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Abstract

Healthcare systems are faced with the challenge of providing access to innovative technologies and drugs, while shouldering the high prices, which pharmaceutical companies often justified by the high costs of pharmaceutical research and development (R&D). An emergent technology that may transform R&D efficiency is Organ-on-Chip technology. Since no quantitative evaluation of the technology exists thus far, we sought to quantitatively establish its impact on R&D costs.

We conducted a scenario-based budget impact analysis of Organ-on-Chip technology over a period of five years. Relative change in costs was assessed through a survey based on an R&D productivity framework that considered each phase of the drug development process and the corresponding main cost drivers. Relative efficiency change was derived by means of expert elicitation, modeling a probability distribution around likely cost estimates.

We conducted 17 interviews with experts in the Organ-on-Chip and R&D fields. Overall, experts expected a significant reduction in the total R&D costs, reaching up to a one quarter reduction in costs. While all cost drivers were impacted, savings were mostly achieved by improving the success rates. The R&D phases in which experts expected the most benefits were the lead optimization and preclinical phases. Our results showed a potential for significant impact of Organ-on-Chip technology on the costs of pharmaceutical R&D. Technological readiness of the R&D environment and acceptance from the regulatory agencies were mentioned as the main barriers for actual implementation.

This study was performed in the context of the H2020 ORCHID (Organ-on-Chip In Development) project, and will contribute to the aims developing a roadmap on Organ-on-Chip technology guiding the R&D efforts, raising awareness and building an ecosystem for this technology in Europe. The focus of the impact study was laid on the effect of the use of Organ-on-Chip models on the costs of the drug development process. Further studies within ORCHID and the final roadmap will define the strategy and priorities to respond to technological and regulatory uncertainties as identified in this study.

The full details and results of the study will be made available after publication of the article.

Introduction

Industry and academia are constantly seeking to increase the efficiency of pharmaceutical R&D by improving the ratio of investment (input) to new medicine (output)¹⁻⁴. An emergent technology that may play a transformative role in R&D is the Organ-on-Chip technology. Organs-on-Chips are microfluidic devices containing chambers with vasculature-like perfusion, that are inhabited by living cell structures that mimic the physiological architecture and function of human tissues and organs in a controlled environment^{5,6}. The technology is thus a promising substitute for traditional *in vitro* and animal models, which have shown limited predictability for the effects of drugs in the human body, as they often inaccurately model human cellular physiology^{7,8}. Organ-on-Chip technology might therefore reduce drug discovery costs by reducing the gap between pre-clinical testing and human trials through a higher chance of success^{9,10}.

Despite the potential for increased predictability in drug modeling, increased success rates and reduced overall R&D costs, the available literature is mostly focused on the technical development of Organ-on-Chip models, while its potential financial impact remains unclear. Thus far, no quantitative study on its budget impact has been published¹²⁻¹⁴. In early stages of technology development decisions are taken with the highest impact on costs and, as cost effectiveness is expected to be increasingly influencing coverage decisions, early-stage health economic models, such as budget impact analyses, are increasingly important to guide research policy decisions.¹¹

The objective of this study was therefore to explore the impact of Organ-on-Chip technology on the costs of pharmaceutical R&D with a horizon of five years, and thus to determine its practical viability in order to inform future decision making in R&D.

Methods

We conducted a budget impact analysis to calculate the expected changes in R&D costs with Organ-on-Chip technology, compared to the R&D process as it stands now with a time horizon of five years. We assessed the expected cost impact of Organ-on-Chip technology by means of expert elicitation. The guidelines on good practice in budget impact analysis of the *International Society For Pharmacoeconomics and Outcomes Research* (ISPOR) were followed and adapted to the study's specificities¹².

