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1 Contents

2 Executive Summary

This deliverable motivates the need for a concise primer on the (potential) use of Organ-on-Chip (OoC) technologies and the ethical implications to enter in a structured way into the dialogue with non-specialists. Part of the deliverable is a concise primer for separate, public distribution. It aims at enabling transparent communication with the public at large, particularly taking into account ethical concerns.

Purpose: OoC technologies are not yet common and mainstream tools. However, they have significant potential to introduce improvements and changes to processes and practises in drug toxicity and safety of cosmetics or chemicals, pharmaceutical drug development including predicting drug efficacy, personalised therapies, and fundamental understanding of disease mechanisms. We are only just beginning a roadmap for OoC and hence are excellently positioned to enter a fruitful dialogue with the public at large with realistic expectations. The public at large does not yet know what OoC technology is, at best the pervading opinion may be empirically regarded as positive. This is a good basis to present a realistic view of OoC. Part of the deliverable is a concise primer for separate, public distribution.

Methodology: An overview of ethical implications of the use of OoC technologies has been prepared in Deliverable D5.1, primarily based on literature and press resources. Additional opinions were collected from remarks on ethical aspects and perception by the public at large expressed through interviews of representative stakeholders organized in WP2 (see D2.2 and D2.3 and their respective annexes), and from participants to the ORCHID Vision Workshop and the ORCHID Strategy Workshop. The ORCHID consortium has also prepared an extensive 30-page brochure "ORCHID - Towards a European roadmap for Organ-on-Chip". Both were used in conjunction with examples from other initiatives to motivate the need and content of a concise primer, directed at the public at large, and to draft such a concise primer. Note that in Deliverable D5.3 we prepare dedicated routes to address interactions with specific stakeholders in the value chain such as industry, government, regulators, etc.

Conclusions: Appropriate engagement with the public at large on the use and potential impact of OoC technologies is important. Timing for communication with the public at large appears appropriate with the exponential increase of activities and scientific media attention on the use of OoC technology. We present a concise primer with appropriate terminology and scope to open the communication with the public at large.

3 Introduction to this Societal Primer

OoC technologies are not yet common, mainstream tools. However, they have great potential to initiate significant improvements and changes to processes and practises in drug toxicity and safety of cosmetics or chemicals, pharmaceutical drug development including improving assessment of drug efficacy, personalised therapies, and fundamental understanding of disease mechanisms.

It is primarily the research community that is well informed on the state-of-the-art around OoC technology. Industry is slowly yet steadily engaging and exploring possible use. Regulators and governments are in consulting or supporting mode. Clinical applications involving patient cells and tissues are in research. The public at large receives comparatively little information which may coincide with the perspective that the lead time to use/market and immediate impact on the citizens is still years ahead.

The window of opportunity for communicating to the public at large is now: We are only at the beginning of a roadmap for OoC and hence ideally positioned to enter a fruitful dialogue with the public at large with realistic expectations.

The public at large does not yet have a clear vision or understanding of OoC technology, at best the impression empirically is that there is positive attitude e.g. with respect to the potential of reducing existing ethical burdens related to animal testing that may be replaced or at least reduced due to OoC.

At present, information on OoC technology reaches general media primarily through press releases by companies or academic groups in collaboration with government funders (e.g. projects at local, national or European level) or regulatory agencies (e.g. FDA in the USA). They start from scientific, community or business news in professional media and are selectively taken up further. Scientific institutions also have produced introductory video material with comparably few assumptions on previous OoC knowledge, such as e.g. the Wyss Institute, to name one example: However, starting with a question such as “What if we could test drugs without animal models?” and answering it by stating that “[...] a multidisciplinary team of collaborators have engineered microchips that recapitulate the microarchitecture and functions of living human organs [...]” is still rather directed at a technology-savvy audience which is aware of today’s technological approaches and looking out to future alternatives.

We begin to see that OoC technology is being mentioned as potential solution to general questions of citizens on how to address present and future societal challenges. The National Science Agenda (NWA)in the Netherlands is one example. Another example is the Flemish Science Agenda, published by the Flemish Science Foundation (FWO) after considering some 10,000 questions of Flemish citizens and listing OoC twice:

- Page 26: "What is the impact of our environment on our health?" and therein the use of advanced mini-organs as laboratory models for the assessment of a.o. toxicity and safety of substances.
- Page 103: "How will we cope with animals in the future?" and therein "Is biomedical research possible without animal tests?" - The use of mini-organs and OoC technology is listed.

A balancing act: In essence, this is a good basis to present a realistic view of OoC technology at this time but without delay since professional media attention is quickly rising for the research community thanks to more professional and structural actions (e.g. through training possibilities such as EUROoC ITN, the scientific community EUROoCS with its annual joint European platform conference and last but not least the European OoC Roadmap). Relying on occasional and non-selective uptake of 'some' news from the professional media, however, may not necessarily create a balanced view and realistic expectations on what OoC technology can mean to the citizen.

