Modelling the Cost Impact of Creating Greater Preclinical Reproducibility Through Digitization of Oncology Efficacy Study Monitoring

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INTRODUCTION

The cost of producing a successful drug

In 2010, the cost of developing a successful drug from the initial phase of target-to-hit to the final phase of launching the drug was estimated at $873 million [1], this is expected to be significantly higher now. Several factors influence this cost within each phase of drug development:

- The probability of the drug successfully moving to the next phase of development (PTS)
- The number of work in progress drugs currently being evaluated in the phase (WIPs)
- The time taken for the drug to reach next phase (CT)

Within the efficacy branch of the preclinical oncology phase, there are preventable limitations that negatively affect these factors, unnecessarily driving up the cost of producing a successful drug. User variability can produce false negative and false positive results [2], reducing the PTS within preclinical and Phase 1 trials respectively. Repeating studies to be certain of drug efficacy also greatly increases the time for a drug to move into Phase 1 trials (CT), driving up costs. The BioVolume 3D and thermal imaging device (3D-TI), is a tumour measurement device which utilises a combination of thermal imaging and stereo RGB photographic images to develop a 3D tumour model. The 3D tumour model is then measured automatically via a machine learning algorithm greatly reducing user variability.
In this report we aimed to investigate the impact on the whole drug development cycle of adopting the 3D-TI during the Preclinical phase, utilising the economic model created by Paul et al in their 2010 analysis. **Figure 1** provides an oversight of the drug development cycle using only the data from Paul et al with 3D-TI's predicted impact indicated.

Aims

- To characterise the reduction in inter-operator variability when using a 3D-TI device instead of callipers and investigate how probability of a drug moving from the Preclinical phase to Phase 1 (PTS Preclinical) is impacted
- To use the model and calculated increased probability of success to compute cost savings of producing a successful drug when using a device with less inter-operator variability

METHODS

Economic modelling estimates the current cost of producing a drug at $873 million [1]

The economic model was built around the requirement that one successful cycle would produce one successful drug launch. To compute the cost of producing said successful drug, two inputs were required; the probability of a drug making it through to the next phase (PTS); and the cost per work in progress drug within a phase (CPWIP). These two inputs were estimated for each phase by Paul et al (**Table 1**).

The number of work in progress drugs (WIPs) required in each phase was computed by starting from the requirement that a single successful drug must be produced at the end of the cycle and using the previous phase's PTS to work back. The cost per phase was then computed by multiplying the CPWIP by WIPs within each phase (**Table 1**). The total cost of producing one successful drug is the sum of the cost per phase. **Paul et al computed the out-of-pocket cost to launch one successful drug to be $873 million.**

Phase (p)	Probability of drug moving to next phase (PTS)	Cost per work in progress drug ($ million) (CPWIP)	WIP's needed for one launch (WIPs)	Cost per one launch ($ million)
Target-to-hit	80%	1	24.3	24
Hit-to-lead	75%	2.5	19.4	49
Lead optimisation	85%	10	14.6	146
Preclinical	69%	5	12.4	62
Phase 1	54%	15	8.6	128
Phase 2	34%	40	4.6	185
Phase 3	70%	150	1.6	235
Submission to launch	91%	40	1.1	44
			TOTAL	$873 million

Table 1 Computed number of WIPs needed and cost per one successful drug launch from the economic model, utilising the PTS and CPWIP for each phase as input.

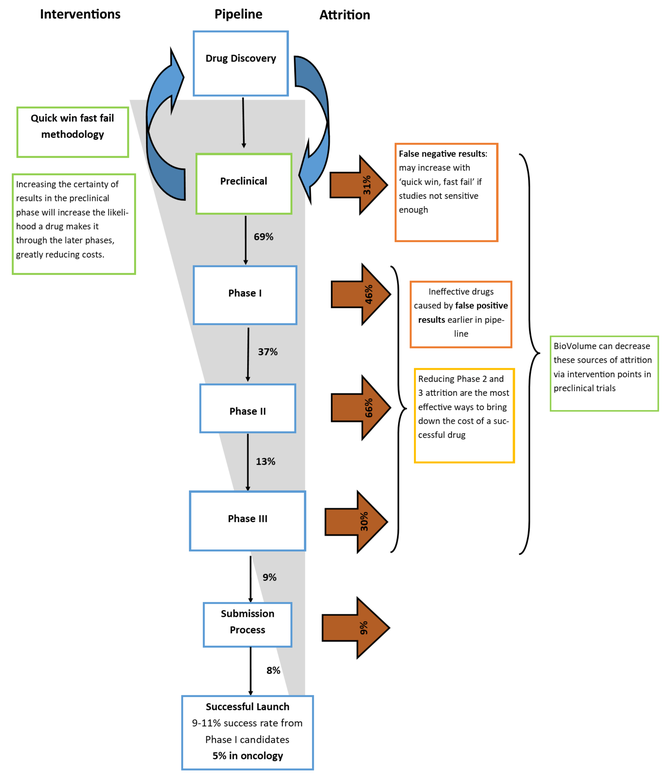

Figure 1. The drug development cycle adapted from Paul et al. 2020 [1] the final phase in the pipeline is adapted to reflect oncology success rates, the theorised impact of 3D-TI is shown in the text boxes surrounding the pipeline.