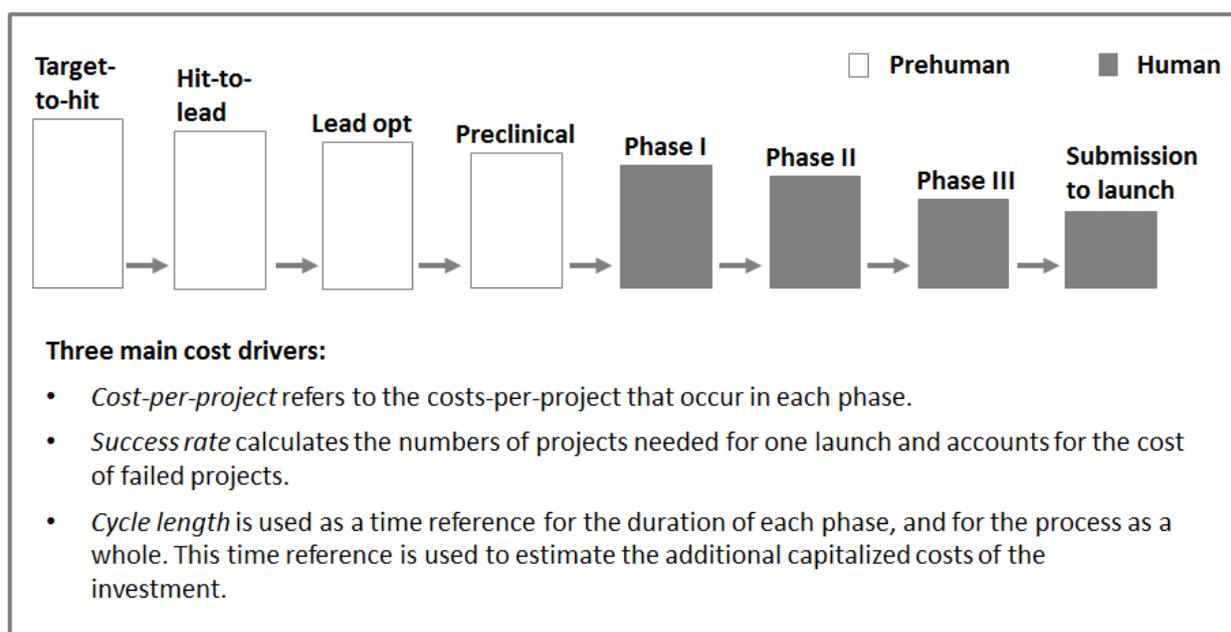
Underlying R&D development framework and baseline cost estimates

The R&D process as it exists today served as a comparator for the budget impact analysis. In literature commonly estimates of R&D costs are used, since actual cost data per phase or successfully launched drug is not publicly available. Various approaches, models and cost-outcomes concerning R&D costs can be found^{1,2,5,18}. We chose the model and cost estimates of Paul et al.² as basic framework because it

allows analyzing cost drivers on the most granular level. Due to this level of granularity, we can capture the experts' opinion on the exact application area of the technology, its impact on the main cost drivers and thus can calculate the corresponding impact on total R&D costs much exacter than with other available models.

Paul et al divides the R&D process into eight phases, starting with the 'Target-to-hit phase', and ending with the 'launch' of the new medicine. The authors then modeled total costs of R&D by considering the three cost drivers *cost-per-project*, *success rate* and *cycle length* for each R&D phases (Figure 1). Converted to 2018 USD million, Paul et al. estimate the total costs of R&D to be \$2060². For a more detailed overview, please refer to the original publication².

Figure 1 | R&D phases, adapted from Paul et al, 2010²



In the literature, cost estimates of R&D costs per new launch (in 2018 USD million) range from \$330 (Young¹³), \$660 (Prasad¹⁴) to \$2760 (DiMasi¹⁵), with the two latter being the most discussed in recent years. All of these estimates have, however, been criticized for various methodological reasons^{14, 16}. Furthermore, costs can vary widely depending on factors such as including the initial, often publicly funded phases, takeover- or licensing, sums of startup companies, internal definitions of pharma on what is to be labeled as R&D, etc.

To cope with the missing of actual cost data and the uncertainty in estimates, we reported the cost change as a percentage. Paul et al. 's absolute cost data were only used as reference points in the interviews. We converted this data to a relative change (for example 30% cost increase or decrease) and applied this relative change to the absolute cost estimates of Prasad et al.¹⁴ and DiMasi et al.¹⁵. We can therefore report a range of the possible budget impact depending on the existing cost estimates.

Expert elicitation

When there is no data available during the early development phases of a technology, cost estimates can be derived from experts¹⁷. Elicitation is the process of expressing a person's knowledge and beliefs about one or more uncertain quantities, as a probability distribution for those quantities¹⁸. This method is used to characterize uncertainty regarding the potential performance of a medical technology, in order to support development decisions¹⁹. We selected experts based on their knowledge of both Organ-on-Chip technology and the R&D process and only experts with experience in both areas were included. The following stakeholder groups were considered: the biotechnology industry, the innovative pharmaceutical industry, the Organ-on-Chip industry, academia and regulatory bodies. We focused especially on the stakeholders in biotechnology and pharmaceutical industry. In addition, to gain a more complete perspective, we also performed interviews with the other stakeholder groups. We compiled a directory of relevant Organ-on-Chip experts using the expert network of the ORCHID consortium. We then selected experts by purposive sampling from this directory, and snowballed to identify further relevant experts. Experts were approached via e-mail to ask for an interview.

