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Impact of organ-on-a-chip technology on pharmaceutical R&D costs

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Healthcare systems are faced with the challenge of providing innovative treatments, while shouldering high drug costs that pharmaceutical companies justify by the high costs of R&D. An emergent technology that could transform R&D efficiency is organ-on-a-chip. The technology bridges the gap between preclinical testing and human trials through better predictive models, significantly impacting R&D costs. Here, we present an expert survey on the future role of organ-on-a-chip in drug discovery and its potential quantitative impact. We find that the technology has the potential to reduce R&D costs significantly, driven by changes in direct costs, success rates and the length of the R&D process. Finally, we discuss regulatory challenges to efficiency improvements.

Introduction

Healthcare systems are faced with the challenge of providing access to innovative and lifesaving treatments while shouldering the cost of expensive medicines. Pharmaceutical companies often justify high drug prices by the costs of pharmaceutical R&D. The actual R&D costs, however, are unknown to the public and highly disputed [1,2]. Because there is no direct relationship between costs and pricing [3,4], transparency in aspects of both processes contributes to the debate on acceptable prices [5]. Additionally, R&D requires a large amount of externally financed capital, which restricts the market entry of biotechnology companies [6]. The cost of R&D, therefore, burdens society by limiting innovation and ostensibly keeping drug prices high. R&D cost and efficiency data are sparse but relevant for all stakeholders.

Industry and academia are constantly seeking to increase the efficiency of pharmaceutical R&D by improving the ratio between investment (input) and new drugs (output). The main drivers of costs are success rates, development time (cycle time) and the direct costs per R&D project (costs-per-project) [7,8]. These cost drivers differ significantly between R&D phases [8]. For instance, 60–75% of all projects that succeed in non-human phases with lower costs-per-project fail in the more expensive Phase II, and 20–30% fail in Phase III [8,9]. About 50% of these failures are caused by insufficient drug efficacy and 15–25% by safety concerns [10,11]. Clinical phase failure is thus considered a major driver of R&D costs [8,12] and better predictive models are needed. A prominent example is the epacadostat/Keytruda® combination – in April 2018 the biotechnology company Incyte announced the failure of its Phase III combinational study in patients with unresectable or metastatic melanomas [13]. Previous studies had shown promising results and other major players were also invested in trials. After the announcement of failure, not only did Incyte's stock price fall by 23% within one day [14] but Roche and Bristol-Myers Squibb also discontinued their trials. This example shows the consequences of late failure and the need for better predictive models.

An emergent technology that might play a transformative part in pharmaceutical R&D is organ-on-a-chip. An organ-on-a-chip is a microfluidic platform creating controlled microenvironments with vasculature-like perfusion, in which human multicellular structures mimicking the physiological architecture and function of human tissues and organs are integrated [15,16]. The technology has been

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developed to substitute *in vitro* and animal models, which often inaccurately model human physiology [17,18]. Organ-on-a-chip technology is thus thought to improve drug discovery by reducing the gap between preclinical testing and human trials [19,20]. Despite the potential for R&D efficiency, the majority of research so far is directed toward the biophysical potential of organ-on-a-chip, leaving its financial impact unclear. Although several research groups have performed studies showing its actual potential in drug research [21–23] and made strong assumptions about a possible impact, no quantitative study has been published. The objective of this study is to explore the quantitative impact of organ-on-a-chip on the efficiency of pharmaceutical R&D. We surveyed experts to evaluate the technology's impact on R&D cost in relationship to the three main efficiency drivers (costs-per-project, success rate and cycle time), per R&D phase, within a timescale of 5 years.

Estimating the costs of R&D

Establishing an appropriate comparator is a challenge in the impact evaluation of any new technology in the pharmaceutical R&D process. We assessed the expected impact of organ-on-a-chip in comparison to the current costs of R&D per new drug. Cost estimates were derived from literature, because actual cost data are not publicly available. Cost estimates per new drug vary widely and range from US$330[†] [24], US $660[†] [2], US$2060 [8] to US$2760[†] [1]. Methodology and data sources are often nontransparent and differ in choices like time horizon and the approach to account for failures [2,25]. The true costs of R&D are hence unknown. To account for this uncertainty, we assessed only a relative change and applied this result to a cost range of US$660–US$2760 per new drug using two mostly cited estimates. We chose the model of Paul *et al.* [8] as a primary comparator to assess the relative change because it demonstrates methodological transparency, and granularly breaks down cost drivers per R&D phase.

