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Executive Summary

Organ-on-chip (OoC) technology is a fast-growing research field and also several companies are commercializing the technology already (for a detailed overview[1]). The ORCHID consortium proposed a roadmap for the future of OoC recently (see ORCHID workshop report published in ALTEX[2]).

The roadmap for OoC technologies presents both opportunities and challenges. In the course of the ORCHID project, WP5 has dived into the aspects of ethics and communications, regulation and standardization. Deliverables D5.3, D5.4 and D5.5 characterize the current landscape and indicate challenges and opportunities without advocating specific routes. The final set of three deliverables addresses actionable routes for specific purposes: D5.6 sets out policy options as input to policy makers to address identified challenges, D5.8 targets OoC for drug discovery as the most promising first route to have an impact in industry and society.

D5.7 acts as a primer linking non-technological aspects of OoC technology to properties from an end user and societal stakeholder perspective. Decision-making along the research & innovation roadmap from science over technology to product needs to reflect that end user and societal stakeholders wish to obtain a desirable, safe and efficient product in their hands.

Offering a 'better' technological solution only is not sufficient to gain impact in the complex application field OoC technologies can target. Instead, OoC technology will only become adopted and gain impact when it enables solutions that are judged desirable, safe and efficient – three properties that draw on a matrix of ethical, regulatory oversight and standardization aspects put on top of the 'better' technological solution. D5.7 advises the research & innovation community on how to embed these three adoption criteria in the technology and product development process and into the decision making. The example case of OoC for drug discovery is addressed in more detail as a case study for illustration purposes.

[1] Organ-on-Chip in Development: Toward a roadmap for organs-on-chip
[2] Building Blocks for a European Organ-on-Chip Roadmap

Introduction

Offering a 'better' technological solution only is not sufficient to gain impact in the complex application field OoC technology can target. Instead, this technology will only become adopted and gain impact when it enables solutions that are judged desirable, safe and efficient – three properties that draw on a matrix of ethical, regulatory oversight and standardization aspects put on top of the 'better' technological solution. D5.7 advises the research & innovation community on how to embed these three adoption criteria in the technology and product development process and into the decision making. The example case of OoC for drug discovery is addressed in more detail as a case study for illustration purposes.

OoC needs to grow from technology to application/solution/product

The emphasis in the community is primarily directed towards OoC technology development, working on specific application cases, and early validation of the OoC technologies.