Hence this primer can be of benefit. It aims at providing recommendations for an appropriate terminology and language for the public at large[1]. Note that proper visual illustration increases recognizability and catches attention of the reader; actual illustrations have been left out at the time of deliverable preparation[2]. It links the potential impact of OoC technology to concrete life scenarios of people; this is particularly important since technology-by-itself may not even be recognizable or recognized and hence not judged while this may very well be the case for its impact e.g. on health outcome or affordability. It sets out how to deal with questions on how likely or futuristic it is that specific OoC uses appear in the daily life, how OoC technology will arrive at the citizen and how the citizen may be informed or consulted. It also stimulates reflection on otherwise unrecognized dilemma's or trade-offs that citizens may be faced with.

Lifetime and relevance: This primer will not be outdated within weeks or a few months but will clearly benefit from regular updates which could be seen as an activity of overarching organizations such as EUROoCS. It is recommendable that regular events such as flagship conferences could coincide with informing general media or responding to their interest in addition to addressing scientific novelties. In this way the primer will become regularly updated, keeping it relevant[3].

[1] Obviously, translation from English into various spoken languages in Europe is mandatory.
[2] Suggestions for illustrations have been made and shall be replaced by actual illustrations that can be publicly and freely be distributed with proper copyright.
[3] It would be intrinsically of interest to keep track and analyze the changes made across versions of the primer and the sources leading to a change in order to understand where assumptions were inaccurate.

4 Societal Primer on Ethical Use and Implications

4.1 Feeling the need

The public at large will not value OoC from a technology point-of-view but will embrace it or reject it from a personal or societal benefit. OoC addressing a concrete need is a good entry point: it may be an alternative replacing limited or undesired practices or offer new perspectives and improvements on personal health.

Recommendations:

- **Explain the potential impact of OoC with respect to a concrete need.** Illustrate the impact as being perceived by the citizen, with the citizen positioned in scenarios and ideally connected to a timeline. Improved drug efficacy testing may lead to shorter time-to-market and earlier availability of novel therapies but may not lead to reduced pricing. Perception of the citizen may vastly differ from the driving forces for the value chain involved. See later on how to balance expectations and avoid overpromising or setting up an unbalanced view that may compromise trust.

- **Give the technology aspect of OoC an appropriate but not central place. The use case is more central.** The entry point should likely not be on the beauty or complexity of a hybrid of biology and chip technology solving a problem. Instead, be specific on how OoC technology helps providing a better solution and addressing a concrete need. Help the audience perceiving the impact of the new OoC-based solution.

- **Give the right perspective for the impact for OoC in time.** Researchers may underestimate that even successfully proven prototype technologies need to pass to qualification and production phases that may prolong time-to-market for years. Consider also that e.g. reducing the time for development of drug efficacy tests may or may not lead to perceivable effects on time-to-use for the citizen. Instead, use of OoC technology may lead to breakthroughs for disease understanding especially where adequate alternative models are lacking. However, predicting time-to-market is difficult here.

- **Be aware that cultural and value differences may influence perspectives.** Preferences and priorities of benefits or perceived risks are very personal, may depend on personal context and relations or culture. E.g. while the use of OoC technology for drug toxicity and safety testing may be one of the first market opportunities, this is partially triggered by political and societal choices, e.g. emphasizing the search for alternative techniques for animal testing[4]. Supporting the replacement or reduction of animal testing triggers different people and people differently (being impersonally vs personally affected) as compared to e.g. advancing personalized therapy. This case may appeal to some but not to everybody. Even counter-opinions are present stating that 3R-induced reductions on animal testing may lead to reduction of research on orphan diseases while OoC-solutions are not yet ready.

[4] Legal and regulatory conditions and practices differ strongly between Europe (strong regulation), USA (somewhat less strong and different regulation), and e.g. China (significantly lower legal and regulatory burdens).

4.2 It all starts with a good definition and the right words

Various definitions and interpretations exist today on what OoC stands for. As one of the first actions, the ORCHID consortium has formulated a sufficiently complete definition supported by a variety of stakeholders as follows:

> *An Organ-on-Chip is a fit-for-purpose microfluidic device, containing living engineered organ substructures in a controlled microenvironment, that recapitulates one or more aspects of the organ's dynamics, functionality and (patho)physiological response in vivo under real-time monitoring.*

One cannot assume that the public at large is familiar with what OoC stands for. The definition above is fairly complete and comprehensive but likely too detailed and broad in terminology use to understand the underlying concepts.

Recommendations:

- **Reduce or translate terms to understandable concepts. Use appropriate language. Use native language.** Picturing an Organ-on-Chip might seem a mission impossible for some while others may simply question feasibility. The term itself needs to be interpreted appropriately, e.g. stating that it is a subset of an organ created from culturing patient cells.

