter timeframes and lower costs, reaching commercialisation sooner and translate research into benefits for patients. Alongside this, target populations for drugs could be more accurately defined, making personalised medicines a reality.

Overall, there was a consensus among the experts that standards promote innovation, knowledge exchange and investments in OoC technology. One principle aim of standards is to protect public health as ultimately expressed in regulations, but they also act as a stimulus for innovation. Standardisation brings people together, from different scientific communities and other related fields. Besides European standardisation bodies, which are the predominant platforms for medical devices, there are several other very important standardisation platforms, such as Organisation for Economic Co-operation and Development (OECD) and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) that are largely being used to bridge research with pharmaceutical and device regulations and markets.

The 2021 PSIS workshop has provided an excellent starting point for researchers, innovators, relevant stakeholders and standards organisations to come together to discuss the future of OoC technology. The next step is to implement the learnings, to prepare a roadmap to outline the most pressing standardisation needs and, in function thereof, define priorities for resource allocation in function of the Pharmaceutical Strategy and its supporting related policies.

[11] www.esfri.eu

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List of abbreviations and definitions

ANSI/SLAS Society for Laboratory Automation and Screening of the American National Standards Institute
CEN European Committee for Standardization
CENELEC European Committee for Electrotechnical Standardization
CiPA Comprehensive in vitro Proarrhythmia Assay
DIN Deutsches Institut für Normung
E&T Education and Training
ECM Extra Cellular Matrix
EMA European Medicines Agency
ESFRI European Strategy Forum on Research Infrastructures
EU European Union
EUROoCS European Organ on Chip Society
FAIR Findable, Accessible, Interoperable, Reusable
FDA Food and Drug Administration
FET Flagship Future and Emerging Technologies Flagship
GCCP Good Cell Culture Practice
GDPR General Data Protection Regulation
GIVIMP Good In vitro Method Practices
GLP Good Laboratory Practice
GMP Good Manufacturing Practice
HTS High-Throughput Screening
ICH International Council for Harmonisation
ICT information Communication Technology
IEC International Electrotechnical Commission
IP Intellectual Property
IPCHEM Information Platform for Chemical Monitoring
IPQ Portuguese Institute of Quality
IQ Consortium International consortium for Innovation and Quality in pharmaceutical development
IQ, OQ, PQ Installation-, Operational-, Performance Qualification
ISO International Organization for Standardization
ISSCR International Society for Stem Cell Research
ITN Innovative Training Networks
IVIVE *in vitro* to *in vivo* Extrapolation
MAD Mutual acceptance of data
MFF Multiannual Financial Framework
MPS Microphysiological System
NCATS National Center for Advancing Translational Sciences
NIH National Institutes of Health
OECD Organisation for Economic Co-operation and Development
OoC Organ on Chip
ORCHID Organ-on-Chip in Development
PBPK Physiologically based pharmacokinetic
PDMS Polydimethylsiloxane
PSIS Putting science into Standards workshops
QA Quality Assessment
QC Quality Criteria
R&D Research and development
SCCS Scientific Committee on Consumer Safety
SOPs Standard Operating Procedures
TOP Translational OoC platform
TRL Technology Readiness Level
WoE Weight of Evidence

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Annexes

Annex 1. Agenda of the Putting Science into Standard workshop

Agenda - Organ on Chip – April 28-29 2021

DAY 1

14:00 - 14:10	Get settled in MODERATOR: Maurice Whelan (EC JRC)
14:10 - 14:30	Welcome and opening Stephen Quest (EC JRC Director General); Ruggero Lensi (CEN Vice President Technical)
14:30 - 15:00	The present and future of Organ on Chip Janny van den Eijnden-van Raaij (EUROoCS)
15:00 - 15:30	What are standards and what are they good for? Lena Morgan (SIS and CEN Advisory Board for Healthcare Standards)
	BREAK
15:30 - 15:45	Standardisation in the pharmaceutical industry Marian Raschke (Bayer)
15:45 - 16:15	Standardisation for regulatory frameworks Sophie Mueller (EC GROW)
16:15 - 16:45	Standardisation opportunities for OoC Monica Piergiovanni (EC JRC)
16:45 - 16:55	Setting up our activities for the day two MODERATOR: Maurice Whelan

DAY 2

PARALLEL SESSIONS

The parallel sessions will be divided in three themes: life science, engineering, and regulatory and data reporting. Participants have to choose in advance and they cannot go from one room to another.