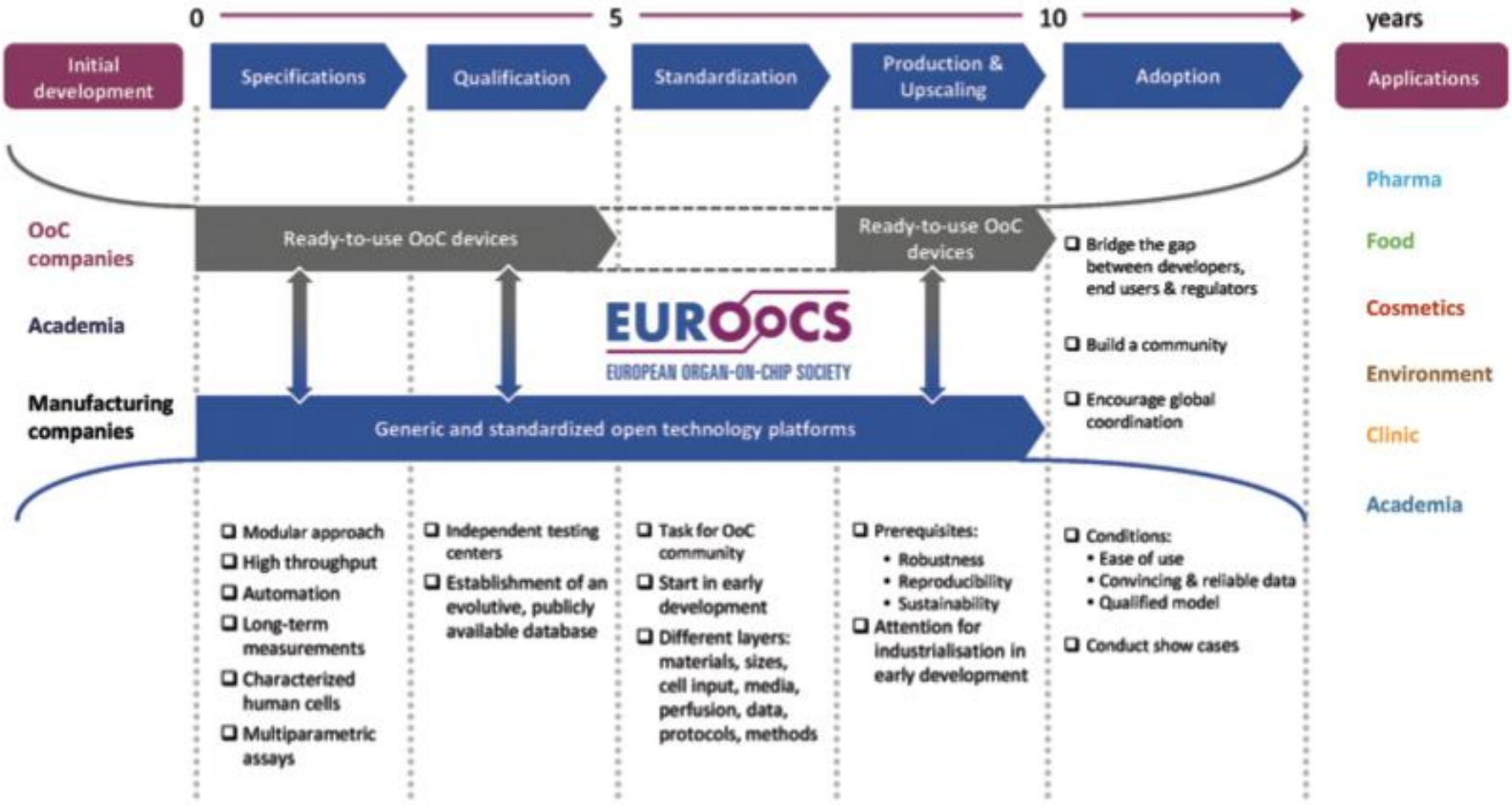
The initial state-of-play report D5.1[3] indicated that hardly any little OoC-specific regulatory context is in place and interaction with regulators is rather scattered. There are no noticeable initiatives on OoC-specific technology standardization or connection with possibly related broader technology standardization. On the ethical side, a positive discourse is going on, mostly driven by the forecast on contributing to 3R efforts on refining, reducing and replacing animal testing.

Adoption of OoC technology requires increased effort on translating selected OoC technologies to a solution/product focus for a specific application. The ORCHID roadmap (Figure 1, reproduced from [2]) has set out steps along a 15-year trajectory that matures the OoC field further. The roadmap encompasses technological, application and non-technological tasks.

The underlying transition process from technology to application/solution/product requires decision-making which may affect non-technological adoption criteria on a shorter term or longer term. In contrast to technology (which can be purpose-neutral), an application/solution/product will need to act in an ethical, regulatory and standardization framework. This deliverable aims to be a primer on how to handle and judge the impact in this framework.

[3] D5.1: State-of-the art on Regulation, Standardization and Ethics.

Figure 1: ORCHID roadmap for OoC technology.



Adoption of technology into Desirable, Safe & Efficient solutions

Adoption of a novel technology does not depend on technological superiority only. Scientists may develop a technological roadmap based on technical specifications which leads to a steadily increasing technology offering or platform, but non-technological constraints need to be blended into that roadmap gradually. Technology improvement relies on decision-making for selecting a particular technical option to proceed with. However, this decision-making process also needs to take into account the non-technological aspects.

OoC technology has its potential in offering solutions in the healthcare area which is heavily dependent on ethical concerns, safety and quality safe-guarded by regulation and (partly) standardization, and efficiency (both regarding efficacy of healthcare products as well as cost. Technology development, and its use in healthcare product development is heavily inter-dependent[4]. Ultimately, adoption of a technology in a specific product is based on appreciation and valuation by the different stakeholders and in particular in the health system, by patients, payers and society.

