



Drug Asset Evaluation: Increasing “Probability of Success” of a Deal

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The current model of drug development has become economically unsustainable. According to Tufts Center for the Study of Drug Development (CSDD), the cost of bringing a new drug to market now tops \$2.6 billion and can take up to 15 years, with less than 12% of drugs entering clinical trials resulting in an approved medicine. With an average of 25 new drugs or biologics approved in a year, the number of companies having successfully crossed that regulatory threshold is quite small. And today, the increased pressure from payers is not just to develop novel drugs, but to create drugs that are “best in value” versus just “best in class.”

Emerging companies constitute about 90% of the total biopharmaceutical market by number of companies, comprising 70% of the global clinical pipeline. Few of these companies have the experience or full expertise to transition biopharmaceuticals from research through to approval. Furthermore, they generally will lack the financial capital required to fund through to product approval. For these companies to be successful, they need to secure a combination of sophisticated investors, partners, and expert consultants with a track records of success in helping bring new, cost-effective therapies to market.

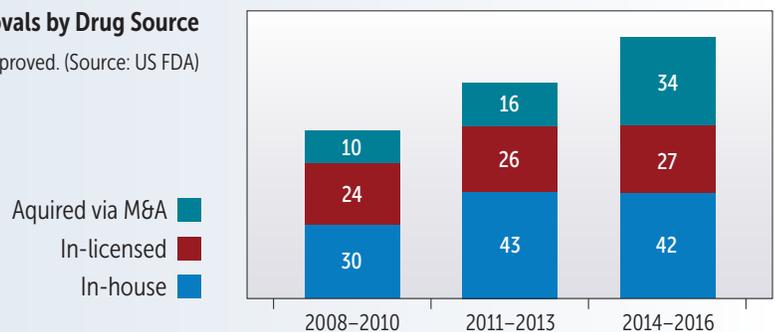
Emerging Companies are the Drivers of Innovation

During the past 15 years, the number of biopharma companies has tripled to more than 3,200. According to the US FDA, almost 11,000 candidates are in the global pipeline (discovery through post-marketing). Of those candidates, only a small number will gain approval; an increasing number of these drugs are being developed by emerging biopharma. According to a report authored by the Pacific Research Institute, “On average, of the medicines that are successful in terms of safety and efficacy, only two in ten are profitable and return an income stream that is greater than the cost of their research and development.” Thus, the odds seem to be heavily stacked against the biopharma company.

Figure 1 shows both the number and percentage of approved new drugs that were developed outside in-house pharma companies. In short, as the number of emerging companies have proliferated, so have the number of compounds they produce, driving the need for increased partnering or M&A advisors to help navigate the odds and successfully bring them to regulatory and commercial fruition.

Figure 1: NME Approvals by Drug Source

Total number approved. (Source: US FDA)



According to the trade association BIO, a total of \$116 billion in investment dollars went into US emerging therapeutic companies through venture capital (\$43 billion), initial public offerings (\$16 billion), and follow-on public offerings (\$57 billion) over the past decade. More than \$144 billion went into payments for either in-licensing assets or acquiring global R&D-stage emerging companies (figure 2).

