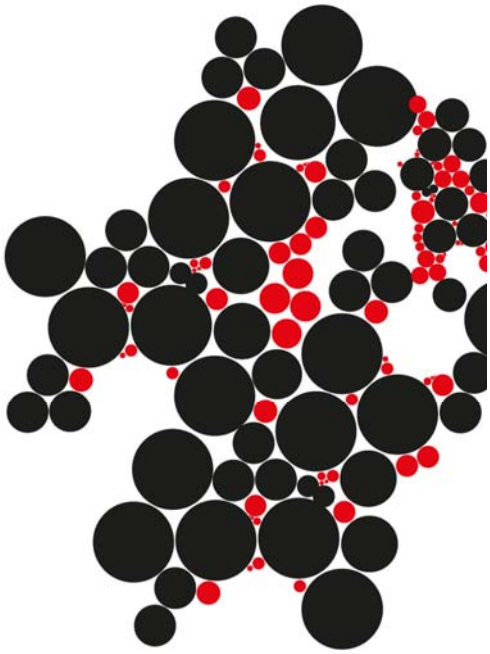

ORGANS-ON-CHIPS: EXPLORING THE UTILITY OF BIOSYNTHESISED ORGAN TISSUE TO IMPROVE EFFICIENCY OF THE DRUG DEVELOPMENT PROCESS

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Summary

OBJECTIVES: Drug development is an expensive process, partly because of the required testing for human toxicity and efficacy of drugs. Organ-on-a-chip is a multichannel 3D microfluidic cell culture chip that simulates the activities and mechanics of entire organs and organ systems. Organ-on-chip is expected to reduce the amount of animal testing, and may increase efficiency of drug development. For instance, when organ-on-a-chip is used to replace or added to in vivo testing experiments, 7.5-10% of drug development costs may be saved. This study explores the expected advantages of organ-on-chip technologies as well as potential barriers to implement.

METHODS: Stakeholders (n=50) in this research were employees of pharmaceutical companies (n=18, 36%), developers of microfluidic systems and university employees affiliated with organ-on-a-chip/ microfluidic systems development and/or drug development (n=22, 44%). Stakeholders were asked their expert opinions about the potential benefits of organ-on-chip using a survey (LimeSurvey), which was based on information previously acquired from expert interviews.

RESULTS: According to stakeholders, organ-on-a-chip may be most promising in the basic research stage (90%) or the preclinical stage (88%) of drug development. Simple models can be used for target identification (70%) while complex models could lead to replacement of animals (78%). However, head-to-head studies are needed to change regulations, leaving organ-on-a-chip as an additional test in drug development for now. There are significant differences between stakeholders' opinions about advantages. Most promising organ-on-chip developments should target organs like Liver (20%), heart (18%) and kidney (17%).

CONCLUSIONS: Organ-on-a-chip can be a valuable additional test in the drug development process, in particular in basic research or preclinical development stage. Given the very early stage of organ-on-chip technologies, it is hard to predict return on investment.

Introduction

Organ-on-a-chip

Organ-on-a-chip (OOC) is a device which can mimic cell responses more accurately than regular in vitro cell cultures. It is a multi-channel 3D microfluidic cell culture chip that simulates the activities and mechanics of entire organs and organ systems[1].

OOC is an integration engineered 3D tissue combined with a microfluidic network system[2]. In this device living cells can be cultured in micrometre-sized chambers which are continuously perfused, therefore it would be able to model a living organ on a small scale[3]. To mimic an organ even further a mechanical strain (or sheer stress) can be added to the cells, as is depicted in Figure 1. The vacuum chambers alongside the channels stretch the cells similar in a way they would in a human body.[4]

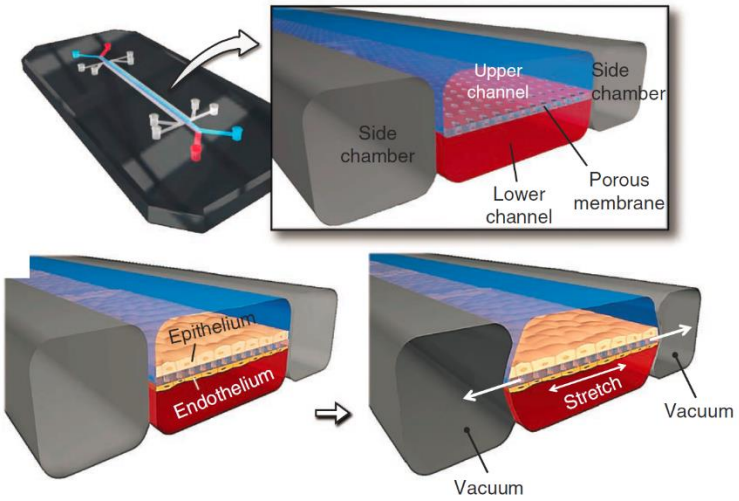


Figure 1: Microfluidic lung-on-a-chip [4]: The chip consists of two channels which represent the lung channel and the "blood" channel. With a permeable membrane in between the cells. The chip is designed to stretch in and out, therefore the cells have the same physical properties as they would have in the human body

The cells can be grown as a monolayer using only one type of cells, or it is also possible to grow different cell types or have a permeable membrane in between epithelium and endothelium cells[5]. Recently there have been developments in which multiple OOC's can be connected, making it possible to observe drug toxicity not only in the target-organ but in surrounding tissues as well[3,6].

OOC is a relatively new technique which is predicted to be useful in testing cosmetics, the effect of chemicals or environmental factors on human tissues as well as the effects of developing drugs on molecular mechanisms, biomarker identification, toxicity and even prioritizing lead candidates[3]. With multiple employable fields this research will focus on

exploring the potential use of OOC to improve the drug development process. Specifically the research will focus on which stage of the drug development process can OOC be implemented to gain most advantages.

Drug failure

Drug development is an expensive and lengthy process. The average drug development time is 12 years[7]. A well-known paper by DiMasi et. al. shows an average cost of US$ 802 million (dollar value of the year 2000) and a large increase in drug development costs once a drug enters the clinical trial phase[8]. More recently, in 2012, a new study was published using numbers published by the Tufts centre which indicates drug development costs are even higher at $1.241 million per successfully developed drug [9]. This indicates that drug development costs are still rising.

To explore reasons for high costs it is necessary to identify different stages of the drug development process, which can be found in Figure 2. The basic research and preclinical development stages can last up to seven years. Of all the drugs with which development is started only 40% will be applied for as an investigational new drug. 75% of these drugs are approved as an investigational new drug. Thus, only 30% of all drugs companies start to develop will reach clinical trial phase one and only 8% of drugs are approved for market.[10]

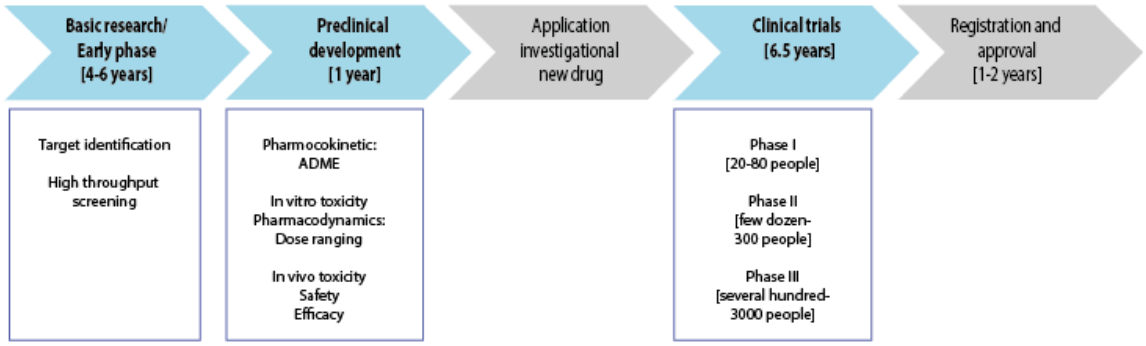


Figure 2: A schematic overview of the drug development process.

Reasons why drugs fail in clinical trials are described by Schuster et. al.[11] Of the drugs that fail in the clinical trials, 43% fails due to a lack of efficacy, 33% fail due to toxicity issues and the remaining 24% are due to several small reasons such as economic reasons and LADME. If the toxicity issues are observed, 37% of these failed drugs are due to hepatotoxicity, 33% of the toxicity failed drugs is a non-specific toxicity and the remaining 30% is divided between cardiovascular toxicity, carcinogenicity, locomotor system toxicity and other toxicities.[11] This

shows that the basic research and preclinical development phases are not predictive enough for efficacy and toxicity in clinical trials. Clinical trials are very expensive, therefore it is essential to identify those drugs that have a high likelihood of passing the evidence requirements.

Potential savings of early screening for efficacy

Using the data published on drug compounds and failures during the development process, it is possible to roughly estimate potential saving if more toxic drugs would be detected earlier in the drug development process. Box 1 depicts a back-of-the envelope calculation of the potential.

Issues in early phase- and preclinical development

Early phase- and preclinical development tests are often performed in 2D in vitro tests. These 2D cell culture models are not accurate measurements of the in vivo cellular environment. Simple 3D models are used as well and are more representative of the in vivo cellular environment, however they do not represent the properties of an organ which are imperative for the function, such as tissue-tissue interfaces and mechanically active micro-environment, such as sheer stress.[12]

There is another issue in the drug development timeline, which occurs later in the preclinical development process. This issue is due to the difference between in vitro cell reactions and in vivo animal models compared to the human body. This can lead to misjudging of the risks of a drug to humans, while the drug can be non-toxic in animals it may be toxic in humans.[13] Furthermore, animal studies are expensive, time-consuming and there are various ethical questions as to the use of animals in drug development[14].

Organ-on-a-chip in drug development

OOC can be a solution for the issues described above. Literature shows different advantages of implementing OOC in the drug development process. Some of the advantages that were mentioned often in literature are: toxicity screening [4,12,13,15–23], possible (partial) replacement of animals[2,4,12,14–17,19,21,24–29] and a higher sensitivity to external stimuli compared to the standard 2D systems [6,13,17,24,30,31].

Apart from the "standard" OOC-models, which represent one (or a part of an) organ, there are disease models on a chip in development. These disease models range from a breast cancer model to polycystic kidney disease to Parkinson's disease. These OOC disease-models could help scientists understand a disease and the drug interaction with the disease as well as the target organ surrounding the disease.[32]

An improvement in toxicity screening was demonstrated by Huh et. al. who used the drug interleukin-2 (IL-2), which is used for cancer patients and can cause pulmonary edema, and a lung-on-a-chip. The model without any mechanical strain (which simulates a breathing lung) shows hardy any toxicity, while the model in which mechanical strain is applied shows a clear toxicity.[33]

The advantages already show the diverse areas of possible use of OOC in the drug development process. It could be a replacement or addition to the current high throughput screening. In the preclinical stage of drug development OOC can be implemented as a test complementary to the animal testing, leading to eventually partial replacement of animal testing in drug development.

Initiatives for OOC development

The hDMT institute (Institute for human Organ and Disease Model Technologies) was founded in the Netherlands. This institute's aim was to form a "laboratory without walls", by combining different areas of expertise and different companies. It is a large cooperation project to develop a representative biosynthesized human test model system for drug development with the secondary goal to reduce the use of animals in the drug development process. [34]

The National Centre for the Replacement, Refinement & Reduction of Animals in Research (NC3R's) has funded many projects with the aim to replace, refine and reduce animals in research. In 2013 they have funded a project to develop an in vitro human based kidney model to measure nephrotoxicity more accurately, therefore reducing the number of animals needed. This project was sponsored by pharmaceutical companies such as GlaxoSmithKline, Pfizer and Roche.[35]

NC3R's has an annual 3Rs prize winner. The 2012 price winner was Professor Ingber from the Wyss institute, who has developed a lung-on-a-chip model[36]. The Wyss institute is acknowledged as one of the leaders in organ-on-a-chip development. It has therefore received

funding by the Food and Drug Administration (FDA) to develop chips to detect the effects of radiation exposure on humans[37]. The FDA has marked the development of OOC as a priority area to modernize technology and enhance product safety and are working together with Defense Advanced Research Projects Agency (DARPA) to realize funding for this development[38].