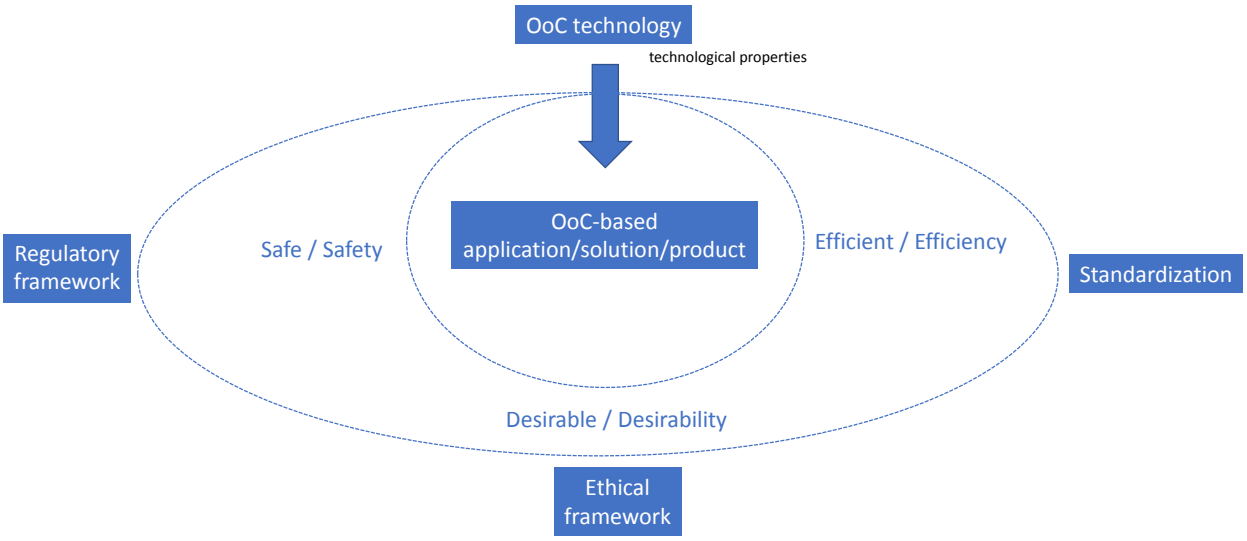


Figure 2: Incorporation of non-technological aspects when transitioning from technology to application/solution/product.

We propose to reflect implications on and of the ethical, regulatory and standardization aspects through representative adoption properties (see Figure):

- **Desirable / Desirability** – primarily relating to the ethical framework; the notion is to reflect that a solution is desirable, i.e. expressing a benefit at the emotional/personal/societal component. It

[4] D5.3 Guideline for the Research Community.

is not meant to reflect a technological superiority or simply lower cost. It is desirable if lower cost would lead through significantly improved affordability to improved population health.

- **Safe / Safety** – primarily relating to the regulatory framework; the notion is to reflect that safe and trustable solutions are provided and processes towards these solutions are safe-guarded, reducing risks. Indirectly, a safer solution is most likely a more desirable solution.
- **Efficient / Efficiency** – primarily relating to standardization; the notion is to reflect how far a solution draws on a broader or longer-term perspective, i.e. better leveraging investments, reducing risks, enabling scalability.
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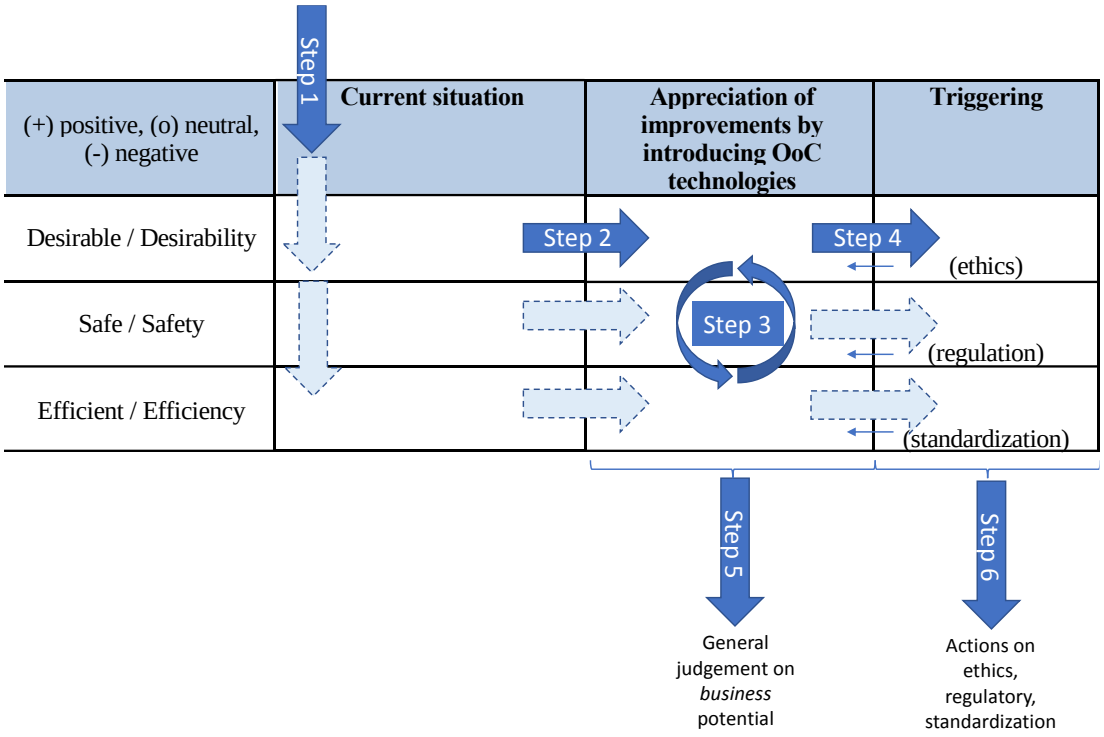
These connotations have been introduced as underlying observations and recommendations in earlier project deliverables D5.1 [3] and D5.3 [4]. While these deliverables give explanations for e.g. inter-dependencies between adoption criteria and dependencies on the non-technological context, they do not yet provide a methodology to assess a specific OoC case. This, however, is an essential step to execute the proposed OoC roadmap and take decisions.