Analysis

The results were synthesized using linear opinion pooling, the most commonly used method in expert elicitation²⁰. To account for heterogeneity among experts, the results were weighted based on self-rated experience in R&D and Organ-on-Chip. For this, we asked the experts to rate their experience on a scale of 0-10, 10 being the maximum.

We also conducted a scenario analysis, using the variation in expert input to create an optimistic, a pessimistic and a medium scenario.

Results & discussion

We identified 24 experts, of which 17 agreed to be interviewed and take part in the reiteration steps. We added two qualitative interviews with regulators to enrich the information on barriers and facilitators. The 17 stakeholders covered the categories: innovative pharmaceutical (n=7) or biotechnology (n=3), academia, (n=3), Organ-on-Chip developer, (n=1) and regulator (n=3).

Our results confirm a significant impact of Organ-on-Chip technology on the costs of pharmaceutical R&D over a modeled time frame of five years. All experts that were consulted estimated a positive (cost saving) budget impact of the technology on total R&D costs. Expected improvements were particularly strong in the aspect *success rates*: Since Organ-on-Chip models can mimic *in vivo* tissue and cellular kinetics with better reliability than current *in vitro* and animal models, predictability of drug effects in the human body is increased. These results are in line with the qualitative impact discussions currently seen in the literature^{5, 8, 9}. We found the highest degree of controversy on the impact of Organ-on-Chip technology on the *costs-per-project*. A small percentage of experts estimated that the *costs-per-project*

would increase due to the cost of the technology, while the majority rationed that the industry is under so much pressure that it does not allow for cost increases and would hence not implement cost increasing technology. The change in *cycle length* showed the highest degree of consensus.

An analysis of the R&D phases, in which Organ-on-Chip technology is expected to have an impact, showed that the most substantial applicability and impact is expected in lead optimization and in the pre-clinical phase. There is however disagreement on its impact on the clinical trial phases. While the technology has a wide range of application possibilities, the industry as a whole has yet to determine its optimal area of application. This was a major justification for the macro perspective design employed in the present study, as it allowed us to capture this range of potential and ascertain the areas of application. Since all of our experts are either already using or highly interested in Organ-on-Chip technology, our results are more likely to reflect a positive view on the technology's potential, rather than a true industry snapshot. Experts who are currently not working with the new technology are likely to have a more critical perspective as is common in the diffusion of innovations. There is, for example, a general skepticism towards the idea that technology can actually reduce costs in R&D. According to Eroom's law, R&D becomes slower and more expensive as a function of time, independent of technological progress²¹. One aspect of why a large cost reduction due to Organ-on-Chip technology is actually plausible is that it primarily affects success rates, which has a large effect on R&D costs².

Despite a clear trend, our response data showed a large variation of uncertainty in answers. Next to uncertainties originating from the study design, there are those caused by specificities to Organ-on-Chip technology, which are of special interest for future decision-making. Specifically, the experts discussed technological and regulatory aspects as the main drivers of uncertainty. While the technological readiness is mostly discussed among experts and literature²², regulatory uncertainties are less discussed. Commercial experts as well as regulators mentioned the regulatory change as a main challenge because it will determine whether Organ-on-Chip technology will be a mere addition to existing R&D procedures, or a real substitute for conventional protocols.

Conclusion

With Organ-on-Chip models evolving from a theoretical concept to an actual alternative to conventional *in vitro* and animal models, regulators and industry are challenged to determine its commercial viability in order to justify further investments. While emphasizing the need to prevent ‘over-hype’, the experts we surveyed clearly saw the technology’s potential for cost savings in the R&D process and a positive budget impact, reaching up to a one quarter reduction in costs. When reinvesting these savings in R&D, patients could profit of a considerable increase in the number of new drugs. While the discussion around Organ-on-Chip’s impact is currently still very technical, it is crucial that decision makers consider the challenge of adapting the regulatory environment to keep pace with the technology’s maturation.

The full details and results of the study will be made available after publication of the article.

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Appendix

The impact of Organ-on-Chip technology on pharmaceutical research and development costs

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