To estimate the costs of a drug launch, Paul *et al.* [8] defined eight phases of R&D (from 'target-to-hit' to 'submission to launch'), and modeled costs per phase along the three most important independent cost drivers: cost-per-project, success rate, cycle time. Cost-per-project refers to the direct costs of a project, for example the costs of running a lab. Success rate describes the numbers of projects needed for one launch and is used to account for the costs of failed projects. Finally, cycle time is used as a time reference for the duration of each phase and the total process. Because the R&D process is lengthy, time is used to estimate the capitalized costs of the investment. All variables are analyzed on a per project basis, for example per single drug candidate. Together, values for each cost driver and phase are used to calculate the overall costs of R&D per new drug [8].

Using this granular model structured the discussion on application and impact with experts. Fifteen experts were surveyed to quantitatively estimate the change in cost drivers per R&D phase. These data were used to rebuild the model of Paul *et al.* and calculate a total change in R&D costs. We also surveyed the underlying uncertainty of estimates and fitted beta distributions to the elicited data. All experts were in leading R&D positions with practical experience with the organ-on-a-chip. They belonged to the stakeholder categories innovative pharmaceutical ($n = 7$), biotechnology ($n = 3$), academia ($n = 3$), organ-on-a-chip developer ($n = 1$) and regulator ($n = 1$). Detailed explanations of the model are presented in supplementary files (see supplementary material S1 online).

Total impact on R&D costs

We sought to fill a gap in the knowledge surrounding organ-on-a-chip by determining its impact on pharmaceutical R&D costs after promising results appeared in several studies regarding its biophysical potential [21–23]. Overall, the surveyed exerts confirmed the significant potential impact of organ-on-a-chip on the total costs of R&D over a modeled timescale of 5 years. With an average total R&D cost reduction of 10–26%, the experts estimated a positive (cost saving) impact of the technology. Experts estimated that the impact of organ-on-a-chip on R&D could range between −32% (reduction) to +3% (increase). Figure 1 shows the combined probability density function of the elicited beta distribution including the 95th confidence interval. Fifty percent of the distribution values fall between −26% and −10% change of total R&D cost reduction, and 80% of the distribution values lie between −30% and −4%. The combined probability distribution of all experts on total R&D costs consisted of the following limits: lower limit −32%; Q1 −26%; median −19%; Q3 −10%; upper limit +3%. The corresponding beta-distribution was defined with parameters $\alpha = 0.9643751$ and $\beta = 1.360814$ standard errors of the elicited limits and percentiles ranged from 1.5% for lower limit and 0.8% for Q3. Applying cost reductions of 10–26% to estimates of total R&D costs, absolute cost savings in an average scenario range from US$66–169 million [2] to US$276–706 million [1]. Further information on a scenario analysis can be found in the supplementary information (see supplementary material S3 online).

Impact per cost driver and R&D phase

The experts reported the most impact in the preclinical phase where 73% of experts identified a change in cost-per-project, 80% in success rate and 40% in cycle time. Lead optimization was the second-most impacted phase (53% cost-per-project, 47% success rate and 67% cycle time). The biggest impact was reported in the cost-per-project in the preclinical phase (Q1 −21%), cycle time in lead optimization (Q1 −19%) and success rate in Phase II (Q3 +17%) (Fig. 2).

We analyzed how the isolated cost drivers impact the cost reduction (Fig. 3). Here, baseline costs were applied to two drivers to examine the total cost change attributable to the third variable. Success rate was the biggest driver of efficiency change (lower limit −22%; Q1 −26%; median −13%; Q3 −10%; upper limit 0%), followed by the costs-per-project (lower limit −14%; Q1 0%; median −4%; Q3 −9% upper limit +5%). The smallest reduction, but the highest level of certainty, was seen in the cycle time (lower limit −5%; Q1 −2%; median −3%; Q3 −5%; upper limit −1%). Additionally, we conducted a series of additional analyses, including two granular cost driver analyses, sensitivity analyses and scenario analyses, which we present in the supplementary information (see supplementary material S3 online).