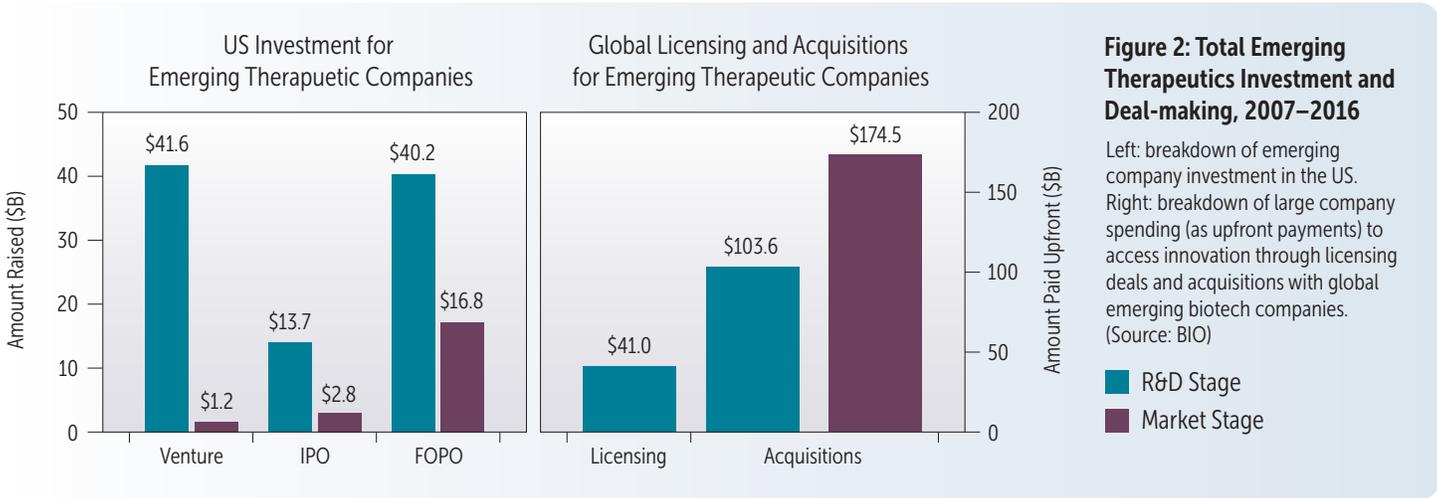


Figure 2: Total Emerging Therapeutics Investment and Deal-making, 2007-2016

Left: breakdown of emerging company investment in the US. Right: breakdown of large company spending (as upfront payments) to access innovation through licensing deals and acquisitions with global emerging biotech companies. (Source: BIO)

Figure 3 details the number of companies by stage of development that were funded by venture capital over the past decade. These investments are for novel drug R&D, including innovative, unique, and potentially disease-modifying agents for diseases with current unmet medical need. With the exception of 2015, there has been a steady increase in the number of companies being funded by venture organizations. Further, the percentage of investment in early stage R&D is growing, indicating a need for expertise in translational science.