Technology foresight and prediction

It generally is acknowledged that is difficult to predict the effects of new technologies in a well-established market, particularly because of the difficulty to predict the progress of the development, the added value and the acceptance of this development by its users.

According to Schot there are three types of actors that can be identified in technological development. Firstly, the actors who are involved in the formulation of the objects such as R&D departments. Secondly, the actors who are involved in the regulations, such as governments. And thirdly, the so called "technological nexus". This last group of actors is important in bringing the technological and regulatory actors together by being able to understand both processes and speaking both languages.[39] The current study is focussed on the first stakeholder group. The technique is not ready to be implemented yet, it is important however to gather the preliminary opinions of this first actor group to observed whether this group has similar interests and ideas about the development of OOC.

Communication is an important factor in understanding the opinions of other stakeholders. Real-time Technology Assessment helps the communication between different stakeholders as well as the social developments. Real-time Technology Assessment attempts to anticipate how social sciences and policy research can be integrated with engineering and natural science, therefore anticipating how these research technologies will interact with social systems.[40] This research can be used to set-up an early warning system. This early warning system can be used as a practical guide in the "front end" of the development process. It can help in understanding the needs and position of developers as well as users and can prevent conflicts later on in the development process.[40] This early warning system should be set-up by an independent actor, should have defined costumers and contain a clear pathway for outputs to reach decision makers, however relevance of the technological development should be taken into account as well.[41]

Real-time technology assessment involves mapping the activity of a research programme as well. This research can be used as a first approach to this longitudinal mapping. The first opinions of stakeholders are gathered to observe whether their ideas are similar in the early development phase of the OOC model.[40] This research can neither predict the course the development will take, nor does it give a perfect foresight of where OOC should be implemented in the drug development process. It attempts to provide an insight in the opinions of stakeholders.

Research question

This paper will explore the expected benefits of using the OOC technology in the drug development process to increase efficiency. The primary research question in this study is:

At *which stage in the drug development process may human organs-on-chip technologies add most value according to preferences identified by stakeholders?*

The research question will explore:

- What are the advantages and disadvantages of implementing organ-on-a-chip in the drug development time-line? And who is influenced by implementing OOC?
- In which part of the drug development process could organ-on-a-chip be implemented and what would be the advantages?
- What advantages do the stakeholders identify? What are the similarities and the differences between the different stakeholders?

Box 1: Exploratory study

This exploratory study will estimate the potential return of early screening.

Of 100 drugs that are started in the drug development process only 8 make it through the process to approval.

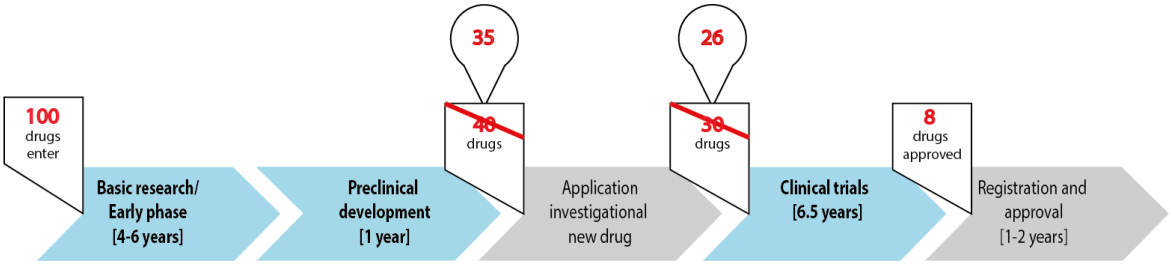
The clinical trial phase is an expensive part of the drug development process. At this stage 30 drugs enter the clinical trials and only 8 of these drugs are approved. Malorye Allison has used publications of the Tufts centre to recalculate costs of drug development which adds up to 1.241 million dollars[9] (see table**Error! Reference source not found.**).

Table: The costs of drug development according to Allison[9]

	Direct costs ($ millions)	**Capitalized costs ($ millions)**
Basic research through preclinical	60	186
Clinical through regulatory approval	109	189
Allocated failures	166	866
Total per approved drug	355	1.241

Of 30 drug started in clinical trials 7.208 fail due to toxicity reasons.

What if we could detect 5 of these 7 drugs before the clinical trial stage? Instead of 40 only 35 drugs will be applied for as investigational new drugs. Under the current circumstances ¾ of the drugs that are applied for investigational new drug are approved to go into clinical trials, therefore this case assumes this will still apply. Therefore the clinical trials are started with 4 drugs less than in the regular process (see figure).



The number of drugs that succeed per drug development stage. The numbers are adjusted to the calculated drugs that could be dropped sooner due to improved toxicity screening

Direct costs per drug in basic research and preclinical development are 60 million dollar and the costs of capital (COC) for this part is 186 million dollar. The costs for the clinical trials are 109 million dollar (direct) and 189 million dollar (COC). Per successfully developed drug the failed drugs have to be paid for as well. Per successful drug this number is 166 million dollar (direct) and 866 million dollar (COC). This adds up to a total of 1.596 million dollar.

With 4 drug less entering the clinical trials these costs are saved, which entails:

4x $109 million= $436 million

4x $189 million= $756 million

This is a total saving of $1.192 million for 8 drugs, and $149 million for a successful drug

In this scenario the new estimated price of the development of a new drug would be $1.447 million per successfully developed new drug.

This is a reduction of 10% per successfully developed drug.

However, the COC would increase per product if there are less products. COC is $189 million, number of drugs was 30, and therefore the total COC was: $189 million * 30 = $5.670 million.

In the new situation there are 26 drugs, increasing the COC per drug to $218 million.

This is an increase of $29 million dollar per drug.

In this scenario the costs per successfully developed new drug would be: $1.596 million - $149 million + $29 million = $1.476 million

This is still a reduction of 7.5% per successfully developed drug.

Methods

A literature study was used to gain a preliminary insight into the possible advantages and disadvantages of implementing OOC and at what stage of drug development OOC can be implemented. A literature search was performed in which search terms were used to find literature, until no new literature could be found. The search terms were: “organ-on-a-chip”, “microfluidic systems” and “disease model (on-a-chip)” in combination with “drug development timeline”, “pharmaceutical”, “cost-effectiveness” and “(dis)advantages. Once no new articles were found a systematic literature review was performed, which included reading the abstract of articles and systematically filtering out the important articles/book sections after which complete articles where reviewed for their opinions about advantages and disadvantages of implementing OOC in the drug development process. Criteria for selecting literature based on the abstracts were the terms: “drug development” and “(dis)advantages”.

The literature study was used to set up an expert interview. Structured open and qualitative interviews were held with key stakeholders (see Appendix X for guidelines of the expert interviews). ATLAS.ti[42] was used to code the interviews and get a schematic overview of the most important (dis)advantages that were mentioned.

The 150 stakeholders that received an e-mail to participate in the survey were identified using online resources. Several search terms were used to identify experts: “organ-on-a-chip development”, “microfluidic systems development” and “seminar organ-on-a-chip”. The last term resulted in speakers of related seminars who could be possible stakeholders who are in the process of developing organ-on-a-chip. The hDMT provided the contact information for people who have participated in OOC workshops. Furthermore snowball sampling was used to find more stakeholders who would be willing to participate. Pharmaceutical companies located in the Netherlands can be found on www.nefarma.nl and www.tifarma.nl, all these companies received an e-mail in which they were asked to participate in the survey. Stakeholders were asked to forward the invitation to other potential stakeholders to obtain a sample as large and varied as possible.

The survey was created using LimeSurvey[43]. The complete survey can be found in Appendix XI.

The data analysis was performed using SPSS 22[44]. A Mann-Whitney U test was used to determine a significant difference in the opinions of people working in a pharmaceutical company versus a university.

To rank the advantages and disadvantages found during the survey Microsoft Excel 2013 was used. Microsoft Excel 2013 also partially provided the pictures.

Framework of the research project

A literature search was performed to detect where OOC would have potential advantage in the drug development process. Literature study showed the use of OOC can have advantages in several stages of the drug development process. Therefore the expert interviews focussed on which stages of the drug development process need to be improved, whether OOC could help in improving the process and what advantages and disadvantages are expected of using OOC to improve the process. The expert interviews provided more information and background on the general subject of OOC as well.

The information obtained in the literature research and the expert interview was used to set-up a survey. The survey contained the following components: “Personal background”, “familiarity with OOC”, “OOC implementation”, “tissue to develop first”, “(dis)advantages of OOC implementation”, “development time and costs of OOC”. The next subsections will clarify why these components were chosen.

Personal background is an important factor of this survey. Especially the question in what type of company do stakeholders work. During the expert interviews, which were divided between stakeholders with a pharmaceutical background as well as OOC developers, no clear difference in opinions about the (dis)advantages of using OOC in the drug development process was observed between the two groups. To observe whether this also held for the bigger population, the question in what type of company do stakeholders work was made mandatory.

Whether stakeholders were **familiar with OOC** was a mandatory question as well. Firstly the stakeholders were shown a definition of an OOC. No common definition of an OOC-model was found in the literature study, therefore during the expert interviews, the experts were asked to give their own definition of an OOC, leading to the definition used in the survey. This definition was shown to all stakeholders before they were asked whether they were familiar

with the concept. The purpose was to present the definition as used in this survey to all stakeholders. After the definition was shown stakeholders were asked whether they were familiar with OOC before the definition was presented. This question could be used later on to observe a difference between stakeholder familiar and unfamiliar with OOC.

It was not clearly indicated in literature where **OOC could be implemented** in the drug development process. The results section of this report shows several advantages found in the literature that can be vague as to the place where OOC should be implemented. The advantage "toxicity screening" can for example be early screening toxicity, however it can also be pharmacokinetic toxicity screening. Leaving the question where to implement OOC unanswered. Therefore the question in which stage OOC can best be implemented was added to the survey.

Tissue to develop first. Stakeholders were asked which organ they thought need to be developed first. Literature review showed a large amount of drugs (33%) which fail in the clinical trials due to toxicity and 37% of these drugs fail due to hepatotoxicity[11]. The expert interviews mentioned hepatotoxicity as well as cardiotoxicity and nephrotoxicity. Stakeholders were presented with 8 options of organs as well as the option other and were asked which three organs should be developed first. By giving the option of selecting three organs there was less risk of bias for there was the option of choosing more than just the area of expertise of a stakeholder. This question helped confirm whether the organs that were found earlier in the study were also selected by the larger group of stakeholders.

The advantages and disadvantages of OOC implementation. Literature research gave an overview of 17 advantages of the use of OOC in the drug development process. After the top 5 was presented to the experts there was a high fluctuation in opinions about these advantages. After the interviews two more advantages were added to the original 17 advantages. The first set-up of the survey was to confirm the top 5 advantages. The expert interviews showed that the top advantages selected by the experts were very diverse. As a result all advantages found in literature with the addition of the 2 advantages mentioned by experts were included in the survey.

There were no disadvantages mentioned during the expert interviews, therefore all disadvantages found in literature were added to the survey as well. Allowing stakeholders to select any expected disadvantages of using OOC in the drug development process.