Proposed methodology - Connecting the dots

In order to assess when, where and which actions on the ethics, regulatory and standardization framework need to be taken at which moment, we propose a methodology that starts from the assessment of an OoC technology on its transformative change and hence appreciation of improvement in the context of a specific application/solution/product or use case.

Methodology: The methodology aims at providing a qualitative, general judgement on the challenge/opportunity of such use case which can be used as a decision-making criterion on whether to engage, and a set of actions towards the ethics, regulatory and standardization framework which could be executed. It is based on table view (see Table 1) with the adoption criteria on one hand (rows) and the thought process to run through (columns, left to right).

Table 1: Proposed methodology.



Step-by-step approach: Steps of the methodology to pass through:

1. Describe the current situation by adoption criterion, using qualitative criteria (+, o, -) for positive, neutral and negative appreciation.
2. Translate by adoption criteria, what the appreciation of improvements of a proposed OoC technology would be on each adoption criterion, using qualitative criteria (+, o, -).
3. Elaborate on the appreciation table, identifying direct appreciation and indirect appreciation effects (across adoption criteria); this may create additional items crossing adoption criteria. This may also create not appreciated effects (-). The difference between direct and indirect impact may allow qualitative prioritization. The resulting column will give a qualitative view on the challenge/opportunity.
4. Translate appreciation of improvements by adoption criterion into concrete actions that reflect the ethics, regulation and standardization framework by row. For this purpose, content of deliverable D5.1 and, in particular, deliverable D5.3 should be reused which provides a large set of possible actions that can be matched to the need.
5. Extract a judgement from the qualitative scores on Desirability, Safety and Efficiency. This will emphasize where effort is needed and whether the case as a whole is promising

or not. This is used for decision-making on whether to engage on the opportunity.

6. Extract concrete accompanying actions next to the OoC technology development in the directions of ethics, regulatory and standardization.

Example case: An example of the methodology is illustrated in Table 2 based on a fictitious case (yet close to reality) where an OoC technology is introduced as a predictive pre-clinical assessment of drug efficacy for neurodegenerative diseases in the case that no predictive established method is in place.

Table 2: Judgement table with a fictitious example where an OoC-technology is introduced that would introduce a predictive pre-clinical assessment of drug efficacy for neurodegenerative diseases (with no predictive established method in place).

(+) positive, (o) neutral, (-) negative	Current situation	Appreciation of improvements by introducing OoC technologies	Triggering
Desirable / Desirability	(-) No prediction at pre-clinical stage in place.	(+, directly) Solution responds to an unaddressed need.	Improving patient outcomes; Reducing clinical testing burdens (ethics)
Safe / Safety	(o) Established methods at later stage. (-) Shortcomings on pre-clinical technology prediction for neurodegenerative diseases.	(+, indirectly) Identify (yet) unknown risks. (+, indirectly) Positive attitude of regulators yet validation needed.	Requires close partnership with regulator given novel approach yet validation needed (regulation)
Efficient / Efficiency	(+) Standardized, affordable technology. (-) Low predictability may lead to late drug failures.	(+) Improve rational decision-making at earlier pre-clinical stages. (+, indirectly) Reducing cost of late failure.	*Note: too early to consider standardization!* (standardization)

If the start scenario is kept rather broad, it is not unlikely that the case needs to be divided into subcases, each representing a separate application/solution. This can happen when performing Step 1, e.g. the new OoC technology is compared against very different established methods. This can also appear in Step 2, e.g. when OoC technology can take up different roles compared to the current benchmark (e.g. delivering complementary data/evidence vs replacing the benchmark).