Connecting impact estimates and areas of application

With 73% of experts believing in an impact on the cost-per-project, and 80% in an impact on the success rates, the preclinical phase showed the highest applicability, followed by the lead optimization phase. Because organ-on-a-chip is thought to substitute animal models and 2D cell culture assays, this confirms the areas of technical application that have been discussed [15,18,19]. As organ-on-a-chip increases the predictability in early R&D phases, success rates increase because only projects with a better chance of success will be selected. Hence, fewer projects at early stages are needed to achieve a launch of a new drug. The large impact on the cost-per-project of the preclinical phase (Q1 −21%) and the cycle time of the lead optimi-

[†] Converted to 2018 US$ million.

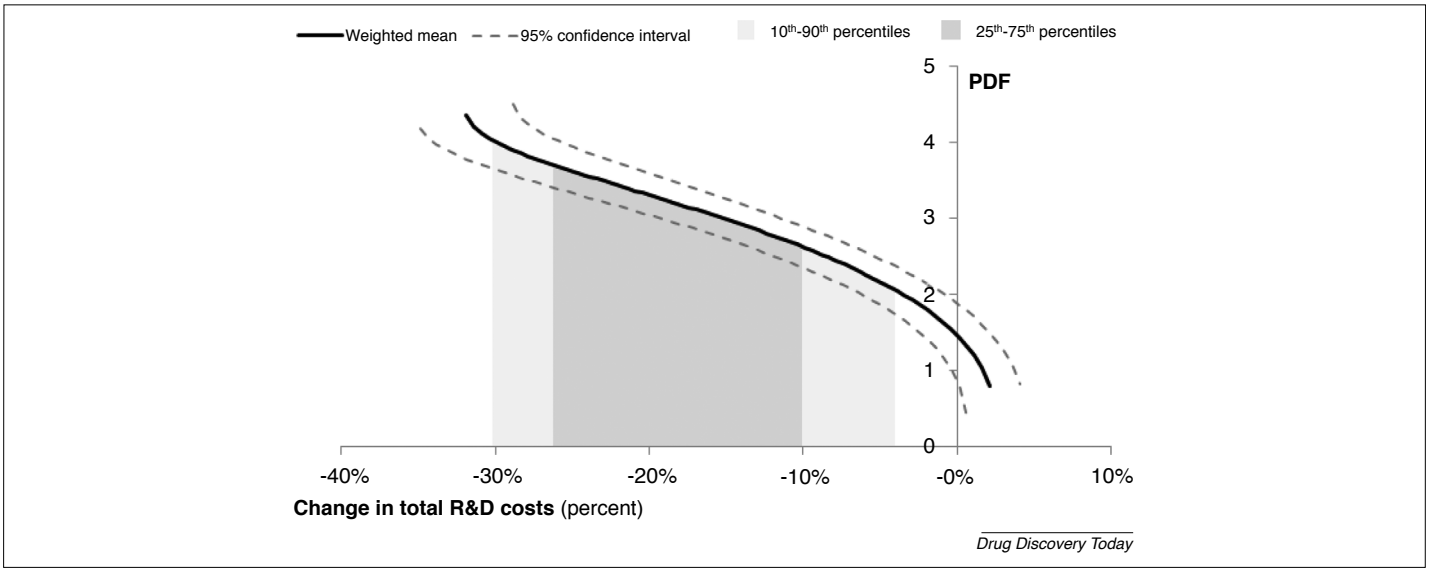

FIGURE 1

Relative likelihood of organ-on-a-chip-induced change in total R&D costs: probability density function (PDF) of the beta distribution. Analysis of the relative likelihood of the change in total R&D costs owing to organ-on-a-chip in 5 years. The probability density function (y axis) is plotted as a function of the from the experts' survey probable change in total R&D costs (x axis). The dashed lines represent the 95th confidence interval of all values. The shaded area represents the area under the curve: 50% of all values show a reduction in total R&D costs of 10–26% (dark gray). Eighty percent of the values show a reduction in total R&D costs of 4–30% (light gray).