A ranking system was developed to observe whether the respondents agree or disagree with the presented (dis)advantages. Ranking started at 1 “I do not see this as a (dis)advantage” up to 5 “I see this as an important (dis)advantage”. Respondent had the option to select “no answer” as well as the option to add additional (dis)advantages.

The **development time and costs of OOC** are difficult to estimate at the early stage of development of this technology. The literature as well as the expert interviews were divided in the opinion how long it would take for OOC to be developed enough to be used in the drug development process. No literature could be found regarding the costs of developing an OOC, the experts were divided in their opinions The respondents were asked how long they thought it will take for an organ-on-a-chip system to be developed enough to be implemented in the drug development process and how much should be invested to develop this well-established OOC-model, to get an overall view of opinions.

Results

Literature review

The literature review was started with 76 found articles that included the used search terms mentioned in the method part of this report. 30 of these articles contained information about the expected (dis)advantages. Table 1 shows the advantages found in the literature supplemented with the advantages that were added during the expert interviews. There are three advantages often mentioned which were “the replacement of animals”, “toxicity screening” and “personalized medicine”.

Table 1: The preliminary advantages of implementing OOC in the drug development process

Advantage:	*Reference:*	*Added after interviews*
Replacement of animals	2,4,12,14–17,19,21,24–29	
Failing animals	2,4,14,15,17,24	
Costs animals	2,4,16,17,19	
Toxicity screening	4,12,13,15–23	
Personalized medicine	2,5,12,13,17,20,26,29,31,32,45,46	
Efficacy	4,12,14,15,17,20,22,26	
Whole body response	12,16,20,21,26,29,46,47	
Costs	2,16,17,19,20,23,25	
Higher sensitivity to external stimuli	6,13,17,24,30,31	
Replacement/reducing human trials	12,16,20,25,26	
Better identification of target organs/drugs	2,17,20,47	
Predict human drug toxicity	12,15,19,23	
Length	2,19,20,23	
PK/PD	12,14,20,48	
ADME	14,19	
Hit Rate (predictability of new drug)	25	
Preclinical	2	
Drug side effect	26	
Safety	4	
Drug-dose response	2	
Better understanding of target		X
Repurposing of drugs		X

Table 2 shows the disadvantages that were found in the literature. There were no additional disadvantages found after the expert interviews. Only three disadvantages were mentioned more than once in the literature. These disadvantages were: “Possible interaction between drug vector and microfluidic system”, “interaction between drug and PDMS” and “only a subset of cells (no connecting tissue)”.

Table 2: The preliminary disadvantages of implementing OOC in the drug development process

Disadvantage:	*Reference:*
Possible interaction between drug vector and microfluidic system	2,21
Interaction between drug and PDMS	4,12
Only subset of cells (no connecting tissues)	4,20
Difficult to monitor genomic levels of cells	2
Models fail to fully mimic organ-specific functions	47
Unclear if models fully mimics functions	13
Not developed enough	25
3D system difficult to sustain long-term	26
PDMS (often used as a membrane) much thicker than normal	4
Difficult to obtain human organ specific cells with both proliferative capacity and full differentiation capability	4
More expensive than well plates	22
Phenotypic mismatch between cell lines and in vivo situation	18

Expert interviews

Seven expert interviews were performed of which four professionals were involved in the development of microfluidic systems and three professionals were involved in drug development. The top 5 advantages found in literature were presented to the experts that were interviewed and there was no pattern found in their rating. Appendix II shows the ranking by the expert stakeholders. Toxicity screening is marked as a real advantage, while whole body response was often ranked low or not at all. The remaining advantages were diversely ranked.

There were several points which were mentioned often in the interviews. All experts saw the use of OOC in the drug development process as complementary to animal testing, mostly due to the lack of predictability of animal models. Experts did emphasize the need of animals, one of the reasons being the lack of immune system in the OOC models. Experts foresee a decrease in drugs which will enter the clinical trials stage, which is an expensive stage. The other remarks of expert interviews can be found in Appendix I.

Results Survey

The survey was send out to approximately 150 people, using an e-mail invitation. The survey was filled out by 50 stakeholders. A total of 42 respondents (84%) were familiar with the concept of OOC before starting the survey. The educational level of respondents started at Bachelor's degree (n=1, 2%), with most respondents having a doctorate degree (n=42, 84%). Table 3 presents the other characteristics of the respondents.

Table 3: Characteristics of Respondents

Characteristic		*Total N=50*
Educational level		
	Bachelor's degree	1 (2%)
	Master's degree	4 (8%)
	Professional degree	3 (3%)
	Doctorate degree	42 (84%)
Type of company		
	Pharmaceutical	18 (36%)
	University	22 (44%)
	Microfluidic systems development	10 (20%)
	Drug development	1 (2%)
	Both	3 (6%)
	Other	8 (16%)
	Commercial	5 (10%)
	Non-profit	4 (8%)
	Other	1 (2%)
OOC familiarity		
	Yes	42 (84%)
	No	8 (16%)

Notes: Numbers do not always add up to the total due to missing data.

First organs to develop

The liver, heart and kidney were mentioned most often as first organs to develop to improve the drug development process with a respectable 20%, 18% and 17%. 4 stakeholders had no opinion on the matter. In Figure 3 it can be observed that the option "other" was selected in 4% of the cases. The stakeholders who selected the option "other" mentioned vascular system often and once bone marrow was mentioned.

There were slight differences between stakeholders from pharmaceutical companies and stakeholders from universities (see Appendix IX). Two highly selected organs that scored equally between the two groups were the liver and the kidney. University stakeholders selected the heart and brain more than the pharmaceutical company stakeholders, the latter however selected the lung and intestines more often.

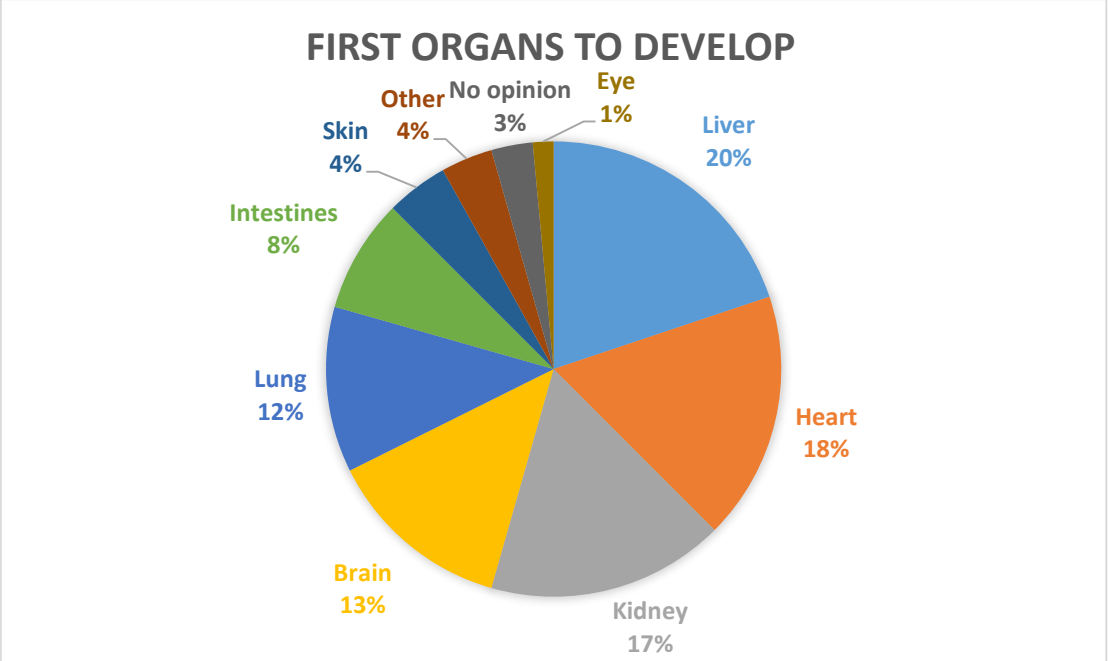


Figure 3Which organs should be developed first as an OOC model according to stakeholders?

Potential improvement drug development process according to stakeholders

Out of the 50 respondents 49 (98%) see improvement possibilities in the drug development process when OOC can be implemented. According to the respondents most improvement of the drug development process could be found in the basic research (n=45, 90%) and preclinical development stages (n=44, 88%). This was a clear difference with the number of respondents that saw improvement in the clinical trials stages of the drug development process, which was

11 (22%). 70% (n=35) of the respondents saw improvement possibilities in the sub-section "target identification" of the basic research. Target validation was an advantage in the basic research stage which was mentioned most often as "other improvements".

The highest scoring improvement point according to the respondents was the sub-section of preclinical development "fewer animals needed due to partial replacement by OOC". **Error! Reference source not found.** shows that 39 of the 50 respondents (78%) see a decrease of animals due to the implementation of OOC as a possibility. It can also be observed that 74% of the respondents also see a possibility of better toxicity screening (in vivo and/or in vitro) after the implementation of OOC.

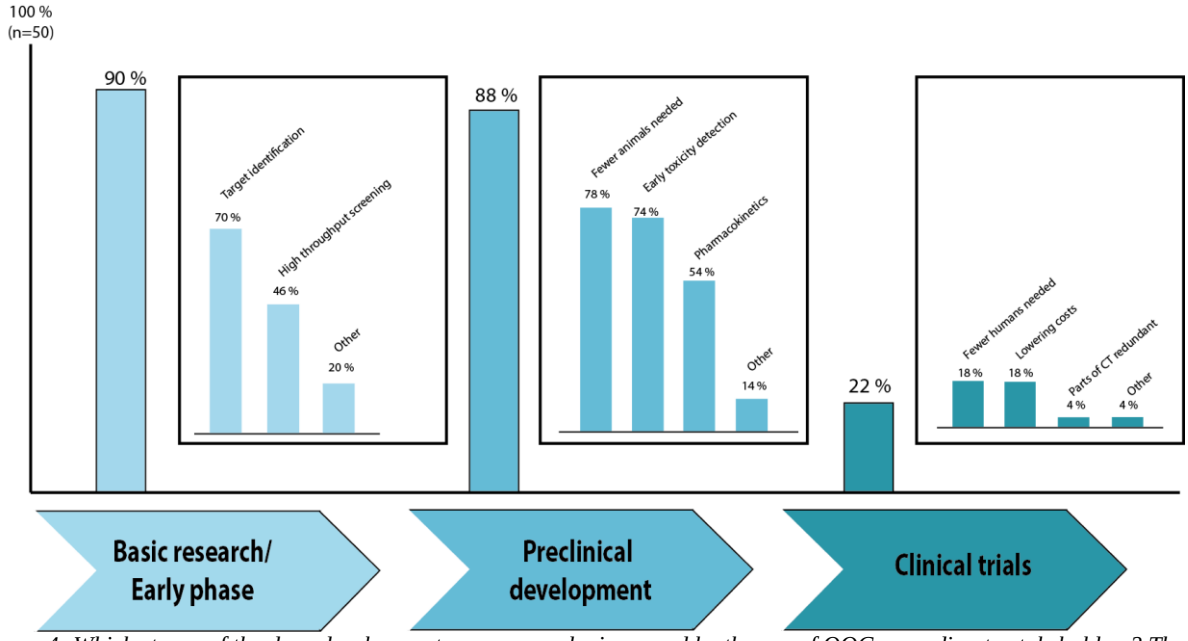


Figure 4: Which stages of the drug development process can be improved by the use of OOC according to stakeholders? The squares represent an overview of the sub categories of the drug development process. Percentages are always calculated from the total n (=50), therefore sub categories can be compared.

