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Fail Early, Fail Fast

Biotech executives are addressing a multitude of strategic priorities on a daily basis. However, prioritizing indications and executing the right portfolio program are becoming more challenging due to two persisting trends:

1. VC funding continues to rise in biotech. According to Crunchbase, biotech startups globally raised just shy of $29 billion in seed money through late rounds from all investors. This is up from $19 billion in 2017; a 52% increase in less than 2 years. Simply put, the increase in funding translates into an increased amount of biotech startups crowding the market and making these type of strategic portfolio decisions that much more of a challenge.
2. So-called platform companies raised $659 million in Series A dollars in the first half of 2019 alone. Platform companies often have many options available to them and their need to make fact-based clinical investment decisions is extremely important. This again leads to the same strategic decision challenges for executives.

With the above trends in mind, we continue to see an abundance of innovative companies emerging. Phenomenal science must be the backbone of these budding companies but when armed with capital, it is easy to think that the sky is the limit. This is not always true as many of these companies eventually find themselves with just enough capital to get them to their next big inflection point. This situation translates to many of them having 1 shot to prove to investors that their technology is viable.

When it comes to making a decision on an indication or clinical development path, there are three core questions that need to be carefully considered. When thinking through each of them, instead of looking for reasons to justify further pursuit of an indication, it can be more productive to try to rule out indications. In other words, if you are going to fail eventually, it's better, and much less costly, to fail earlier; so fail fast. How can you approach these core questions with this modified objective in mind?

1) <u>Does the technology have the capability to address a particular disease state?</u>

For this first question, one must think critically about the disease. Regardless of how a technology addresses a disease (curative, preventative, progression slowing, etc.), there needs to be an assessment of what the technology can actually do. For example, some RNAi therapies are designed to silence specific gene mutations that result in neurodegenerative diseases. The silencing of particular genes decreases, and sometimes eliminates, the production of faulty proteins. If this can be achieved, these devastating diseases may be completely cured in some instances. In this example, given there are a myriad of neurodegenerative diseases, identifying which diseases are caused by specific genetic mutations needs to

be the core of the technical assessment. However, before investing too many resources in doing a deep technical assessment, it would be beneficial and best to start by phoning knowledgeable colleagues who understand your technology and do not have a vested interest in your success. Receiving honest and objective opinions from trusted individuals and listening to them regardless of what they have to say should be the first step in trying to fail fast. You may want to ask are you honest enough with yourself and with your potential investors to seek this type of objective feedback early in the process.

2) **Does a regulatory path to market exist?**

When it comes to the ensuring a regulatory pathway exists, the best thing one can do is engage directly with the regulators early in the process. Formulating intelligent questions and asking those questions to the right stakeholders can be extremely informative. The sooner these questions are answered, the sooner organizations can react and build a clinical development strategy that is aligned with the FDA's requirements. Although evaluating analogues can provide guidance and help shape a development strategy, there is no substitute for engaging directly with the KOLs and SMEs that will ultimately decide the fate of a drug. Understanding these barriers and uncovering potential speed bumps ahead of time can shave significant time of drug development, which translates to realizing ROI more quickly. For example, look at analogues related to clinical endpoints. If other therapeutics are failing with similar science due to trial design, take those learnings into your protocol development. If you have enough data that tells you that you are going to get the same results, wipe the board clean (i.e. fail fast) and start over.

3) **Does commercial viability exist?**

Assuming all things are equal after the technical and regulatory boxes have been checked, and there is still a need to narrow or prioritize indications, the commercial component is often leveraged to drive this decision. The key to a successful commercial analysis is backing market assumptions with facts and data. For example, evaluating the epidemiological trends and aligning these with the evolving treatment paradigm will provide insight into the addressable patient population assumption. To understand market share, in addition to being aware of what is already on the market, it is important to identify development programs that could disrupt the market in the near future. This is also an important exercise because if there is risk that the standard of care could change before a product gets to market, this is critical information to have while designing subsequent trials. Another key commercial assumption is related to market access. It is important to remember that getting FDA approval is not the ultimate win. The ultimate win is getting therapies to the patients. Recognizing that pricing and reimbursement play a major role is fundamental.

Each one of these questions carries a long list of further detailed questions. However, if these questions can be answered, the decision tree becomes much clearer. If they cannot be answered, well, you know the mantra. Some organizations are able to conduct a robust assessment that addresses all three lines of questioning in parallel, but others are forced to answer each line of questioning in a phased approach due to resource constraints. These can create an additional list of challenges. With such a scenario, the technical question must take precedence and be evaluated first. After all, if the technical feasibility does not exist, a freshly paved and traffic-free pathway to an attractive market is a moot point.

Technical, regulatory, and commercial considerations are all critical when selecting indications for a platform technology. How an organization weighs each of them will differ but there must be an understanding of each component before further investing in a clinical program. It is important to remember that despite a thorough and objective process following the selected indication, failure is the most common result in drug development. In this line of work, it is about asking challenging questions, mitigating risk, moving forward, and going through the process in a methodical and strategic manner to provide the highest probability for success. However, it is also true in this line of work that the process must include a honest and objective progress with possible endpoints that include disqualifying and failing faster to allow reallocation of time (the most expensive and unrecoverable resource), people (the second most expensive resource), and all other limited resources.

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