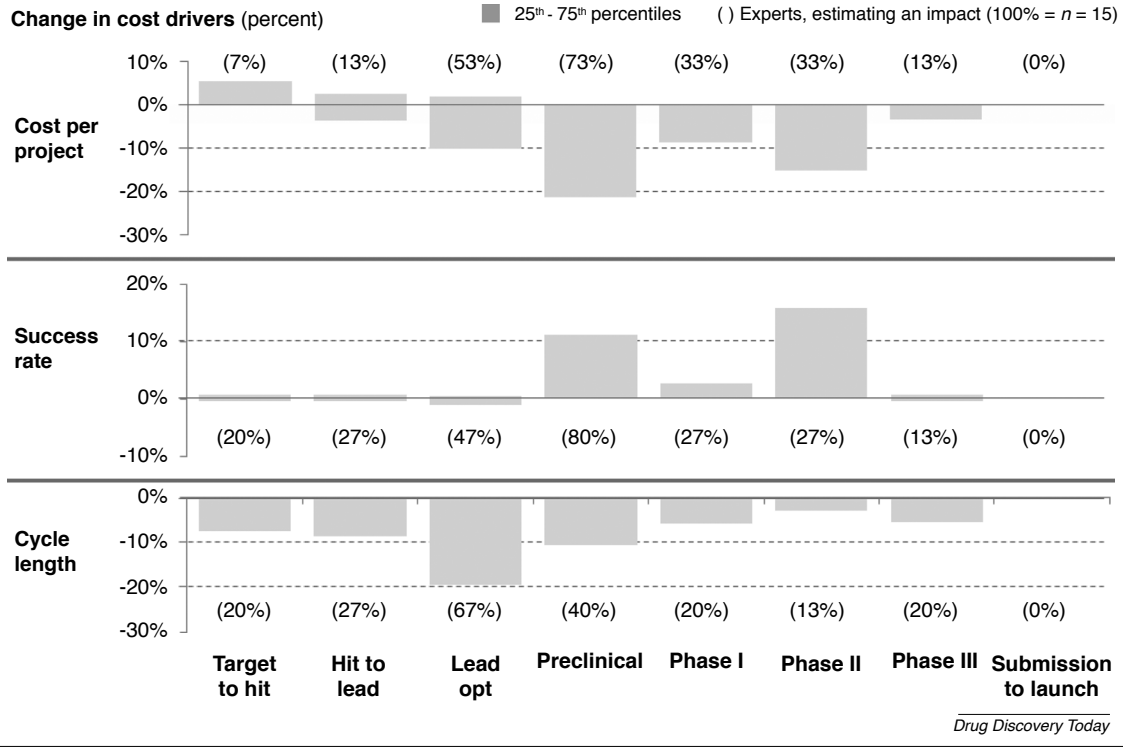

FIGURE 2

Impact of organ-on-a-chip on cost drivers per R&D phase. Analysis of the change in cost drivers per R&D phase owing to organ-on-a-chip in 5 years. Experts (n = 15) were allowed to choose a maximum of three phases per cost driver, in which they estimated organ-on-a-chip to have the most impact. The percentage of experts that believe in a change is shown in brackets. The level of relative change in cost drivers (percent) per R&D phase is represented by the bars.

zation phase (Q1 −19%) are also a result of better predictability. The experts believed that the technology will help to make quicker and more-precise decisions during these stages. We also reported an effect on the success rates (Q3 −17%) and cost-per-project (Q1 −15%) of Phase II. Our results showed, however, disagreement among experts whether and to what degree the technology will increase predictability in clinical phases within 5 years. Only 13–33% of experts (depending on the cost driver) expected an impact in Phase I–III. From these experts, the

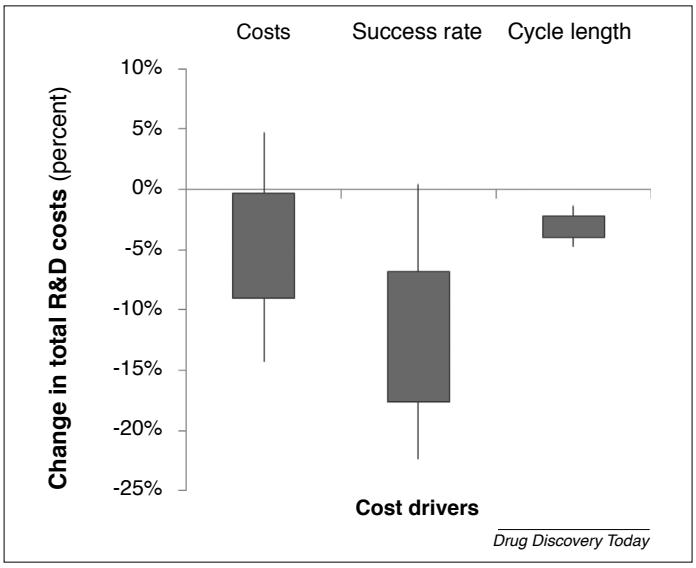

FIGURE 3

Cost driver analysis. Analysis of the impact of the cost drivers on a change in total R&D costs. The vertical lines show the range of possible values and represent the minimum and maximum values. The gray columns represent the interquartile range of the results (n = 15).

