Biases in Pharma R&D Decision-Making: Optimism Bias

Introduction

As we wrote recently, the pharmaceutical and biotechnology R&D productivity has been difficult to improve, despite continuous scientific advancements in biology, medicine, data science and through multi-year focused endeavors in many organizations to establish scientific frameworks and leveraging quantitative approaches. We believe that more attention could be paid to the behavioral biases that often affect the decision-making processes across the pharmaceutical R&D value chain, considering their prevalence and high potential to affect decision makers.

In this brief article, we will highlight **optimism bias** in the context of pharmaceutical R&D decision making. This is the second in a series discussing cognitive and behavioral biases with the aim to draw more attention to these biases and spur the dialogue and exchange of ideas that could help to mitigate their impact.

Optimism bias is omnipresent... and is one of the most frequently occurring behavioral biases. Who doesn't know of a big infrastructure or IT project that got significantly delayed with many fold-increase of the initially estimated cost? This often is an impact of optimism bias when deciding on large and complex investments spanning multiple years. As a personal example of one of the authors, their recent home improvement project turned out to be way more costly and took much longer than they originally estimated. Sharing this anecdote with friends seems to confirm that very few home improvements are cheaper or more quickly completed than expected. Without bias, one would expect that half of the projects would cost less and half would cost more than initially projected. However, that this is generally not the case. It is much more common for projects to cost more and/or take longer to be

completed than to be under budget and/or delivered in less time than originally planned, no matter whether the project is conducted at a government, company, or personal level. No wonder, as it is inherently very difficult to estimate the interdependencies, predict unexpected events and include all the potential issues that can eventually lead to a lower probability of success of completing in time and within budget.

Optimism bias occurs when decision makers are overly optimistic about the outcome of planned actions, including overestimation of the frequency and size of positive events and underestimation of the frequency and size of negative ones. It is somewhat similar to taking credit for past "good" decisions but attributing a "bad" outcome from a past decision to some other factors out of our control (as if that makes a difference). One can argue that optimism bias also is fed by the hindsight bias: "I should have invested in Apple or Amazon when these companies were just starting", without acknowledging that there were hundreds of other similar companies that did not succeed over time, but they may have looked equally good (or risky) when they were all just starting. For a balanced view, we will need to understand and consider both the numerator and denominator of the number of decisions.

Optimism bias also plays a role at an individual level when someone believes that they themselves are less likely to experience a negative event. Such as when optimistically biased individuals assess their risk of developing a serious disease or the risk of getting infected with COVID as lower compared to others, and thus may be less prone to avoid situations that could increase the risks. Conversely, optimism bias also may lead to overestimation of one's own abilities, as was highlighted in the excellent article on 'Delusions of Success' in Harvard Business Review quoting a survey of 1 million students to rate themselves against their peers, in which 70% of the students said they were above average in leadership ability, while only 2% rated themselves below average.

What can go wrong if we are not aware? In pharma R&D project teams are continuously competing for finite resources. Project leaders are incentivized to be optimistic around the speed, costs and complexity, as their investments needs otherwise may not be granted. Being realistic could reduce the probability for funding when multiple projects are competing for the same limited resources. Also, decision makers may think they are good at decision making: "my last project became a commercial blockbuster and therefore my judgement is very good". This ignores or dismisses the other less successful decisions that led to projects that were terminated (and are thus no longer visible in the pipeline or driving revenue). However, we should all be aware of the opportunity costs, i.e. representing lost revenues to the organization (and perhaps more importantly denying patients access to novel treatments) that comes with progressing one asset over another that could have been more successful.

Examples how the optimism bias impairs decision-making in pharma R&D

Assets

- The costs and/or timelines of clinical development programs more often increase than decrease because we do not sufficiently account for all the factors that can impact a large multi-year program (e.g., by not accounting for all risk factors, calculating impact of competition, or unexpected delays)
- Probability of Success (PoS) in clinical development is also affected by optimism bias, but in a way that can be more difficult to spot. The reason is, that perceived PoS for an individual project typically goes up over time because we have progressed from Phase 1 to 2 and 3. Yet very often our initial assessment of potential risk factors proves to have been incomplete resulting in higher than initially estimated number of failures on a portfolio scale.
- Drug developers overestimating the difference of their molecule with the same mechanism of action (or technology platform) than others that have been stopped or failed by their competitors earlier. Optimism makes us think we will nail it where others have failed.
- The paper 'Pharmaceutical forecasting: throwing darts?' assessed the accuracy of forecasting of predicted vs actual sales and shows that a significant fraction the assessed drugs have an over-prediction (rather than following a normal distribution, only 15% of forecasts had been underestimated by more than 40% while 43% had been overestimated by more than 40%; half of the overestimates being outliers with forecasts exceeding the actual peak value by over 160%).