Efficiency in the drug development process was seen as the highest scoring (82%) overall improvement of the drug development process after implementation of OOC (see Appendix III). Followed by a reduction is costs (68%).

Potential (dis)advantages according to stakeholders

Advantages

The highest scoring advantage was “better toxicity screening”, with a mean ranking score of 4.19 out of 5. This advantage was closely followed by “better identification of target organs/drugs” and “better understanding of the target” which both scored a mean ranking of 4.09 out of 5. The top 5 is closed by two advantages which scored and mean of 3.98 out of 5, which were “predict human drug toxicity” and “replacement of animals”. See Appendix V for the ranking of all advantages.

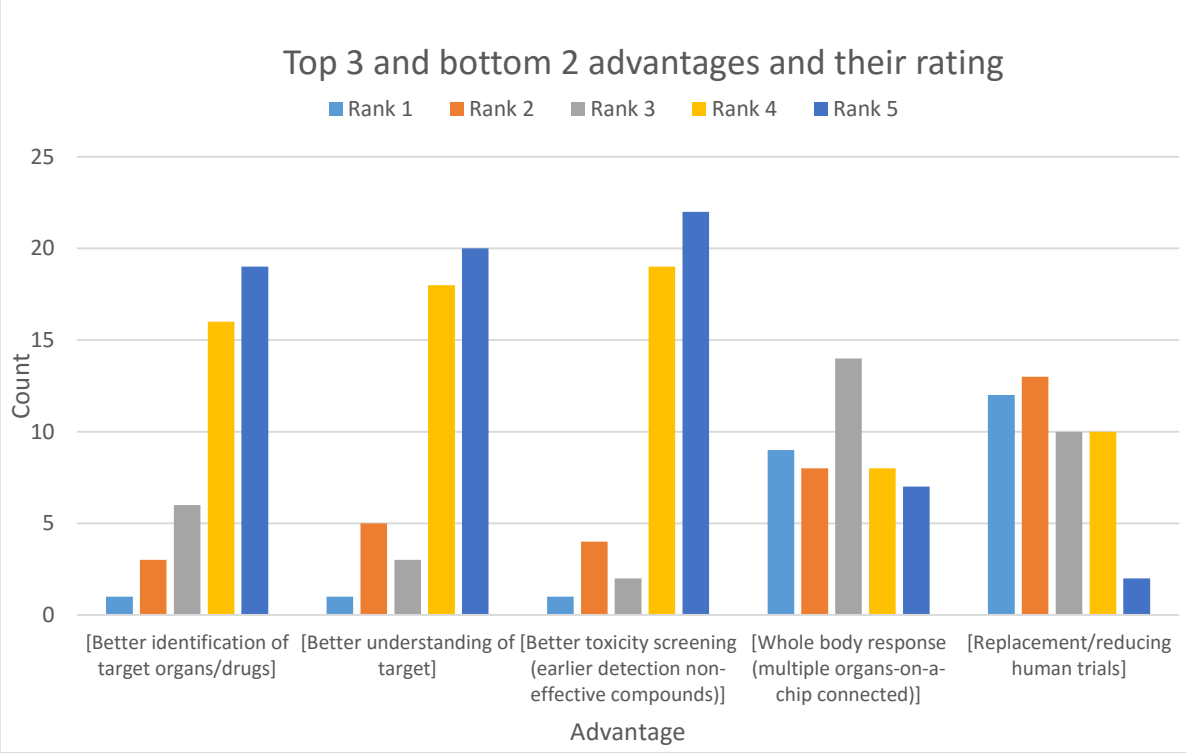


Figure 5: The top 3 and bottom 2 advantages according to the ranking system of the stakeholders

Figure 5 shows the top 3 of highest ranking advantages and the top 2 bottom ranking advantages. It can be observed that the distribution of the top 3 advantages is left skewed. Most of the counts are in the ranking 4 and 5 of these advantages. Which is also clearly represented in appendix VII which shows the percentages of stakeholders who ranked the advantages. All five highest ranking advantages were ranked as an advantage by 70-80% of the respondents, with approximately 10% of respondents who do not see the advantages.

The lowest ranking advantages were “whole body response” with a mean score of 2.91 out of 5 and “replacement/reducing human trials” with a mean score of 2.51 out of 5. These scores are comparable to the distribution which is normal in “whole body response” and slightly right skewed in “replacement/reducing human trials”, which can be observed in Figure 5.

The statistical analysis showed a significant difference in the opinions of stakeholders working in pharmaceutical companies versus stakeholders who work for universities for the advantage “replacement/reducing human trials”. With an alpha of 5% and a p-value of 0.015 the hypothesis that the distribution of ranking between pharmaceutical company stakeholders and university stakeholders was similar could be rejected. Figure 6 shows the distribution of ranking of both groups. It can be observed that the university stakeholders see a higher potential for the replacement of- or reducing human trials.

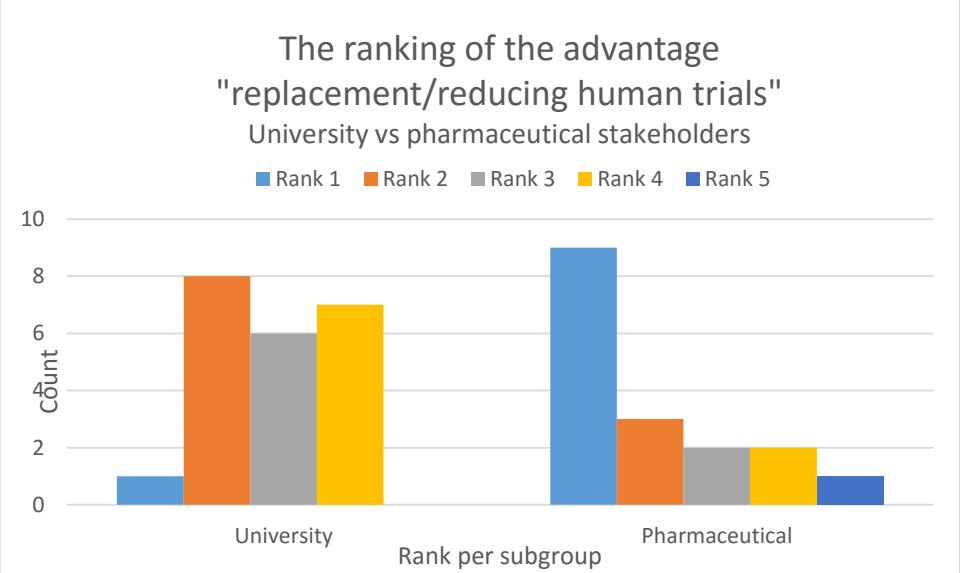


Figure 6: The distribution of ranking for the advantage “replacement/reducing human trials” by university stakeholders versus pharmaceutical company stakeholders.

Other advantages with a significant difference in ranking between pharmaceutical company stakeholders and university stakeholders were “personalized medicine can be developed easier” (p=0.033) and “shorten the length of the drug development” (p=0.020). Both of these advantages were ranked higher by university stakeholders (see appendix IV).

Disadvantages

The top 5 highest ranking disadvantages were ranked neutral. The highest ranking disadvantage was “not developed enough”, which was ranked with a mean score of 3.45 out of 5. Figure 7 depicts this neutral ranking over all the top 5 disadvantages. The only outlier is the ranking of 4 for the “not developed enough” disadvantage.

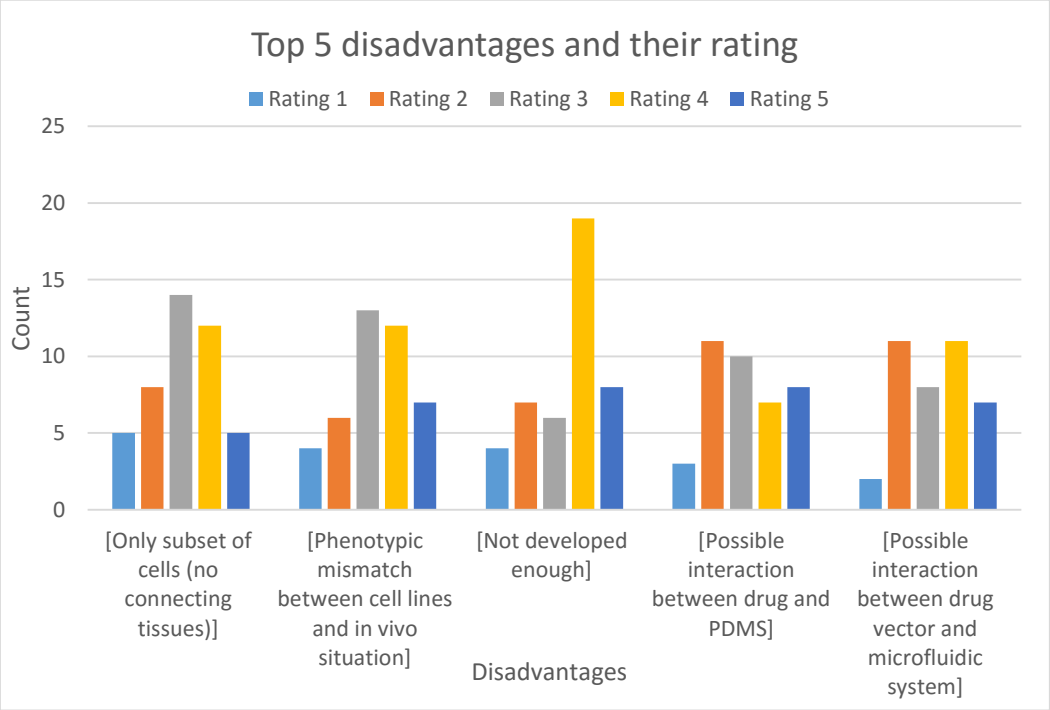


Figure 7: The top 5 highest rated disadvantages identified by stakeholders and the counts of the different rankings

All other disadvantages were ranked neutral, which can be observed in Appendix VI.
This could be confirmed after the percentages were calculated of the stakeholders who see the disadvantages as such. In Appendix VII it can be seen that, except for the disadvantage “not developed enough”, the percentages of stakeholders who see a disadvantage as such is almost equal to the percentage of stakeholders who do not see a disadvantage.

There were however two disadvantages that were rated significantly different by stakeholders from a university versus a pharmaceutical company. Stakeholders from pharmaceutical companies see the disadvantages “difficult to obtain human organ specific cells with both proliferative capacity and full differentiation capability” and “more expensive than well plates” as real disadvantages, while the ranking of university stakeholders is much lower, ranking it as no disadvantage (see Appendix VIII).

Development of organ-on-a-chip

The estimated development time is hard to determine, due to the different complexities of systems and the different applications of the OOC system. 34% of the respondents thinks OOC will be developed enough to implement in the drug development process in five years. However, 34% of the respondents thinks that OOC would be developed enough within three years or less and 14% of the respondents thinks it will be ten years or longer. Stakeholders from pharmaceutical companies were more optimistic about the development time 61% of these respondents saw the development time of OOC as five years or less, while 77% of the stakeholders from universities saw the development time of OOC as taking five years or longer.

84% of the respondents do think the development time could improve when there would be more collaboration between pharmaceutical companies and OOC-developers. 66% believed the development time would decrease if more money was invested and 54% think a clear target for the development of a specific organ (i.e. kidney designed specifically for nephrotoxicity screening) would help. However, a factor that was mentioned to improve the development time as well is the acceptance by the regulatory systems.