OoC-enabled drug discovery as beach head market: a case study

There has been large consensus that processes in the pre-clinical stages of pharmaceutical drug discovery are the most likely ones to offer a beach head market to OoC technology[2] [5]. From these processes, OoC for drug toxicity and OoC for drug efficacy were selected as topics for the ORCHID Strategy Workshop in Leiden for further investigation. The following case studies draw on participant feedback at the workshop, included in its consolidated report[2] and are based on the methodology introduced earlier.

Drug toxicity

Situating the case: Drug toxicity testing is an established stage-gating step that the entire pharmaceutical industry uses to pass on candidate compounds/drugs towards the following stage in the drug development process. Failing toxicity testing is a no go. Established methods exist and are re-used but mostly involve animal testing (either in vivo tests or using biological material from test animals). Regulatory bodies are well familiar with the established methods. Predictability from animal to human remains an issue, though. Differences across human subjects remain a largely unsolved issue, rather addressed by statistics and safety margins. Pharmaceutical companies, regulators and clinicians call for higher predictability and complementary data. Drug toxicity testing is an essential yet costly step while it does not address the core property of the drug, i.e. efficacy.

Judgement of the current situation and the transitional effort (see Table 3): Drug toxicity contributes actively to Safety but suffers from neutral and negative scores for Desirability and Efficiency. The introduction of OoC technologies would score positively on Desirability (reducing ethical/societal concerns) in a direct way, positively on Safety (increasing predictability) in a direct way and positively on Efficiency (risk for failure costs) indirectly.

While Safety (validation against established reference methods proves improvement) and Efficiency (validation against established reference methods proves improvement, costs under control or lowering) come with the necessary effort, Desirability comes basically for free. The major embedding activities thus require (1) partnering/co-development of OoC method acceptance with regulators to address the Safety aspects jointly and (2) driving/benefitting from standardization/reuse of technology to keep technology cost under control. On Desirability, this may result in an opportunity for positive communication but does not require any preemptive action.

This is a very positive starting point and hence the reason to consider drug toxicity a beach head application/market for OoC that would face comparably low burdens for adoption.

[5] D5.8: OoC for drug discovery.

Table 3: Judgement table for OoC for drug discovery

(+) positive, (o) neutral, (-) negative	**Current situation**	**Appreciation of improvements by introducing OoC technologies**	**Triggering**
Desirable / Desirability	(o) Drug toxicity testing does not work on the core property of a drug. (-) Testing procedures involving animals raise ethical questions. (-) Society triggers with legislative/regulatory push towards alternative methods, e.g. already in place for cosmetics, chemicals.	(+, directly) Ethical concerns in society may diminish by OoC reducing and/or partially replacing animal testing.	Opportunity for positive communication on 3R (ethics).
Safe / Safety	(+) Drug toxicity testing is an essential step for safety and is an absolute must for regulatory approval and access to the market. (+) Established know-how on what is acceptable practice across drug developers and regulators. (-) Limited predictability of animal-based test methods from animal to human compromises safety.	(+, directly) Safety increases by using more predictable methods or adding complementary data. This is an opportunity for OoC but requires validation showing the benefit.	Engage in co-development with regulators (regulation).
Efficient / Efficiency	(o) Established animal-based methods are reused and as such efficient. (-) Demand for more complex toxicity assessments may lead to new and more complex test methods. (-) Limited predictability from animal to human may lead to late failure and thus unnecessary development costs.	(+, indirectly) Efficiency increases by using more predictable methods or adding complementary data. This is an opportunity for OoC but requires validation showing the benefit. (o, directly) The cost component in efficiency needs to be proven. This is an opportunity for OoC but requires an eye on OoC test cost.	Drive standardization to share/lower technology development cost (standardization).