09:00 - 10:10

Cells and Tissues
CHAIR/SPEAKER: Christine Mummery (LUMC) RAPPORTEUR: Sofia B. Leite
ROUNDTABLE MEMBERS: Jochen Kuehnl (Beiersdorf); Olivier Frey (inSphero); Paula Alves (iBET)

Sensing and Integration
CHAIR/SPEAKER: Ignacio Ochoa Garrido (University of Zaragoza) RAPPORTEUR: Ozlem Cangar ROUNDTABLE MEMBERS: Dries Braecken (imec); Jannis Meents (MCS); Marco Rasponi (Polytechnic University of Milan)

Good experimental practices
CHAIR/SPEAKER: Sandra Coecke (EC JRC) RAPPORTEUR: Monica Piergiovanni
ROUNDTABLE MEMBERS: Pelin Candarlioglu (GSK); Rhiannon David (Astrazeneca); Sonja Beken (FAGG)

The parallel sessions will be divided in three themes: life science, engineering, and regulatory and data reporting. Participants have to choose in advance and they cannot go from one room to another.

10:30 - 11:30

Biomaterials and 3D printing
CHAIR/SPEAKER: Peter Loskill (University of Tübingen) RAPPORTEUR: Sofia B. Leite
ROUNDTABLE MEMBERS: Bas Trietsch (Mimetas); Lorna Ewart (Emulate); Hector Martinez (CELLINK)

Interoperability and control systems
CHAIR/SPEAKER: Andries Van Der Meer (University of Twente) RAPPORTEUR: Ozlem Cangar
ROUNDTABLE MEMBERS: Holger Becker (microfluidic ChipShop); Sébastien Cargou (Elvesys); Wolfgang Eberle (imec)

Data acquisition and management
CHAIR/SPEAKER: Martin Golebiewski (HITS) RAPPORTEUR: Monica Piergiovanni
ROUNDTABLE MEMBERS: Christian Maass (ESQlabs); Patrick Courtney (SiLA); Andreas Bender (University of Cambridge)

11:50 - 12:50

Assays and biomarkers
CHAIR/SPEAKER: Adrian Roth (Roche) RAPPORTEUR: Sofia B. Leite
ROUNDTABLE MEMBERS: Francesca Pistollato (EC JRC); Katherine Czysz (Fujifilm); Ofra Benny (Hebrew University of Jerusalem)

Microfluidics
CHAIR/SPEAKER: Mathieu Odijk (University of Twente) RAPPORTEUR: Ozlem Cangar
ROUNDTABLE MEMBERS: Nicolas Verplanck (CEA Leti); Alexios Tzannis (IMTAG); Marko Blom (Micronit)

Characterisation and reporting
CHAIR/SPEAKER: Ilka Maschmeyer (TissUse) RAPPORTEUR: Monica Piergiovanni
ROUNDTABLE MEMBERS: Albert van den Berg (University of Twente); Peter Ertl (Vienna University of Technology); Raffaella Corvi (EC JRC)

12:50 - 14:15 LUNCH BREAK PLENARY

14:15 - 15:00 Flash Summaries of parallel sessions

15:00 - 15:45 **Panel discussion on ways forward**
MODERATOR: Maurice Whelan (EC JRC)

ROUNDTABLE MEMBERS: Christine Mummery (EUROOoCS); Fergal Donnelly (EC RTD); Ivan Rusyn (Texas A&M); Lena Morgan (CEN Healthcare Advisory Board); Karl Gruen (Austrian Standards);
Thomas Steger-Hartmann (Bayer)

15:45 - 16:00

Workshop Closing
Fabio Taucer (EC JRC) and Ruggero Lensi (CEN Vice President Technical)

Advisory board members

Alexios Tzannis	(IMT)
Andreas Jenet	(European Commission – JRC)
Andries van der Meer	(University of Twente)
Anna Herland	(KTH)
Anne Riu	(L'Oréal)
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Ozlem Cangar	(European Commission – RTD)
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