Discussion

This research started with literature study. The literature study had a difficult start. There is no single definition for the concept of an OOC and this concept is not yet commonly known as an OOC. Search terms therefore included microfluidic systems, lab-on-a-chip organ etc. and a definition was created using the expert interviews and literature. This definition was used in the survey:

"Organ-on-a-chip is a multichannel 3D microfluidic cell culture chip that simulates the activities and mechanics of entire organs and organ systems"

Based on the literature study a top 5 advantages of implementing OOC in the drug development process was created. The selecting of this top 5 was done by selecting those advantages that were mentioned most often. These advantages were:

- Replacement of animals
- Toxicity screening
- Personalized medicine
- Whole body response
- Efficacy

The interviews did not result in a definitive ranking of these 5 advantages. The experts were divided in their opinions which advantages were best and added two advantages which were not found in the literature which were “better understanding of target” and “repurposing of drugs”. All advantages found were presented to the stakeholders in the survey. The survey response was low, 33% (n=50). Due to time restriction no reminder was send out during the research project, which could lead to a higher response rate. The survey resulted in a different top 5 in advantages:

- Better toxicity screening
- Predict human drug toxicity
- Replacement of animals
- Better understanding of target
- Better identification of target organs/drugs

The expert interviews were conducted with experts with different backgrounds this can result in differences in opinions about advantages of OOC. The literature is written by developers of OOC while the interviews and survey included stakeholders from pharmaceutical companies as well. Toxicity screening occurs in both lists. The list that resulted from the survey includes

advantages that require a simple OOC model, while the advantages obtained from the literature study require more complicated OOC models.

The disadvantages that were presented to the stakeholders were not all disadvantages of implementing OOC in the drug development process. Some of the disadvantages could be called underdevelopments. These factors have to be improved before OOC can be implemented in the drug development process. This was also reflected by the disadvantage "not developed enough" which was highly ranked in the survey. The other highest ranking disadvantages scored neutral (average rank of 3), the majority of the respondents did not view these as disadvantages.

The results of the top 5 advantages were consistent with an earlier question in the survey in which respondents were asked which stage in the drug development process could be improved by implementing OOC. 90% of respondents saw improvement possibilities in the basic research, especially in target identification and 88% of respondents saw improvement possibilities in preclinical development, especially in toxicity screening and number of animals needed.

A mere 54% of respondents chose the improvement in pharmacokinetic measurements. There are multiple explanations for this occurrence. Respondents either did not see this as a possible improvement or started doubting the ability to measure these end points due to the complexity of the OOC model that would be needed to measure pharmacokinetics.

When asked what would be improved by implementing OOC respondents selected the efficiency of drug development (82%) most often, followed by costs reduction (68%). These factors can be related. If more toxic drugs could be detected earlier in the process, the costs could reduce (see exploratory study). Notable is the percentage of respondents who thought the quality of drug development would improve. This was only 54%, while it was expected that this was closely related to the efficiency of the drug development which scored higher.

The liver, the kidney and the heart are the first organs-on-a-chip models that should be developed according to stakeholders. These three organs were expected to score high after the expert interviews which mentioned these three organs due to the difficulty of measuring in vivo toxicity for these organs. The literature study showed a high drug failure due to hepato- and cardiovascular-toxicity as well. The survey confirmed that the organs found in the

literature and the expert interviews are seen by stakeholders as “risk” organs that need to be developed first.

There were significant differences in opinions observed between stakeholders from pharmaceutical companies and stakeholders from universities. These significant differences were found for the advantages “shorten length of drug development”, “replacement/reducing human trials” and “personalized medicine can be developed easier”. The first two advantages are based on conjecture and can most likely only be proven when OOC is accepted into the drug development process and fully developed. University stakeholders ranked the advantage “personalized medicine” significantly higher than stakeholders working at a pharmaceutical company. A reason could be that pharmaceutical companies do not see enough profits from personalized medicines and therefore the pharmaceutical company stakeholders are not as familiar with the concept as university stakeholders are.
Due to the small number of stakeholders working at a university (n=22) no statistical analysis was performed to observe a difference in opinion between university employees who work in drug development (n=1), OOC development (n=10), both (n=3) or have another position (n=8). Therefore the university employees were used as one group to compare to the pharmaceutical company employees. The number of respondents working for a (non-pharmaceutical) commercial company (n=5) a non-profit organisation (n=4) or another type of company (n=1) were similarly small and therefore not used in the statistical analysis.

A calculation was performed to estimate the economic benefits if a greater number of toxic drugs would be detected before the clinical trial phase. The calculated saving was 7.5-10% which amounts to $120-149 million on a drug which first developed for $1.596 million. The calculations were based on assumptions. It was calculated how many drugs fail due to toxicity (n=7). The number of toxic drugs detected at an earlier stage (n=5) was an assumption, based on the results of the expert interviews which mentioned a higher predictability in toxicity screening.
This calculation assumes detection before the clinical trials stage, after the animal studies. When OOC could be implemented earlier, this could save more money. Information obtained from an expert interview estimates animal toxicity studies at €15,000-€20,000 per drug, which

can be saved if drug failure can be established before the animals' studies. This is only a small amount compared to the millions that are saved in the exploration study. However, this indicates a larger saving when OOC is implemented earlier in the drug development process.

A remark mentioned in the expert interviews as well as the survey comments was about the regulatory agencies. The FDA, for example, invests in OOC development, however the rules for drug development still state a specific amount of animal testing should have been performed before a drug can be applied for investigational new drug.
Another remark mentioned in the expert interviews and survey comments was "the technique is not validated enough". There should be funding for head-to-head studies, comparing in vitro and in vivo systems to OOC systems. When and if these studies prove the equivalence or even the superiority of these OOC systems compared to the current systems, then the regulatory agencies will be able to change the rules and can OOC be implemented in the drug development as a complementary test which can possibly result in the reduction of the number of animals.

To determine the true benefits of using OOC technology in the drug development process it would be recommended to use one specific OOC (disease) model. This model could be used as an economic case study. This research can be used as the start of an early warning system. It is now known that stakeholders who develop OOC systems have the same opinions about the stage of the drug development where OOC will be most beneficial. The next step is to translate user requirements and wishes into the technological language used by developers. A technological nexus should be appointed. By filling the gap between developers and users, users will have more influence in the development of an OOC system. With this influence users could for example ask for specific modifications in the OOC model, which will lead to them using less animal models. The technological nexus can then determine the number of animals saved during the development of one drug. This hard data can be presented to investors as (societal) benefits of OOC in the drug development process.

This research can be used as a first step in the longitudinal mapping system. This mapping involves communicating all developments of a new technology to all stakeholders involved. A yearly survey to the stakeholders involved could give insight of their opinions and whether they have changed as well as informing about their own research developments. The results can be used to inform other stakeholders such as rule making bodies. With a keen insight in both the technological challenges and the requirements imposed by potential costumers the technological nexus is well suited to communicate with the rule making bodies. By eliciting more preferences and capabilities from stakeholders and communicating this effectively the nexus can be a key player in the next step in the Real-time Technology Assessment[40].

Conclusion

The use of an organ-on-a-chip model in the drug development process can be beneficial in either the basic research stage or the preclinical stage. It can be an addition or replacement of the 2D or non-microfluidic 3D screening systems currently in use for target identification. Furthermore the more complex OOC-systems, containing multiple connected cell types and tissues, could be a beneficial complementary test to the animal models. This could change the drug development process by (partial) replacement of the animal models. Hepatotoxicity is an important reason for drugs to fail during the clinical trial phases. Therefore development of a liver-on-a-chip should be a priority for improving the drug development process. This is in concordance with the opinion of stakeholders who would prioritize the development of liver-, heart- and kidney-on-a-chip.

There are differences in opinion between stakeholders from pharmaceutical companies and stakeholders from universities, however these differences are not on the important views of where to implement OOC, but rather on what the advantages of implementing OOC would be.

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Appendix

Appendix I: The most important remarks from the expert interviews
Appendix II: The advantages presented to the experts during interviews with their ranking
Appendix III: Stakeholders opinion; where would implementing OOC be beneficial and what would improve?
Appendix IV: The differences in ranking between pharmaceutical company stakeholders and university stakeholders
Appendix V: All advantages and their ranking
Appendix VI: All disadvantages and their ranking
Appendix VII: The top 5 (dis)advantages of implementing OOC in the drug development process and the percentage of stakeholders who see the disadvantage
Appendix VIII: The different distributions of ranking of disadvantages by pharmaceutical stakeholders compared to university stakeholders
Appendix IX: Which OOC organ model should be developed first according to different stakeholders?
Appendix X: Expert interviews
Appendix XI: Survey

Appendix I: The most important remarks from the expert interviews

	TOTALS:
Add-on animal testing	7
Animal models not predictive	5
Animals needed	5
Personalized medicine	5
Less drugs in clinical trials	5
Implementation in high throughput	4
Proof of concept	4
Toxicity	3
Clinical trials expensive	3
Need solid data	3
Regulation should change	3
3R's	2
Implementation before animal testing	2
Improvement drug understanding	2
Improvement safety of drugs	2
In vitro not predictive enough	2
Difficult to mature cells	2
Disadvantage PDMS	2
Not whole body, but interaction between organs	2
Missing immune system	2
Toxic drugs fail in clinical trials	2
Understanding neurological diseases	2
Understanding target	2
Use stem cells	2
Difficult to link different organs	1
Disease model on a chip	1
Early discovery	1
First small pharma, then big pharma will follow	1
Less animals needed	1
Need ready product to present	1
Needs development	1
Not personalized medicine	1
OOC better toxicity than animal models	1
Prioritize organs	1
Repurposing	1
Small improvement pharma relevant	1
Too simple, need more cell types	1
Vascular models	1
Where are animal models less predictive?	1

Appendix II: The advantages presented to the experts during interviews with their ranking

The advantages presented to the experts during interviews with their ranking. Ranking 1 is considered a real advantage. If the advantage was not mentioned in the ranking a - was marked

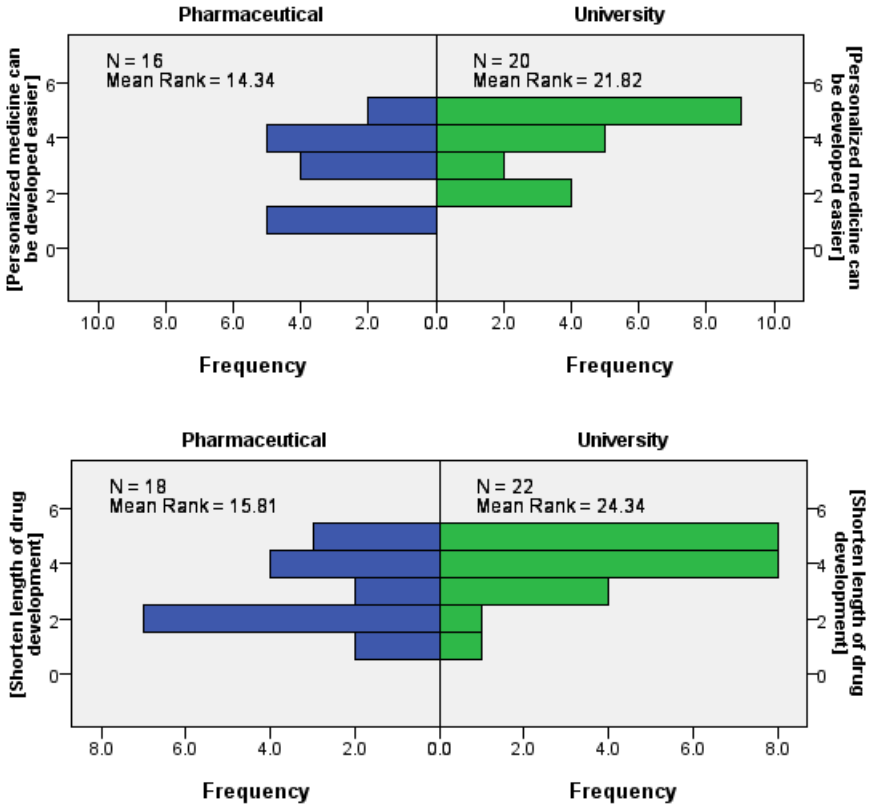
	Rank						
	Int. 1	Int. 2	Int. 3	Int. 4	Int. 5	Int. 6	Int.7
Toxicity screening	2	3	1	1	1	1	1
Efficacy	2	1	-	2	1	4	3
Replacement of animals	ethical	4	2	3	1	2	4
Whole body response	-	-	-	5	2	5	5
Personalized medicine	1	2	-	4	2	3	2

Appendix III: Stakeholders opinion; where would implementing OOC be beneficial and what would improve?