Portfolio

- Companies estimating that they are / can be better than industry benchmarks/averages in e.g., PoS, efficiency, timelines, trial enrollment, net present value (NPV) calculations.

- When competing for limited resources, proposals with more optimistic projections in terms of PoS, budgets and timelines are more likely to be supported over those will less optimistic projections. This provides an incentive to be more optimistic rather than realistic.

Business Development

- Biotechs often sell the 'promise' without yet having sufficient evidence to support the claims that are made. It is often by necessity, as small companies can be forced to seek external funding to be able to run the full (and expensive) validation in the first place. While a systematic due diligence is expected to adequately identify risks, it is not uncommon to see that development plans made at time of the deal appear afterwards more optimistic than realistic.

Leadership

- As asset leader one needs to be optimistic in 'selling' to the decision-makers, otherwise investments won't be granted. Being realistic may reduce the PoS for funding. In addition, if a leader is realistic then such leader can be perceived as disloyal, and this may diminish the chances for funding as well.

- Leaders with track record of success are more likely to get their ideas across and their ideas are automatically assigned higher probability of success (also called champion bias).

Decision making

- Decision makers tend to be overly optimistic about their ability to make good decisions. They take credit for past "good" decisions but quickly attribute a "bad" outcome from a past decision to some other factors out of their control (Proof of Concept (POC) trial failed because of X, Y, Z factors, as if that means the decision was good but something external caused the project to fail).

Resources

- Skipping comprehensive experiments/data collection as overruled by optimistic framing could lead to increased complexity, time delays and more workload down the line – however, this is often not recognized as part of the decision-making fallacy as implications show up later in time when historical context is lost due to team or decision maker transitions.

How can we mitigate the optimism bias?

Let us first say that optimism bias is not necessarily bad or should be completely outrooted. As the 'Delusions of Success' article in HBR says: optimism generates much more enthusiasm than does realism, and it enables people to be resilient when confronting difficult situations or challenging goals. Therefore, companies certainly should promote optimism to keep employees motivated and focused. However, there needs to be a healthy balance between optimism by individuals and project teams versus more objective, evidence-based decisions by senior leaders who have to select between competing projects and large investments.

The obvious step towards success is simply being aware of the optimism bias when making high-stakes decisions in pharma R&D. Each project team aims to 'sell' to the governance their investment need with an optimistic view. Therefore, a correction factor may need to be applied to cost and timelines based on bench marking data or derived from other independent sources. The UK government has done so, as laid out in the Green Book, requiring infrastructure planners to explicitly apply adjustment to both timeline and cost – either based on historical performance or generic adjustments. This measure was specifically designed to counter optimism bias. However, optimism can be very "noisy" with different individuals applying different amounts of it to their assessments, which could lead to prioritization based on biased data. A potentially successful mitigation measure to counteract this is leveraging the outsider view, where a group of people who do not have any stakes in a drug development project are specifically tasked to address the optimism bias, or to compare all projects using the exact same objective set of parameters.

So, what other options exist?

There is certainly potential in a rational design of a decision-making framework that leverages IT systems and mathematical algorithms to support informed decision making in pharmaceutical research and development. Underlying this could be a broader use of systematic assessment of PoS of proposed clinical trials or late-stage drug development programs. Quantitative scientists, such as pharmacometricians and statisticians can play important roles, along with other scientists and clinicians, by applying principles of model-informed drug development to estimate the probability of success of clinical trials and development programs based on a totality of evidence mindset. Clinical pharmacologists can also play an important role as there are many examples in drug development that demonstrate that the risk and benefit (i.e., the balance between efficacy and safety risks) are often related to the dose/exposure or

trial subjects' adherence to the dosing regimen and therefore not two independent probabilities.

Beyond assessing the drug potential, other elements such as observed success rates, financial profiles, and opportunity cost analyses can be included in these algorithms. To successfully inform decisions, however, these data need to be systematically collected across the full portfolio – and strengthened using external observations (e.g., on clinical progression of similar molecules) – to make sure failed projects and overruns are recorded and not clouded by hindsight. And obviously we will need the decision-makers to systematically include these algorithms in their decision-making process.

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The views reflected in this article are the views of the authors and are not associated with the views of any of their respective professional affiliations.

References and further reading

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[The Green Book (publishing.service.gov.uk)]()

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[Biases in Pharma R&D Decision-Making: Sunk Cost Fallacy | LinkedIn]()