majority reported an effect in Phase II, suggesting that the technology's advantages are mainly in terms of efficacy and not safety. Experts discussed that a better understanding of the target population could lead to easier, more-targeted patient recruitment. One expert remarked that, if organ-on-chip was capable of identifying appropriate biomarkers, it would be the 'Holy Grail' of biotechnology.

Looking at the importance of the different cost drivers, our results showed a significant 10–26% reduction potential in total R&D costs, mostly driven by improvements in success rates (Q1 +12%; Q3 +38%) and the cost-per-project (Q1 −1%; Q3 −9%). The high impact of the changed success rates shows the high influence of the indirect costs of failure. In our model and that of Paul *et al.* [8], the success rate of Phase II was the most important efficiency driver [8]. However, as previously discussed, there is disagreement between experts as to whether organ-on-a-chip will fulfill this potential within 5 years. The importance of other drivers of R&D costs differs between our results and the model of Paul *et al.* [8] – success rates in the preclinical phase and the cost-per-project in Phase II are less important in the latter model (rank 12 and 8) and are thus a result of a large change rather than the sensitivity of the model. The success rate in Phase III was ranked second place in terms of sensitivity by Paul *et al.* [8] but did not drive the impact of organ-on-a-chip in our analysis.

Changes in the R&D environment

Organ-on-a-chip could considerably change the existing R&D framework. At the current technological stage, changes are driven by developers and pharmaceutical companies. With better predictive tools, the industry is likely to move toward a model where a proof-of-concept is sought at a much earlier phase. This potentially reduces financial risks and capital requirements of pharmaceutical companies. Next to uncertainties originating from the study design (see supplementary material S5 online), there are technical uncertainties that reflect this initial change within pharmaceutical companies. The extent to which organ-on-a-chip can evolve in terms of predictability and applicability to the human biophysiology is yet to be seen. Challenges of automation, parallelization, standardization and ease of use remain, which are crucial for the adoption in an industrial setting [26–28]. Additionally, technical requirements and adoption speed will evolve differently for therapeutic areas and mechanisms-of-action of the diseases [29]. These concerns are driving the current technical discussions among experts.

Another driver of uncertainty is how regulation will adapt to technological changes. This process will determine whether organ-on-a-chip will be a mere addition to existing R&D procedures or a substitute to conventional protocols, triggering a fundamental change in the R&D. There is uncertainty as to how a highly regulated environment such as the pharmaceutical R&D process could change the status quo of *in vitro* protocols and animal models that, although with limitations of their own, are very well defined. Surveyed regulators stressed this challenge and emphasized the importance of meaningful data provision from industry.

Skepticism that technology can reduce R&D costs

Overall, the modeled cost reduction of 10–26% in the average scenario is substantial and leads to savings of up to US$169 million [2] and US$706 million [1] per new drug reaching the market. Although our results showed a clear trend, the actual magnitude of impact can only be an estimate. Because all of our experts are either already using or highly interested in organ-on-a-chip, our results are more likely to reflect a positive view on the technology's potential. 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 toward 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 progress [30]. Often the expected results, as anticipated by innovators and early adopters, take much longer to materialize when meeting the skepticism of the 'late majority and laggards'. If organ-on-a-chip increases R&D turnover, improves drugs and/or reduces the usage of animal models, the technology clearly produces social benefits. In addition, because public investments play an important part this can also trigger a public discussion if potential efficiency improvements have to be openly monitored and passed along to society in terms of lower drug prices.

Concluding remarks

With organ-on-a-chip systems evolving from a theoretical concept to an actual alternative in drug discovery and development, decision makers are challenged to determine their commercial viability. Based on the expert's input we estimated a reduction of 10–26% in R&D costs per new drug, and thus a positive cost impact. Although the discussion regarding organ-on-a-chip 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. More research is necessary to analyze regulatory challenges as well as actual insight in the exact cost impact. A public discussion is also needed to establish the importance of social returns, specifically in the form of lower drug prices.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.drudis.2019.06.003.

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