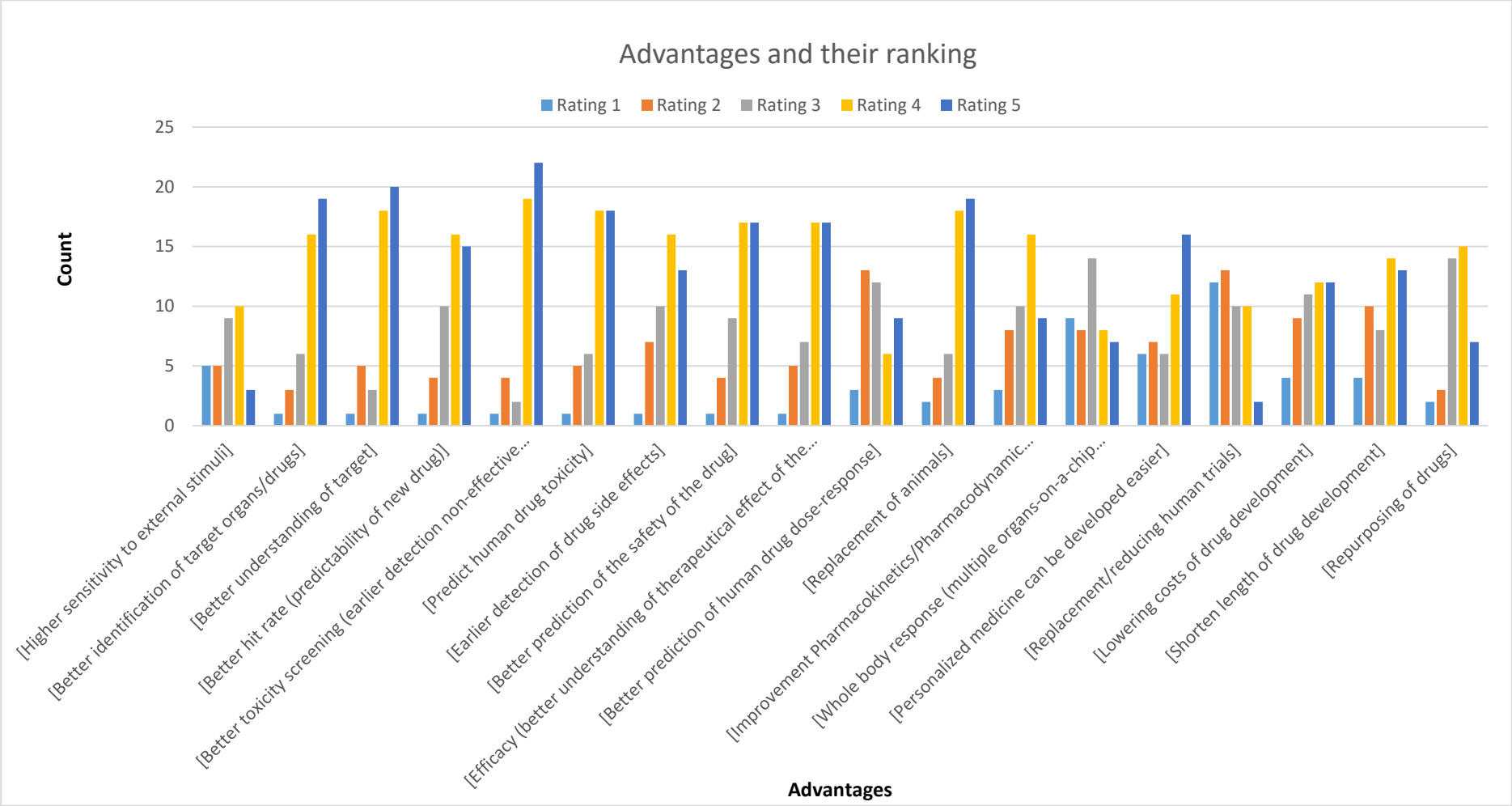
		Total N=50	*Total percentage*	*Adjusted percentage*
Improvement in basic research:		45	90%	
	Target identification	35	70%	78%
	High throughput screening	23	46%	51%
	Other	10	20%	22%
Improvement in preclinical development		44	88%	
	Pharmacokinetic measurements	27	54%	61%
	Earlier detection of in vitro toxicity (pharmacodynamics)	34	68%	77%
	Earlier detection of in vivo toxicity (safety/efficacy)	32	64%	73%
	Fewer animals needed due to partial replacement by organ-on-a-chip	39	78%	89%
	Other	7	14%	16%
Improvement in clinical trials		11	22%	
	Replacement of humans	3	6%	27%
	Fewer humans needed	9	18%	82%
	Duration of clinical trials	4	8%	36%
	Less costs due to fewer drugs that start in clinical trials	9	18%	82%
	Phase 1 trials are redundant	2	4%	18%
	Phase 2 trials are redundant	1	2%	9%
	Phase 3 trials are redundant	0		
	Other	2	4%	18%
Respondents who see improvement possibilities		49	98%	
	Efficiency of drug development	41	82%	84%
	Quality of drug development	27	54%	55%
	Reducing costs	34	68%	69%
	Time-to-market of new drugs	28	56%	57%
	Other	2	4%	4%
Nowhere		1	2%	9%

Appendix IV: The differences in ranking between pharmaceutical company stakeholders and university stakeholders

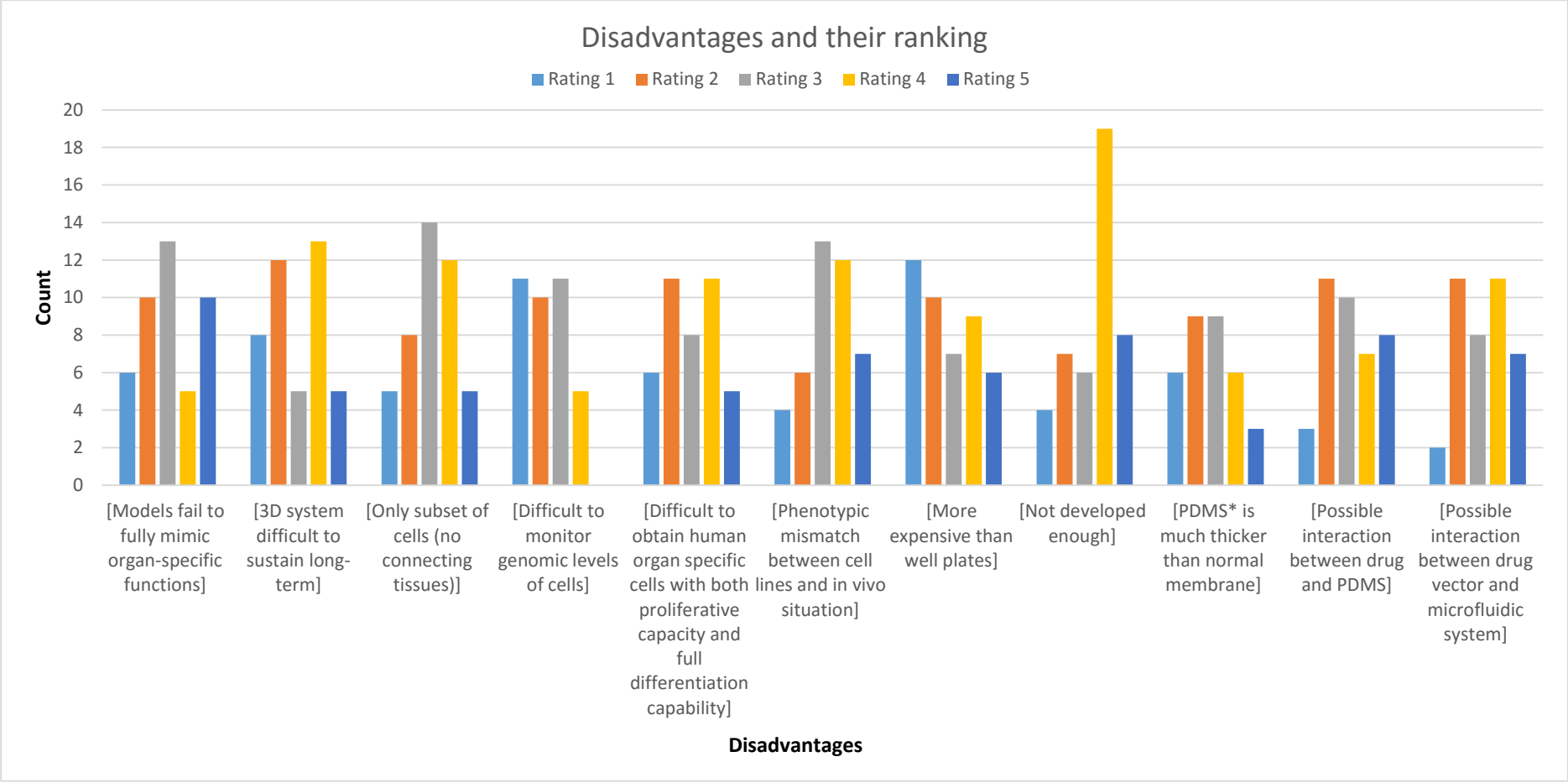
The differences in ranking between pharmaceutical company stakeholders and university stakeholders regarding the advantages “personalized medicine” and “shorten length of drug development”.