- **Use subsets of OoC terminology suitable for the audience, emphasizing a few selected but not all aspects.** It is too complex to convey all aspects of OoC to the public at large. A layered communication approach is required. Choose the specific characteristics that make sense for e.g. a specific application of OoC or a specific benefit or a specific audience. Conceptual simplicity is essential. A red line between use of OoC technology and impact should become visible for the audience addressed. As an example, an OoC application for investigation of the harm of substances in automotive exhaust may try to resemble the major function of lung tissue exposed to various substances present in exhaust, simulating the human inhaling; all of which is part of a safety test performed by the manufacturer to fulfil requirements for admission or further improvements of the product.

- **Explain underlying rationales to create ground for understanding.** There is no single, simple narrative for the citizen that represents all opportunities of OoC technology. Do not easily assume that complex business, market or health system concepts are well known and understood. Explain underlying concepts and value chains and time perspectives where needed. It is essential to simplify as much as possible while keeping the motivational and rational narrative. Where is the fundamental issue that OoC solves for the individual or the society? How far away is the citizen from benefitting from OoC technology? OoC may lead to better drug efficacy tests and thus to faster availability of novel and more targeted drugs, but this is about transformation of the workflows in the pharmaceutical industry, normally not visible to the public at large. By contrast, using OoC with patient-donated cells in a personalized therapy will directly bring the individual patient in the loop.

4.3 Putting things in the right place

OoC is an emerging and complex technology. The public at large cannot have a natural or learnt perception on OoC since the technology is too complex and too different from present experiences. This means that expectations regarding time-to-availability, affordability, and applicability need to be carefully phrased.

Recommendations:

- **Give a notion of time-to-market with respect to the experience of the citizen**. There is a difference between time-to-research or investigational use and availability as a routine solution offered by a clinician. Present a realistic view on challenges, both on the scientific-technical side as well as on non-technical challenges (regulation, admission, market access, reimbursement).

- **Give a notion of time-to-benefit or likeliness-to-benefit.** Donation of patient cells for OoC-driven drug development may or may not lead to an individual benefit. Yet it is essential to gain access to data derived from such patient material, possibly to improve outcomes for other patient groups. It will be essential to convince citizens to embrace donation of personal data as an investment into personal and societal health, similarly to today's private and public tax and/or insurance-based contributions. This fits into the idea of moving from 'sick care' to more prevention and early diagnosis. Incentives can be more frequent feedback on lifestyle, motivation by identification with peer groups.

- **Reveal the impact of OoC on society in general that may be hidden in internal processes in research and industry.** Benefits of OoC may not be easily visible to the public at large. Improvements on drug efficacy testing may benefit the society or specific patient groups. Replacing animal experiments may only appear in statistics. In such cases, the public should be informed on how such improvements could be perceived. It may be beneficial to address such questions from government side, regulators, community actors (e.g. EUROoCS) or specific interest groups.

4.4 Embracing change but staying on top of the wave

Expectation management is important. Introducing OoC as a novel technology may create fear for those who expect changes for themselves but it may also create unrealistic promises for others that may expect breakthroughs in healthcare tomorrow. Change needs to be managed properly, with a realistic pace and with controlling and monitoring progress, always consulting all affected actors and thus also the public at large.

Recommendations:

- **Explain benefits but also address obligations or caveats that may come along**. Especially for personalized therapies, significant changes to the diagnosis and treatment process involving the citizen as a healthy person and possibly patient are expected. Donation of patient material, use of patient-specific data etc. require appropriate consent and thus ways to properly inform citizens so that they understand the consequences and needs to change procedures. Streamlining of consent processes may be important to keep this manageable for the individual.

- **Avoid information overload and confusion.** The public wants to be informed but information overload must be avoided. Keep concepts and terminology as consistent as possible. Aggregate findings regarding expectations in roadmaps and adaptations to such roadmaps e.g. based on consensus (cfr ORCHID roadmap). It will be essential to maintain such efforts (similar to the semiconductors industry roadmap which comes with regular, predictable updates). While the research community is already experiencing difficulties in keeping track of the exponential output in science and technology for OoC and resorts to structural, collaborative solutions (e.g. EUROoCS, joint conferences, key journals), the public at large should not be burdened with this information burst.

- **Situate ethical questions and implications in the science & technology roadmap for OoC.** Time-to-market allows in most cases to address ethical and impact questions alongside with further technological development such that a fruitful ground can be prepared for regulatory support, market access, or health systems and for adoption by citizens.

5 Conclusions

Appropriate engagement with the public at large on the use and potential impact of OoC technologies is important. Timing for communication with the public at large appears appropriate with the exponential increase of activities and scientific media attention to the use of OoC technology. We present a concise primer with recommendations for the use of appropriate terminology and realistic scope for communication with public at large or as an introductory starting point for more specific communication.

Next steps: The primer itself will be made available as public information material through the ORCHID website. It can be integrally used or used in parts. Use in parts is considered when it comes to participatory workshops with e.g. citizens or even as introductory material for the preparation of consent forms for patients. Uptake into outreach and communication of EUROoCS will be considered. Many recommendations presented here will be translated into detailed actions in the further course of the ORCHID project and both progress and future advice will be summarized in deliverables D5.6 and D5.7 upon availability of the OoC technology and application roadmap.

6 References

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