Drug efficacy

Situating the case: Drug efficacy testing is a mandatory step that the entire pharmaceutical industry uses to determine the capacity of compounds/drugs for sufficient therapeutic effect or beneficial change in a clinical setting. Failing efficacy testing will also fail market access. Methods have been well established but a large variety of context settings exists given the variety of relevant biological contexts (tissue, tissue interface, organ, multi-organ, …). Regulatory bodies are familiar with such methods. The focus is on efficacy in humans. Variety across humans and personalized treatments are challenges to the current approach. Unavailability of ex vivo models is a serious limitation in certain disease areas. Alternatives to clinical testing with high predictability towards clinical tests are sought by pharmaceutical companies, regulators and clinicians. Drug efficacy testing in an essential and costly step and relates to the core property of the drug. It impacts treatment options and market access directly.

Judgement of the current situation and the transitional effort: A first look into the case already reveals at Step 1 of the methodology that in one scenario, OoC technology would fill a significant gap, while in the other scenario, OoC technology would rather complement than replace an established technology. Consequently, the drug efficacy case is split in these two subcases.

Subcase 1: OoC technology provides a novel predictive method (filling a gap; see Table 4 For those applications where an ex vivo disease model is basically unavailable (e.g. Alzheimer's disease), this is a very positive starting point to consider drug efficacy a beach head application/market for OoC that would face comparably low burdens for adoption. Desirability is very high. Little convincing effort may be needed but over-selling (time-to-product should be avoided. Development needs a very tight interaction with regulators since there may be no familiarity at all with the OoC technology proposed. Investment costs may be very high, but reuse/standardization may be too limiting/time consuming, i.e. too early. This is a high-risk high-gain scenario.

Table 4: Judgement table for OoC for drug efficacy: No pre-existing pre-clinical solution

(+) positive, (o) neutral, (-) negative	**Current situation**	**Appreciation of improvements by introducing OoC technologies**	**Triggering**
Desirable / Desirability	(-) No ex vivo solution available.	(+) OoC fills a gap with a clear need. (+) Possibly, the non-predictive animal testing can be replaced by a predictive method.	Build on expressed, well-known need in society; patients, clinicians are convinced. Convincing payers remains. The 3R benefit is second. (ethics)
Safe / Safety	(-) Difficult and late safety assessment due to bad predictability.	(-) Little benchmark data to compare with in pre-clinical phase (validation!) (-) Regulators may not be familiar with novel OoC approach (validation!)	Requires early involvement of regulators. Exploit special routes if available. (regulation)
Efficient / Efficiency	(o) Limited methods in place but possibly relying on well-known standards.	(-) May require from scratch investment in technology and its validation.	Standardization is too early. Cost may be second in the beginning. (standardization)

Subcase 2: OoC technology complements existing methods (see Table 3): For the case, where OoC technology is positioned to provide complementary data, this would primarily serve for either improving outcome and/or reducing cost of failure/risk of limited market size. Desirability requires clear positioning and depends on which improvement compared to the non-OoC approach is expected. Since the OoC technology appears as a delta on top of existing techniques which are not replaced, it is important to e.g. share/reduce costs by standardization. On the regulatory side, this can build further on existing efforts. Hence, where existing ex vivo disease models are incomplete (e.g. adding immunology properties), this is a positive starting point to consider drug efficacy a beach head application/market for OoC that would face comparably low burdens for adoption. Desirability is high, but it will be essential that OoC technology outperforms current practice in an efficient way. Cost needs to remain under control.

Table 3: Judgement table for OoC for drug efficacy: Improving predictability of pre-clinical solution

(+) positive, (o) neutral, (-) negative	**Current situation**	**Appreciation of improvements by introducing OoC technologies**	**Triggering**
Desirable / Desirability	(-) limited or unclear indication or outcome	(o) 3R may not be positively affected. (+) better targeting / outcome of drug treatment.	Primarily statement towards better outcome (longer term), i.e. priority setting (ethics)
Safe / Safety	(-) Limited predictability of existing solution. (+) Established procedure known to regulators and mastered by users.	(+) Complementary data view; positive support from regulator yet added benefit of complementary data should be validated.	Work explicitly on the data with the regulator; exploit established relationship. (regulation)
Efficient / Efficiency	(o) Established solution works. (-) Risk of late failure or reduced efficacy affecting indication/patient target group.	(-) May increase short-term costs if both methods are used in co-existence. (+) May reduce long-term costs if failures can be reduced or improved efficacy can be proven.	Cost-sensitivity: as an add-on technology this would benefit from standardization/sharing effort (standardization)