Meeting Report

Heads on! Designing a Qualification Framework for Organ-on-Chip

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Introduction

The workshop “Heads on! Designing a Qualification Framework for Organ-on-Chip” was organized by the EU Reference Laboratory for alternatives to animal testing (EURL ECVAM) of the European Commission’s Joint Research Centre (JRC). It was held in Berlin in June 2023 as a pre-conference event of the Microphysiological Systems (MPS) World Summit 2023.

The aim of the workshop was to collect input from stakeholders from different domains and backgrounds who are interested in the qualification of experimental methods based on organ-on-chip (OoC) devices for use in the pharmaceutical sector. To set the scene, ECVAM gave an introductory presentation in which the term “qualification” was clarified. For the purposes of the workshop, “qualification” was explained along the lines proposed by the European Medicines Agency (EMA), i.e., an evaluation process to reach the conclusion that innovative methods can be relied upon to have an application for a specific intended use in the context of research and development into pharmaceuticals. It was also acknowledged that although a catalogue of resources1 that includes existing guidance on standardization and qualification, is already available, there is a clear need for qualification criteria specific for OoC that reflect their unique characteristics and embrace the rapid progress in the field.

The workshop participants were divided into four groups. Each group was instructed to propose an outline of a qualification framework based on their own experience and perspectives, indicating these specific aspects:

- what features should a framework have and what elements of OoC should be qualified;
- how can these features and elements be addressed in practice;
- who should be involved and responsible for which aspects.

The qualification framework proposals from each group were shown on a poster-sized canvas, and each group pitched them to a panel of 3 experts from the pharmaceutical industry, regulatory authorities, and academia. The expert panel gave a detailed critique on each proposal in addition to some general feedback on what was presented to them. Finally, an open discussion involving all workshop participants helped distil out some key observations and take-home messages.

Summary of the proposed qualification frameworks

Many common elements could be identified across the four proposals, as summarized in Table 1.

Expert feedback

The key starting point for obtaining regulatory uptake of an OoC-based method is a clear definition of its intended context of use (CoU). Only when the CoU is fully described and understood, does it make sense to start pursuing qualification in a meaningful way. Most OoC models have been developed for biomedical research purposes rather than regulatory applications, thus developers and end-users have to adapt these models and figure out how to use them to address regulatory information requirements. As an example, the same liver OoC model could in principle be used in a preclinical setting to evaluate the metabolic biotransformation of a new drug candidate, its pharmacological efficacy, or its potential to induce liver injury. These represent three general but distinct CoUs, which address different questions that a regulator may have.

More refined descriptions of CoU also specify aspects such as therapeutic target group, population variability, and anticipated off-target pharmacology. In addition, CoU includes an indication of what other information sources are used in conjunction with the OoC-derived information, and in that frame, how the OoC results can be interpreted to arrive at a conclusion. In the preclinical assessment of new drug candidates, the context in which efficacy is assessed differs significantly with respect to the assessment of safety. With the former, the pharmacological effect is already known and thus therapeutically targeted organs need only be considered. For the latter however, potential off-target effects in non-target organs have to be accounted for, which typically makes it more challenging to employ OoC for safety assessment.

When devising qualification strategies for OoC methods used in efficacy or safety studies, the relevant exposure scenario has to be considered, including the nominal dose, the route of exposure (e.g., dermal, inhalation or oral), and whether the drug is administered once or repeatedly over a period of time. For efficacy assessment, the comparative standard is usually the treatment applied in clinical practice, thus in-vivo-to-in-vitro extrapolation and related allometric-type scaling are required to ensure an equivalent internal dosing scenario within the OoC model.

A satisfactory level of qualification can only be achieved with a sufficient level of standardization, and vice versa. Thus, the development of OoC qualification frameworks and associated criteria should both reflect and influence ongoing efforts to address standardization of OoC (Piergiovanni et al., 2021a,b). Standards have an important role to play throughout the OoC innovation cycle, from R&D to qualification, through to production and commercial application. Demonstrating that OoC devices and methods are compliant with recognized standards will also help greatly in facilitating the acceptance and use of OoC-derived data for regulatory purposes. In addition, being able to assure the quality of data by carrying out OoC studies compliant with

1 https://data.jrc.ec.europa.eu/dataset/7bcb1db5-5c7e-460b-b79e-ca5f642514a4 (accessed 08.02.2024)
Good Laboratory Practice (GLP) will become more desirable as the importance attributed to OoC data in regulatory assessments increases over time.