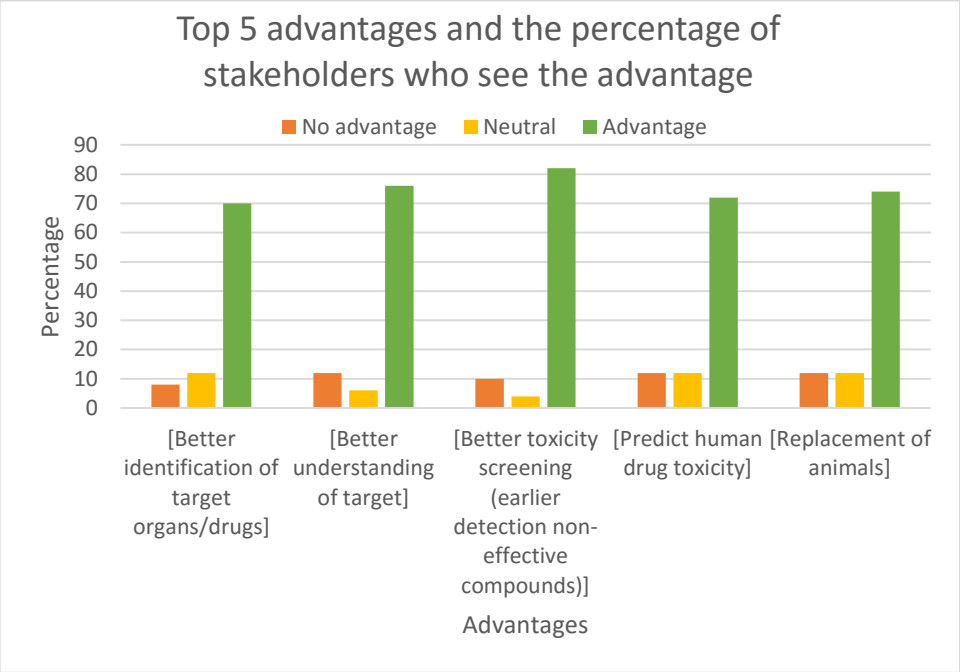
Appendix V: All advantages and their ranking

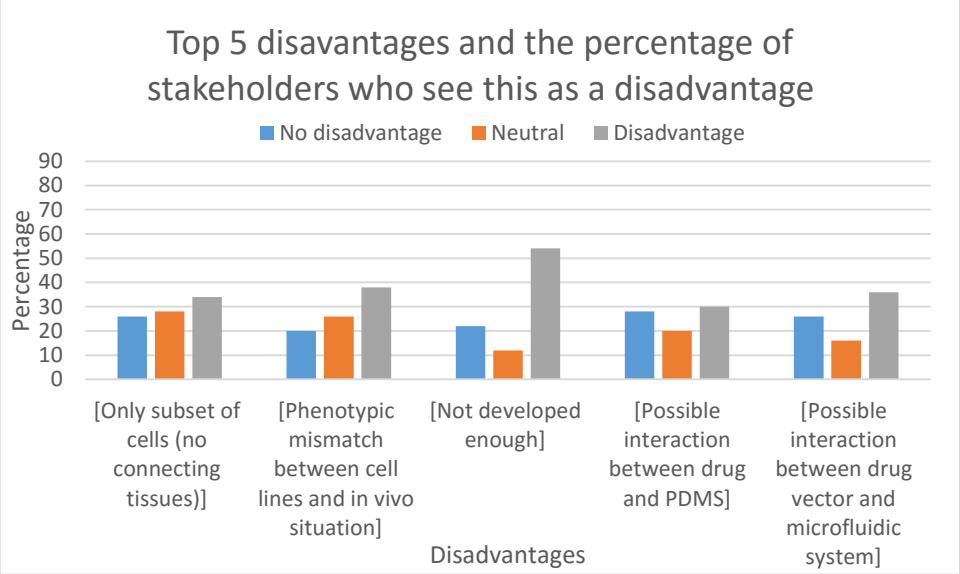


Appendix VI: All disadvantages and their ranking

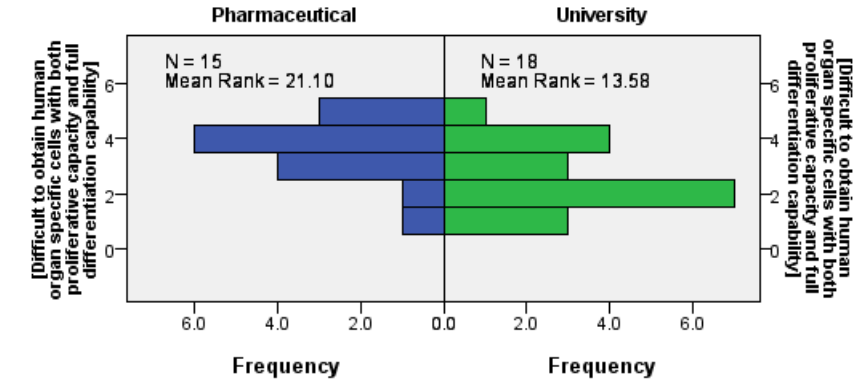


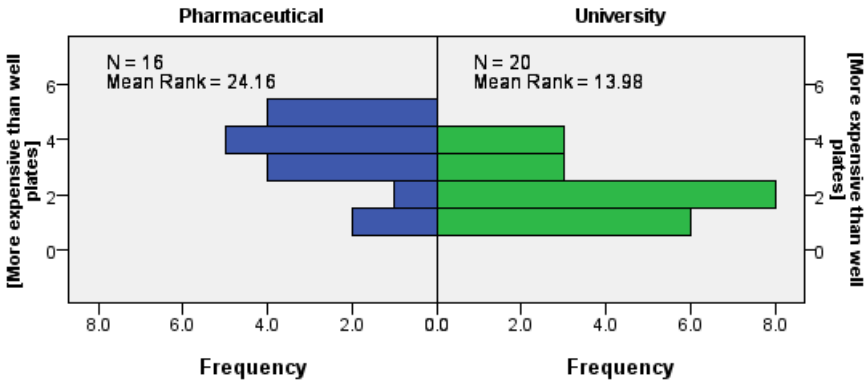
Appendix VII: The top 5 (dis)advantages of implementing OOC in the drug development process and the percentage of stakeholders who see the disadvantage.





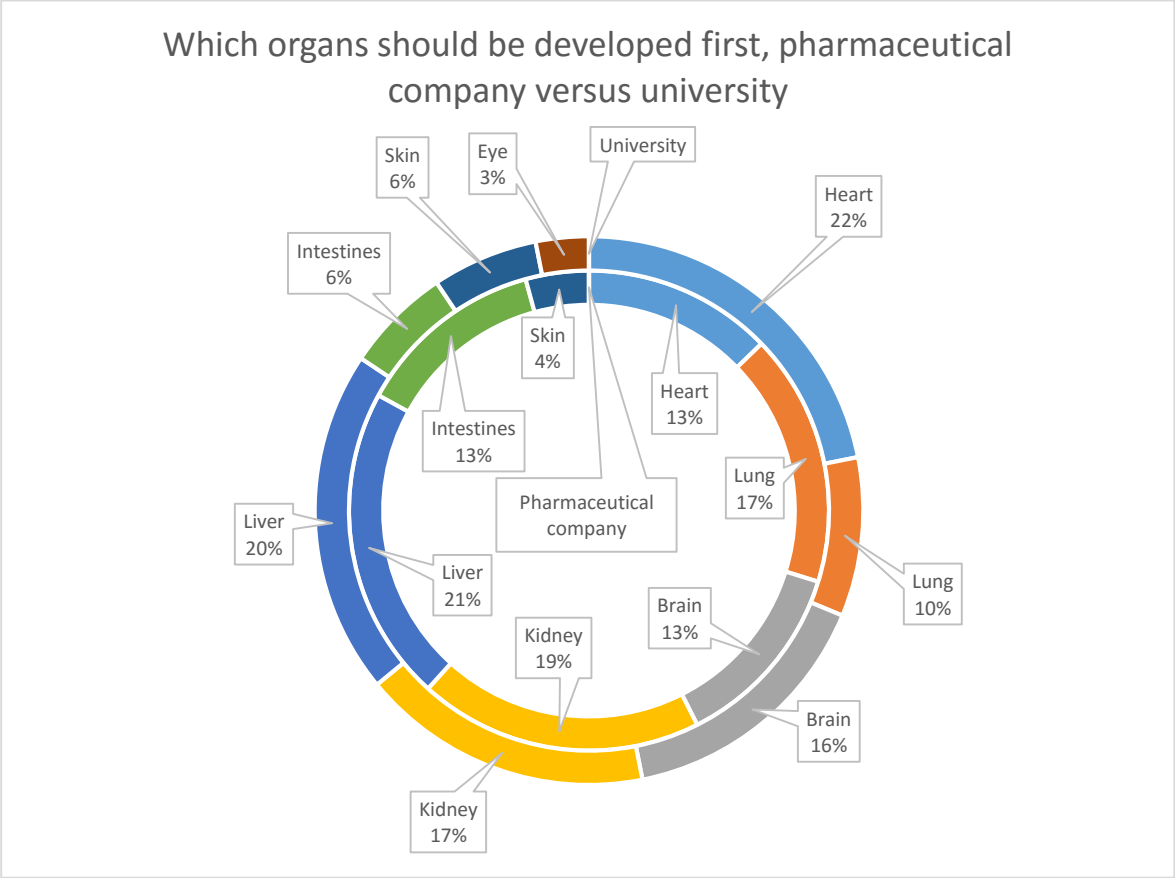
Appendix VIII: The different distributions of ranking of disadvantages by pharmaceutical stakeholders compared to university stakeholders





Appendix IX: Which OOC organ model should be developed first according to different stakeholders?

Pharmaceutical versus university



Appendix X: Expert interviews

1. **What is your job-description**
2. **What is your educational level/education background?**
3. Picture drug development process
4. **Where does the drug development process work properly and where can there be improvements?**

5. (For developers only: **Why do you develop OOC?** Specific goals or just to build and find purpose later on)
6. **In your opinion, would organ-on-a-chip be a solution for the aforementioned problems in the drug development timeline?**
    a. If implemented instead of animal studies, Can all animals be replaced
7. **Where in the drug development timeline would you suggest organ-on-a-chip to be implemented?**
8. **What are the advantages of implementing OOC in the drug development process?**

Rank advantages found including their advantages

9. **Would there be disadvantages in implementing OOC in the drug-development timeline**?

10. **In your opinion, are there diseases for which OOC would be more beneficial in the drug development timeline? And where would it be more beneficial?**

11. **Do you think the technique is developed enough to implement? Or what would be the time when it can be implemented?**

12. **If you were in the position in the pharmaceutical company to decide where to invest, would you invest in OOC?**
13. **Why would/wouldn't you?**
14. **Would the investment choice be influenced by the number of patients that can be treated?**

Advantage:	Rank:
Toxicity screening	
Efficacy	
Replacement of animals	
Whole body response	
Personalized medicine	

Appendix XI: Survey

The survey as it was send to the stakeholders can be found on the following pages.

Implementation of organ-on-a-chip in the drug development process

This survey is set-up to gather your thoughts and opinions regarding the possible implementation of organ-on-a-chip in the drug development process.

Thank you for agreeing to participate in this survey about the **possible implementation of organ-on-a-chip models in the drug development process**. The objective of this survey is to gather your opinion and thoughts regarding the subject. All input is very much appreciated.

Completing this survey will take about **10 minutes** of your time.

This is an anonymous survey and all provided answers will be kept in the **strictest confidentiality**.

If you have any questions regarding this survey, I would be pleased to answer them via e-mail. Please take notice of the fact that it is possible to stop the survey and resume at a later moment in time.

Good luck with completing the survey.

Heleen Middelkamp

Master student Health Sciences, University of Twente

E-mail: h.h.t.middelkamp@student.utwente.nl

There are 25 questions in this survey

Background information

First some general questions are asked to obtain insights into your professional background.

[]What is your sex?

Please choose **only one** of the following:

- ○ Female
- ○ Male

[]What is your age?

Please write your answer here:

[]What is the highest degree or level of school you have completed?

Kies maximaal één antwoord

Please choose **all** that apply:

- ☐ Primary school
- ☐ High school (or equivalent)
- ☐ Tradeschool/MBO
- ☐ Associate degree (for example: AA, AS)
- ☐ Bachelor's degree (for example: BA, BS)
- ☐ Master's degree (for example: MA, MS, MEng, MEd, MSW, MBA)
- ☐ Professional degree (for example: MD, DDS, DVM, LLB, JD)
- ☐ Doctorate degree (for example: PhD, EdD)
- ☐ Other: _____

[]In which country are you currently working?

Please write your answer here:

_____

[]What type of company do you work for? *

Please choose **all** that apply:

- ☐ Pharmaceutical company
- ☐ University
- ☐ Commercial company
- ☐ Non-profit organization
- ☐ Other: _____

[]What is the type of work you perform for your university?

Kies maximaal één antwoord

Please choose **all** that apply:

- ☐ Drug development
- ☐ Organ-on-a-chip (microfluidic systems) development
- ☐ Both
- ☐ Other: _____

[]What is your job description?

