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Probability of Success in Drug Development

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In this issue of *Clinical Pharmacology & Therapeutics* (CPT), Hampson and colleagues¹ present a framework to assess the probability of success (PoS) of clinical development programs before pivotal trials begin (**Figure 1**). In the accompanying Commentary, Lalonde and Peck² underscore the importance of making an informed and objective decision before proceeding to phase III trials. At this stage, the stakes (costs) are high and ~90% of drug candidates fail during clinical development. It has been suggested that 60% of all research and development (R&D) costs are due to attrition.³ However,

obtaining a single estimate of PoS is not trivial, since a variety of diverse elements need to be considered and integrated. Thus, the definition of “success” is multifactorial and includes technical, medical, regulatory, and commercial success. Lalonde and Peck discuss that getting to an unbiased and reliable estimate of PoS in real life is often challenging in an environment with competing interests and organizational pressures, and that more often than not, drug development teams may be wearing rose-tinted glasses when deriving PoS for their program. For example, “anchoring” is a common cognitive bias that results in

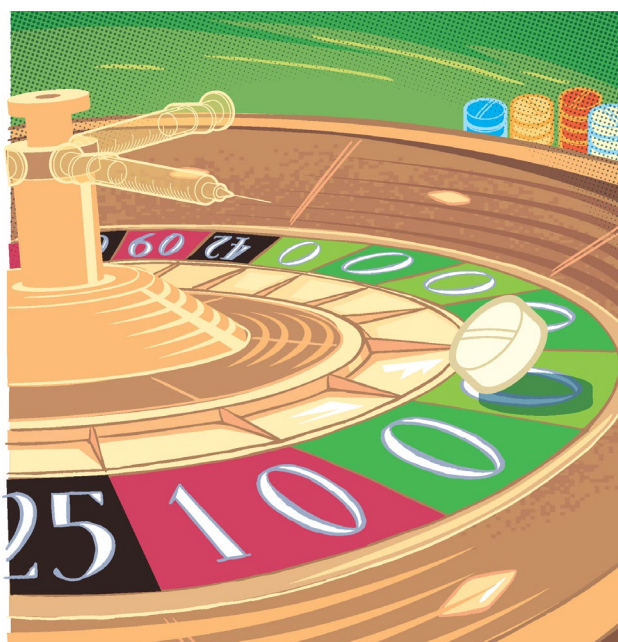


Figure 1 *Clinical Pharmacology & Therapeutics* May 2022 cover image: Probability of Success in Drug Development.

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overestimating PoS by assuming an observed (phase II) effect can be replicated in future (phase III) studies.² Therefore, there is a clear need for better, data-driven approaches. The comprehensive new framework proposed by Hampson *et al.*¹ is an important contribution and example that can be adopted by other drug developers. Their four-step approach uses a sophisticated Bayesian approach to synthesize the totality of evidence and data. One limitation of the framework is that phase III failures are only considered to be due to efficacy or safety and that these are independent outcomes.² A more general limitation is that the proposed framework only considers the probability of phase III success at the end of phase II. At an individual program level, a late-stage (phase III) failure is of course most costly; however, it has been argued that at a portfolio/industry level the accumulated effect of earlier (specifically phase II) attrition may be greater. For example, between 2016 and 2020 the average industry success rates for phase II and phase III were 29–34% and 70–73%, respectively.³

Pfizer recently shared its learnings on increasing “end-to-end” success, which is currently almost twofold higher than the industry benchmark; whereas, in the previous decade it was consistently lagging behind its peers.³ A major driver for this turnaround was a remarkable increase in phase II success, which is currently 50% higher than that of the rest of the industry.^{3,4} The company has described the three building blocks behind its increased R&D productivity as follows:

1. Biology: deeper understanding, emphasis on science, and sharper focus on specific therapeutic areas;
2. Modalities: broadening the toolbox to a range of modalities beyond small molecules; and
3. Decision making: incorporating more systematic and consistent use of quantitative metrics.

The third building block relates directly to the framework of Hampson *et al.* but expands the utility to earlier phases of development through, for example, the “3 Pillars” and “Signs of Clinical Activity (SoCA)” paradigms. Due to this more holistic approach, the concept of PoS can be expanded to “quality of success”³ (QoS; **Figure 2**).

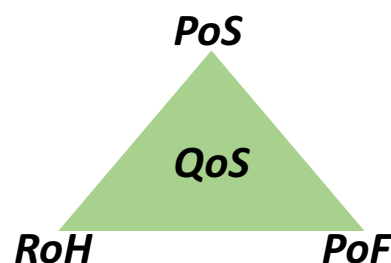


Figure 2 Quality of Success (QoS) in drug development: balancing Probability of Success (PoS), Probability of Failure (PoF), and Risk of Harm (RoH).

If all successes are not equal, we should also not forget that not all failures are the same and that probability of failure (PoF) cannot simply be defined as $PoF = 1 - PoS$. This was perhaps best illustrated by the dissection of the tragic BIA 10-2474 trial in a recent issue of *CPT*.^{5–7} The fact that this compound attrited in phase I was of course completely dwarfed by the fatal outcomes of the trial in healthy volunteers. Such cases are (thankfully) very rare, and therefore determining risk of harm (RoH) cannot rely on the Bayesian principles underpinning the PoS framework.^{1,2} Cohen and colleagues used the Bial case to illustrate how a more structured approach to this challenge based on the “IB-de-risk tool” can provide a more objective and data-driven assessment of potential tolerability issues ahead of any clinical studies.⁶ They state that “this unfortunate trial shows again that studies primarily focused on tolerability and NOAEL [no observed adverse effect level]–based dosing in humans should be a thing of the past. Such classical phase I tolerability studies are not pharmacologically or clinically justifiable and should no longer be permitted by regulatory authorities and ethics committees.”

Success in drug development may mean different things to different people, and its definition changes during the course of a typical R&D program, but surely a constant and overriding criterion should be the ultimate positive impact on patients and absence of any negative consequences for clinical trial participants.

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CONFLICT OF INTEREST

The author declared no competing interests for this work.

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1. Hampson, L.V. *et al.* A new comprehensive approach to assess the probability of success of development programs before pivotal trials. *Clin. Pharmacol. Ther.* **111**, 1050–1060 (2022).
2. Lalonde, R.L. & Peck, C.C. Probability of success: a crucial concept to inform decision making in pharmaceutical research and development. *Clin. Pharmacol. Ther.* **111**, 1001–1003 (2022).
3. Fernando, K. *et al.* Achieving end-to-end success in the clinic: Pfizer's learnings on R&D productivity. *Drug Discov. Today*. **27**, 697–704 (2022).
4. Wu, S.S., Fernando, K., Allerton, C., Jansen, K.U., Vincent, M.S. & Dolsten, M. Reviving an R&D pipeline: a step change in the Phase II success rate. *Drug Discov. Today* **26**, 308–314 (2021).
5. Peck, R.W., Holstein, S.A. & van der Graaf, P.H. BIA 10–2474: some lessons are clear but important questions remain unanswered. *Clin. Pharmacol. Ther.* **111**, 343–345 (2022).
6. Cohen, A.F., van Smeden, J. & Webb, D.J. De-risking clinical trials: the BIAL phase I trial in foresight. *Clin. Pharmacol. Ther.* **111**, 362–365 (2022).
7. Rocha, J.-F. *et al.* safety, tolerability, and pharmacokinetics of FAAH inhibitor BIA 10–2474: a double-blind, randomized, placebo-controlled study in healthy volunteers. *Clin. Pharmacol. Ther.* **111**, 391–403 (2022).