Testing reference compounds that are negative or positive for a certain biological effect is an established way to assess the relevance and predictive value of an OoC method. However, a challenge facing developers and end-users is the fact that OoC studies are typically low in throughput and expensive to conduct, needing extra time and specialized human resources. Moreover, there are many CoUs for regulatory purposes that can be identified during the drug development process, making it challenging to produce enough high-quality data for assessing all of them. As a first practical step towards qualification, therefore, it would make sense to start with a basic OoC setup that addresses a simple, well-defined CoU to limit the number of reference compounds that would need to be tested to build confidence in the system.

Developers and end-users interested in regulatory applications of OoC need to invest more into learning about the regulatory world, identifying needs and priorities, and importantly, understanding the regulatory mindset (Avila et al, 2020, 2023; NASEM, 2023). Scientific fora such as the European Society for Organ on Chip (EUROoCS) provide opportunities for informal
dialogue and knowledge sharing through activities of its regulatory advisory board, which can be followed up in more concrete terms through the Innovation Task Force\(^2\) and the qualification and scientific advice programme\(^3\) at EMA.

**General discussion and conclusions**

As the workshop progressed, consensus emerged on what elements should be addressed within a qualification framework, although certain terms and definitions would need to be refined and agreed upon, and practical guidance and resources developed. Questions arose then about how to operationalize qualification frameworks to put them into practice. In addition, it was discussed what motivation drives the different actors to invest the considerable time and resources required to undertake qualification studies.

A general understanding among participants was that the end-users, namely pharmaceutical companies, are pivotal in creating and driving a qualification ecosystem. The pharma sector clearly needs to reduce costs and attrition rates in drug development. In addition, companies within the EU have to adhere to the provisions of Directive 2010/63/EU on the protection of animals used for scientific purposes, for example by reducing animal numbers needed in the preclinical setting where possible. OoC data are already used for internal decision-making on the selection of new drug candidates for further development. However, qualification of OoC methods is a prerequisite for companies to start introducing OoC data into regulatory dossiers, and collaborative initiatives such as the IQ MPS\(^4\) consortium represent a significant step in this direction (Baran et al., 2022; Candarlioglu et al., 2022; Tomlinson et al., 2023). OoC developers should tackle the issue of guaranteeing continuous availability of OoC models to end-users by scaling up the production of the devices and identifying reliable sources for the biological models, which need to produce enough volume and quality to sustain the increasing market demand. Building up capacity within contract research organizations (CROs) is also necessary, but typically CROs respond to end-user demand rather than proactively on-boarding new testing technologies and approaches.

There was some debate as to the willingness of regulatory agencies and assessors to shift to non-animal methods and how qualification can be perceived as more of a barrier than a vehicle to translate OoC methods into regulatory practice. The recent initiative by the 3Rs Working Party of EMA to update its guideline on the principles of regulatory acceptance of 3Rs testing approaches, including the definition of qualification criteria specific to OoC, was acknowledged as a positive step forward and indicative of a desire within the EU regulatory community to encourage and facilitate developers and end-users to scale up their qualification efforts.

The developers who participated to the workshop highlighted that funding for qualification is very hard to come by, and there is little academic incentive to pursue such activities. Thus, establishing independent qualification test facilities could be an attractive prospect to support the transfer of OoC technology out of research labs and into industry, especially if the qualification protocols and results were made open access. However, the experience from the Tissue Chip Testing Center at Texas A&M University (now evolved into the TEX-VAL Tissue Chip Testing Consortium) suggests that even if public money is used to initially establish testing centers, they can only be economically sustainable with investment from industrial companies through, for example, a “try before you buy” business model (Rusyn et al., 2022).

Overall, the workshop proved to be a useful and fruitful means to gather and discuss ideas and viewpoints from a cross-section of stakeholders with varied backgrounds. It also demonstrated the strong interest there is in the community to address the qualification of OoC in a more systematic and purposeful way, reflecting the increasing maturity of the field and the belief that OoC have the potential for real regulatory, industrial, and societal impact. An important take-home message was that although any qualification framework needs a solid scientific basis, more consideration should be given to how it can be implemented in practice and what support and incentives are needed to drive qualification forward within an industrial ecosystem.

**References**


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\(^4\) https://www.iqmps.org/publications (accessed 08.02.2024)


Conflict of interest
The authors have no conflicts of interest to declare.

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