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Introduction and Overview

Organ-on-Chip (OoC) models aim to recapitulate aspects of human physiology and pathology for the use in drug discovery development, toxicology testing and even personalized medicine. As they eventually aim to replace animal studies by using human-based stem cell models, they also intend to abolish the ethical concerns related to animal use.

The ORCHID project has brought together specialists and stakeholders with different backgrounds, i.e. academia, developers of OoC devices and methods, pharmaceutical and cosmetics industry, patient groups, ethics schools, and regulatory bodies. The latter group has indeed been actively involved in several discussions to assess the regulatory hurdles to bring OoC devices into existing validation processes. Hence, novel methodologies that are going to be used in several critical stages of drug development need to go through qualification and validation steps, as was also outlined in several ORCHID reports[1], and in the Guidelines of ECVAM[2,3].

In this report, that builds on the insights of the ORCHID work, we present an outlook on the regulatory pathway for OoC devices specifically, based on the lessons learned in the ORCHID project, complemented with the view of regulatory experts that were contacted to contribute to this document[4]. Challenges and shortcomings of existing regulatory processes on national, European and international level are presented. In addition, we have identified exemplary cases for OoC-based product innovation trajectories and suggest actions for regulatory pathway improvements.

Outlook on the regulatory pathway...

Similar to other novel technologies and methods, the use of OoC models for drug development/toxicity needs to become accepted by the regulatory bodies[5]. This means that OoC models need to undergo a qualification test, the results of which can be discussed with regulatory bodies to seek acceptance. The dialogue with the regulators should happen at any stage of the qualification process, starting even before qualification. The regulators indicate that qualification of OoC models needs to occur in the correct context of use, which is somewhat different from what is seen traditionally, such as in the case of biomarker qualification. It is also clear that qualification will take a significant amount of time. In the European context, this is mainly due to the absence of testing and qualification centers or laboratories for

[1] https://h2020-orchid.eu/

[2] Balls M, Blaauboer BJ, Fentem JH, Bruner L, Combes RD, Ekwall B, Fielder RJ, Guillouzo A, Lewis RW, Lovell DP, Reinhardt CA, Repetto G, Sladowski D, Spielmann H and Zucco, F (1995) Practical aspects of the validation of toxicity test procedures. The report and recommendations of ECVAM workshop 5. ATLA 23: 129-147.

[3] https://www.ema.europa.eu/en/regulatory-acceptance-3r-replacement-reduction-refinement-testing-approaches

[4] Jan Willem Van Der Laan, *Chair Safety Working Party at EMA*; Sonja Beken, *Member Safety Working Party at EMA.*

[5] https://h2020-orchid.eu/wp-content/uploads/2018/11/D51-State_of_art_RSE-PU-v1.0.pdf/

OoC. These centers, in analogy to the FDA testing laboratories in the USA, could generate the data needed to accelerate regulatory acceptance and finally harmonization of international guidelines (such as ICH).

The EMA held a workshop on October 5th, 2017 to discuss non-animal approaches in support of medicinal product development with a focus on micro-physiological systems/OoC models[6]. **Challenges** for acceptance of OoC models in the drug development process that were identified in this workshop were: *(i)* the weight of evidence is currently based exclusively on current animal models; *(ii)* OoC models are not cheap to run or develop, and *(iii)* there is a big need for collaboration and dialogue between all stakeholders. It was also considered during the workshop that more detailed guidance is required, that needs to be developed together with all stakeholders.

Qualification of newly developed methodologies can be performed under so-called *safe harbor programs*, where results from OoC models can be performed in concert with the original test methods (e.g. relevant animal models). This generates a parallel data set, coming from the OoC models, that have no influence on the regular validation process for drug toxicity or efficacy. This might be a strategy that can be followed for specific contexts of use for OoC models. In practice, the OoC models should thus be qualified within a specific context, e.g. together with end users, such as a pharmaceutical company, or in a current program (IMI and other EU programs) and starting with a standardized set of (reference) compounds. This qualification, preferably in independent testing centers, will bring confidence about their added value compared to the current animal models. Conditions for the qualification process can be provided by the OoC community.

There are **historical examples** of regulatory efforts that might give insight to the OoC community how to proceed with the regulatory pathway. The guidelines for reproductive toxicity[7] for example have undergone similar regulatory approval pathways towards acceptance. In this context, also a few in vitro, non-animal tests have been endorsed by ECVAM, but they cannot be used to replace animal testing[8]. Another example can be found in the Skin Sensitization testing, where validated non-animal methods have been developed to replace animal testing of chemicals and allergens, such as the KeratinoSens™ and hCLAT tests[9].

Finally, all stakeholders that attended the ORCHID workshops and discussions, as well as the two regulators, that were also separately contacted to give their view, agree that the **OoC community** plays an important role in driving the development of OoC models towards validated methods used in tests during the drug development process. The European Organ-on-Chip Society (EUROoCS) can play a pivotal role in this. A recommendation of the regulatory bodies is that EUROoCS can bring together a broad spectrum of stakeholders, including regulators, also after the ORCHID project has been finalized. EUROoCS can play the role of an honest broker to stimulate the dialogue between stakeholders, facilitate the

[6] https://www.ema.europa.eu/en/documents/report/report-first-ema-workshop-non-animal-approaches-support-medicinal-product-development-challenges_en.pdf
[7] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-risk-assessment-medicinal-products-human-reproduction-lactation-data-labelling_en.pdf
[8] http://alttox.org/mapp/toxicity-endpoints-tests/reproductive-developmental-toxicity/
[9] https://tsar.jrc.ec.europa.eu/test-method/tm2008-05

qualification process, including the establishment of testing centers, and help to change or implement the guidelines.

Recommendations

For OoC models to be adopted by the regulatory bodies, the community needs to organize itself and ask input from all stakeholders involved. Qualification of OoC models needs to be performed in a specific context of use, and in collaboration with industry (end users) and regulatory bodies. Regulatory acceptance of related technologies and existing regulatory pathways such as for reproductive toxicity can be used as a guideline for OoC models. Finally, EUROoCS is advised to play an important role as facilitator and stimulator to push this technology forward in the future.

Summary

In summary, the outlook for the OoC community regarding regulatory approval faces traditional challenges that are related to introduction of novel model systems. Qualification needs to be performed in the right context of use, and in dialogue with industry (end users) and regulatory bodies. EUROoCS can play a crucial role in driving the community forward towards adoption of this technology as novel test method in regulatory pathways.