Utilising 3D-TI in Preclinical phase reduces false negative and false positive results in efficacy studies

(A)

Treatment Effectiveness	Probability of false negative with BioVolume	Probability of false negative with callipers
Most effective (950mm³ mean group diff)	0.0%	0.7%
Effective (800mm³ mean group diff)	0.2%	4.1%
Least Effective (650mm³ mean group diff)	2.6%	18.5%

(B)

Treatment Effectiveness	Probability of false positive with BioVolume	Probability of false positive with callipers
No effect (0mm³ mean group diff)	18.2%	41.3%

3D-TI has been shown to significantly reduce user variability over the industry standard measuring device, callipers [3]. It was found that depending on the effectiveness of treatment, user variability can produce false negatives as much as 18.5% and false positives 41.3% of the time when using callipers (**Table 2**).

Table 2A. Probability of incorrectly determining and effective treatment to be ineffective due to user variability for BioVolume and Callipers, analysis from [2].

B. Probability of incorrectly determining and ineffective treatment to be effective due to user variability for BioVolume and Callipers .

3D-TI's improvements in PTS and estimating cost savings

3D-TI reduces the chance of getting a false negative in comparison to callipers by approximately 7% on average (6.8%) and reduces the chance of getting a false positive by 23.1%. As false negatives are effective treatments which appear ineffective, reducing the false negative rate will increase the PTS within the preclinical phase of the model without increasing the cost of this phase.

False positives are ineffective treatments which appear effective, these would pass Preclinical efficacy trials then fail in either Phases 1 or 2. In this analysis it is assumed that Phase 1 primarily assesses toxicity and as such efficacy testing begins in Phase 2, this means that the PTS within Phase 2 of the model would increase from using 3D-TI.

PTS in the Preclincal Phase and Phase 2 are 69% and 34% respectively, resulting in failure rates of 31% and 64%. In 2000 in the Preclinical phase, it was found that roughly 27% of study failures are due to lack of efficacy [4]. In Phase 2 between 2011-2012, it was found that 59% of study failures were due to lack of efficacy [5]. Assuming that 50% of failures due to lack of efficacy were from false results in the Preclincal phase and 30% in Phase 2, then the improved PTS in Preclincal and Phase 2 offered from using 3D-TI in the Preclinical phase will be 69.2% and 36.2% respectively.

RESULTS

It was found that with the 0.2% increased PTS in the preclinical phase and 2.2% increased PTS in Phase 2 due to 3D-TI, that **the cost to produce one successful drug was $835 million, a reduction of $38 million** (**Figure 2**).

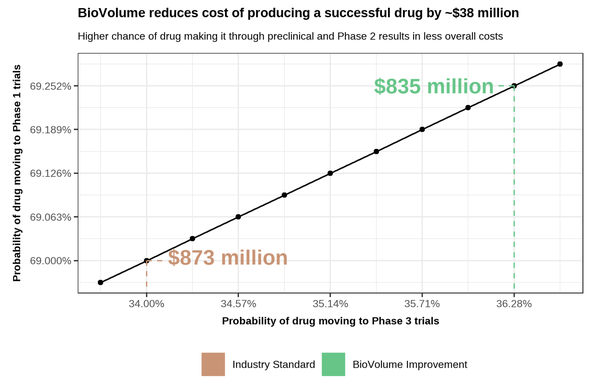

Figure 2 Utilising 3D-TI in efficacy testing in the preclinical phase of drug development reduces costs to produce a drug by $38 million. False negative rate was computed for the 3D-TI and the industry standard measuring devices, the improvement offered by 3D-TI was input in the model to compute cost savings. Graph plotted using data from model from Paul et al [1], fit to data from the PBF.

Using 3D-TI also provides a shift to the "Quick win, fast fail" methodology through increased workflow

Quick win, fast fail methodology is a cost-reducing solution in which a much larger volume of drug candidates are tested within the preclinical phase through proof-of-concept studies [1]. This increased emphasis on preclinical testing results in increased certainty that the drug is effective earlier in the development cycle and can filter out ineffective drugs before they reach the more costly phases (PTS for Phases 1, 2 and 3 increase). **An increase in PTS of 10% within Phase 3 can result in a cost saving of ~$100 million.** Adopting 3D-TI as the new measurement standard in preclinical studies can help facilitate a shift toward the "quick win, fast fail" methodology through a combination of greater throughput and increased PTS in the Preclincal Phase and Phase II. 3D-TI also improves the workflow of testing a drug within the preclinical phase through its fully traceable image data hosted on our secure cloud platform and accessible anywhere to the relevant people.

CONCLUSION

In conclusion it was found that in 2010, with the industry standard tools and methodologies still in use today, the cost of producing one successful drug was estimated to be $873 million. Factors such as high measurement device variability affect study reproducibility, contributing to high costs. Adopting new technologies such as 3D-TI and digitizing preclinical processes within efficacy testing in the preclinical phase increases confidence in results by reducing the chance of missing a drug effect by 7% on average and incorrectly detecting an effect by 23%, **reducing the cost to produce a successful drug by $39 million**. A more productive and efficient digital lab can also facilitate the shift toward the 'quick win, fast fail' paradigm greatly saving costs. This investigation clearly demonstrates that by digitizing and creating more reproducible preclinical study methods by using 3D-TI, the impact on translatability, cost of development and cycle times can be impacted in a significant way.

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