Please write your answer here:

_____

Explanation Organ-on-a-chip

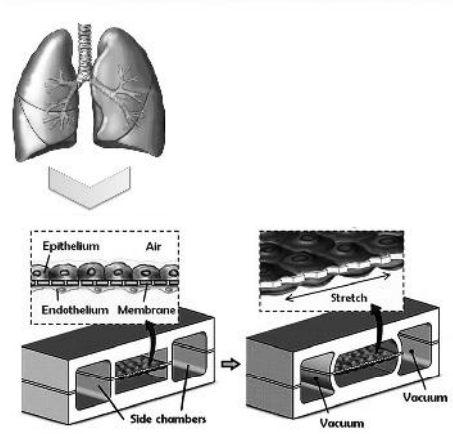
Before the survey continues a general description of organ-on-a-chip is provided.

[]

"Organ-on-a-chip is a multichannel 3D microfluidic cell culture chip that simulates the activities and mechanics of entire organs and organ systems"

Currently there are several organ-on-a-chip models in development, for example a heart-on-a-chip and a kidney-on-a-chip. There are several reasons to develop organ-on-a-chip. This survey will focuss on the development of organ-on-a-chip for implementation in the drug development process.

Another example of an organ-on-a-chip is the lung-on-a-chip (see figure below). The chip consists of two channels which represent the lung channel and the "blood" channel. With a permeable membrane in between the cells. The chip is designed to stretch in and out, as a real lung, therefore the cells are exposed to similar stress and flow as they would experience in an actual lung.



Source: http://upload.wikimedia.org/wikipedia/commons/5/52/Lung-on-a-Chip.jpg

Familiarity with organ-on-a-chip

[]Were you familiar with the concept of organ-on-a-chip before the explanation on the previous page? *

Please choose **only one** of the following:

- ○ Yes
- ○ No

Organ-on-a-chip

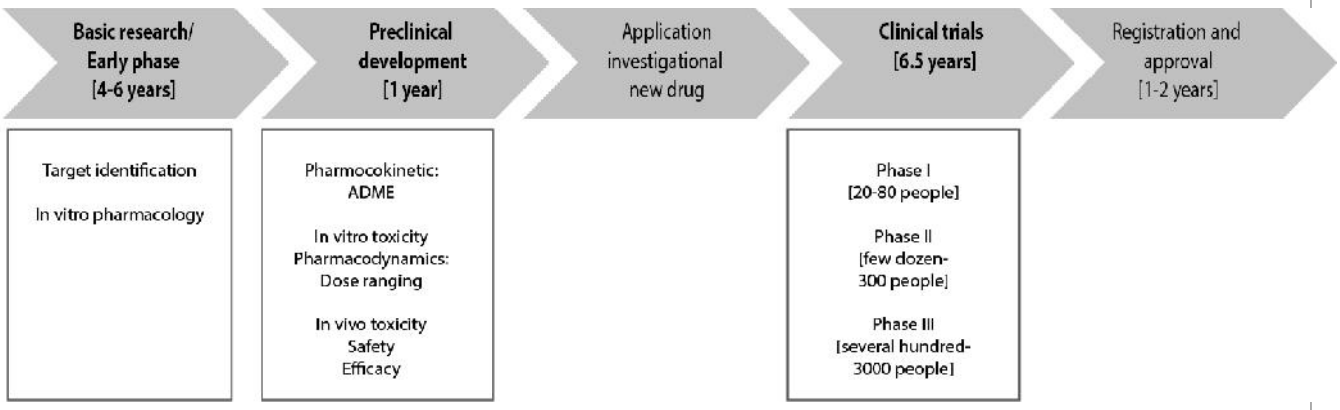
Where in the drug development process could an organ-on-a-chip implementation be beneficial and what in your opinion would be improved?

[]

Organ-on-a-chip could possibly be applied in the drug development process.

The drug development process consists of five phases. Three of these phases are research phases. These research phases are the basic research phase, the preclinical development phase and the clinical trials phase.

The following picture represents a schematic overview of the drug development process.



What part of the drug development process do you think can be improved by implementing organ-on-a-chip?

Please choose **all** that apply:

- ☐ Basic research
- ☐ Preclinical development
- ☐ Clinical trials
- ☐ None

[]What would be improved in the basic research phase by implementing organ-on-a-chip?

Please choose **all** that apply:

- ☐ Target identification
- ☐ High throughput screening
- ☐ Other: _____

[]What would be improved in the preclinical research phase by implementing organ-on-a-chip?

Please choose **all** that apply:

- ☐ Pharmacokinetic measurements
- ☐ Earlier detection of in vitro toxicity (pharmacodynamics)
- ☐ Earlier detection of in vivo toxicity (safety/efficacy)
- ☐ Fewer animals needed due to partially replacement by organ-on-a-chip
- ☐ Other: [ ]

[]What would be improved in the clinical trial phase by implementing organ-on-a-chip?

Please choose **all** that apply:

- ☐ Replacement of humans by organs-on-chips
- ☐ Fewer human testing needed due to better toxicity screening in earlier phases
- ☐ Duration clinical trials
- ☐ Less costs due to fewer drugs that start in clinical trials
- ☐ Phase 1 clinical trials are redundant
- ☐ Phase 2 clinical trials are redundant
- ☐ Phase 3 clinical trials are redundant
- ☐ Other: [ ]

[]What will improve if organ-on-a-chip is implemented in the drug development process?

Please choose **all** that apply:

- ☐ Efficiency of drug development
- ☐ Quality of drug development
- ☐ Reducing the costs of drug development
- ☐ Time-to-market of new drugs
- ☐ Other: [ ]

Organ-on-a-chip model

[]

The previous questions focussed on the implementation possibilities of organs-on-a-chip in the drug development process.

As mentioned in the description of an organ-on-a-chip, there are several organ models which are in development. Which 3 organs do you think are most important to develop first with regards to improving the drug development process?

Kies maximaal 3 antwoorden

Please choose **all** that apply:

- ☐ Heart
- ☐ Lung
- ☐ Brain
- ☐ Kidney
- ☐ Liver
- ☐ Intestines
- ☐ Skin
- ☐ Eye
- ☐ No opinion
- ☐ Other: _____

(Dis)advantages organ-on-a-chip implementation

[]

Below you will find several advantages that could apply to the implementation of organ-on-a-chip in the drug development process. How would you rate these advantages?

For example, selecting 1 means that you do not see this as an advantage and selecting 5 means that you see this as an important advantage.

If you have no opinion or do not know whether the option could be an advantage you can use the "No answer" option.

Please choose the appropriate response for each item:

	1	2	3	4	5
Higher sensitivity to external stimuli	○	○	○	○	○
Better identification of target organs/drugs	○	○	○	○	○
Better understanding of target	○	○	○	○	○
Better hit rate (predictability of new drug)	○	○	○	○	○
Better toxicity screening (earlier detection non-effective compounds)	○	○	○	○	○
Predict human drug toxicity	○	○	○	○	○
Earlier detection of drug side effects	○	○	○	○	○
Better prediction of the safety of the drug	○	○	○	○	○
Efficacy (better understanding of therapeutical effect of the drug)	○	○	○	○	○
Better prediction of human drug dose-response	○	○	○	○	○
Replacement of animals	○	○	○	○	○
Improvement Pharmacokinetics/Pharmacodynamic prediction	○	○	○	○	○
Whole body response (multiple organs-on-a-chip connected)	○	○	○	○	○
Personalized medicine can be developed easier	○	○	○	○	○
Replacement/reducing human trials	○	○	○	○	○
Lowering costs of drug development	○	○	○	○	○
Shorten length of drug development	○	○	○	○	○
Repurposing of drugs	○	○	○	○	○

[]Do you miss any possible advantages of implementing organ-on-a-chip in the drug development proces? If so, please add them in the text box below.

Please write your answer here:

[]

Below you will find several disadvantages that could apply to the implementation of organ-on-a-chip in the drug development process. How would you rate the following disadvantages?

For example, selecting 1 means that you do not see this as a disadvantage and selecting 5 means that you see this as an important disadvantage.

If you have no opinion or do not know whether the option could be a disadvantage you can use the "No answer" option.

Please choose the appropriate response for each item:

	1	2	3	4	5
Models fail to fully mimic organ-specific functions	○	○	○	○	○
3D system difficult to sustain long-term	○	○	○	○	○
Only subset of cells (no connecting tissues)	○	○	○	○	○
Difficult to monitor genomic levels of cells	○	○	○	○	○
Difficult to obtain human organ specific cells with both proliferative capacity and full differentiation capability	○	○	○	○	○
Phenotypic mismatch between cell lines and in vivo situation	○	○	○	○	○
More expensive than well plates	○	○	○	○	○
Not developed enough	○	○	○	○	○
PDMS* is much thicker than normal membrane	○	○	○	○	○
Possible interaction between drug and PDMS	○	○	○	○	○
Possible interaction between drug vector and microfluidic system	○	○	○	○	○

*PDMS: Polydimethylsiloxane; this is often used as a membrane.

[]Do you miss any possible disadvantages of implementing organ-on-a-chip in the drug development proces? If so, please add them in the text box below.

Please write your answer here:

Development of organ-on-a-chip

[]In your opinion, how many years do you think it would take for a organ-on-a-chip system to be sufficiently developed to be implemented in the drug development process?

Kies maximaal één antwoord

Please choose **all** that apply:

- ☐ <1 year
- ☐ 1 year
- ☐ 2 years
- ☐ 3 years
- ☐ 4 years
- ☐ 5 years
- ☐ 6 years
- ☐ 7 years
- ☐ 8 years
- ☐ 9 years
- ☐ 10 years
- ☐ >10 years
- ☐ No opinion

[]In your opinion, which of the following options would decrease the development time of organ-on-a-chip?

Please choose **all** that apply:

- ☐ More collaboration between pharmaceutical companies and organ-on-a-chip developers
- ☐ Financial investments for developers
- ☐ Clear target for the development of a specific organ (i.e: kidney designed for nephrotoxicity screening)
- ☐ Other: [ ]

[]Could you estimate the size of the investment you think is neccecary to develop a well established organ-on-a-chip model?

Kies maximaal één antwoord

Please choose **all** that apply:

- ☐ < €1million
- ☐ €1-5 million
- ☐ €5-10 million
- ☐ €10-15 million
- ☐ > €15 million
- ☐ No opinion

[]If organ-on-a-chip can be implemented succesfully in the drug development process, in what period of time do you think a pharmaceutical company will get a return on investment?

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Please choose **all** that apply:

- ☐ 0-2 years
- ☐ 3-4 years
- ☐ 5-6 years
- ☐ 7-8 years
- ☐ 9-10 years
- ☐ >10 years
- ☐ No opinion

[]If you were in the position to decide your company's investments, would you invest in organ-on-a-chip? Why would / wouldn't you?

Kies maximaal één antwoord

Please choose all that apply and provide a comment:

- ☐ Yes
- ☐ No

Final information

[]To end this survey, you can use the text box to provide additional information or to comment on the survey.

Please write your answer here:

Thank you for your participation!

I would be pleased to answer any questions or remarks regarding this survey via e-mail.

It would be very much appreciated if you would share this survey with other people working in the drug development process and/or organ-on-a-chip development. You can share this survey by forwarding the invitation e-mail or by the following link:

https://surveys-igs.utwente.nl/index.php?r=survey/index/sid/633555/lang/en

Best regards,

Heleen Middelkamp

Master student Health Sciences, University of Twente

E-mail: h.h.t.middelkamp@student.utwente.nl

Submit your survey.
Thank you for completing this survey.