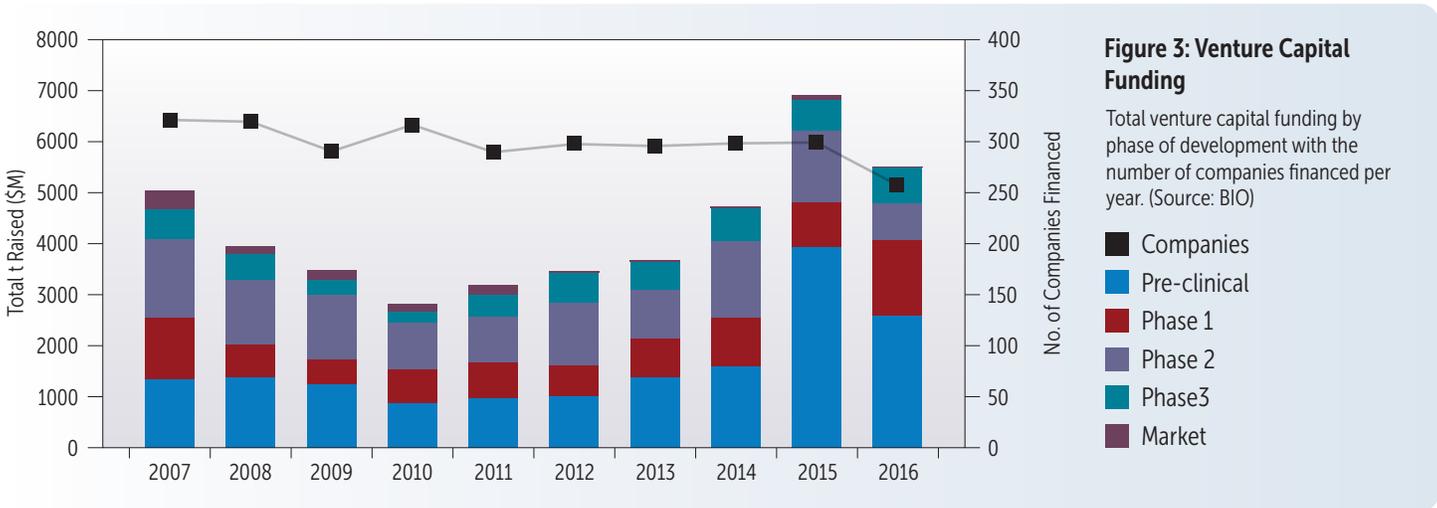


Figure 3: Venture Capital Funding

Total venture capital funding by phase of development with the number of companies financed per year. (Source: BIO)

Finally, universities and research institutes are playing the game, with the view that they may find commercial returns from their academic innovations. Although most are struggling to move beyond the research phase as they do not have the requisite competencies in product development and commercialization, some are finding success. A recent example is The Walter and Eliza Hall Institute of Medical Research that recently announced a landmark deal worth up to \$325 million from the partial sale of royalty rights in anti-cancer treatment venetoclax.

Getting It Right: Asset Evaluation

Partnering and acquisition of drug product candidates is an essential part of the pharmaceutical business ecosystem. While emerging companies are focused on drug discovery and early development, they often do not have the funding or experience to manage the complex, expensive, and time consuming path to regulatory approval. As seen above, the go-forward path for these promising drug products is to work with venture capital, private equity, or established pharma companies.

Getting it right requires starting with the “end” in mind and defining a Target Product Profile that defines the features and benefits a drug must have to be competitive in the market. Through the process of due diligence, it is possible to understand and quantitate the technical and commercial probabilities of success at each stage of drug development. This informs the relative risk and valuation for each investment. Due diligences are typically staged, with the first stage involving performance of a stage-specific gap analysis against the Target Product Profile to identify any data gaps either at a technical, regulatory, or commercial level that would ordinarily be expected for a drug at this stage of development.

Investors often engage third parties to either lead or provide particular functional area experts to perform these diligences. Such third parties need to include a team of functional experts in non-clinical, clinical, regulatory, commercial, chemistry, manufacturing and controls (CMC), intellectual property (IP), and more. The team must have the experience to ask and answer a broad range of questions around the clinical, technical, and commercial viability of the asset to synthesize that information into a quantitative assessment of product opportunity and liability.

Factors Affecting Probability of Success

A recent article published in *Nature* analyzed the reasons for Phase 2 to 3 drug failure over the period of 2013–2015. The failure during this translational phase is well recognized and has been a focus of both drug developers and regulators. In fact, the FDA published a paper on this topic earlier this year, called *22 Case Studies Where Phase 2 and Phase 3 Trials Had Divergent Results*.

The analysis in *Nature* shows that the majority of failures were due to a lack of either efficacy (52%) or safety (24%), where safety includes those failures that were due to an insufficient therapeutic index, strategic (15%), commercial (6%) and operational (3%) reasons. As you parse the data further, it is clear that the Phase 3 failures are more weighted toward both efficacy (compared to efficacy and safety in Phase 2), and commercial (vs strategy and commercial in Phase 2). This analysis helps guide our work in performing asset evaluation/due diligence for new drug products.

The Nuts and Bolts of Asset Evaluation

Asset evaluation involves a cross-functional due diligence team to pressure testing and quantify risk in the following areas:

- **CMC/Drug Product**—To analyze the drug substance, drug product characteristics and identity, manufacturability, quality, strength, and stability
- **Toxicology (safety)**—Drug toxicity refers to the level of damage that a compound can cause to an organism; the toxic effects of a drug are typically dose-dependent

- **Clinical Pharmacology**—The relationship between drugs and humans, clinical pharmacology is focused on drug action and pharmacological principles such as drug absorption, distribution, metabolism, and excretion (ADME); dose justification is key to the clinical pharmacology due diligence program
- **Clinical Development and Clinical Safety**—Evaluation of the planned clinical trials and study design and endpoint criteria are addressed, along with safety analysis and evaluation of adverse events
- **Therapeutic Area**—Expertise in the specific TA from both a scientific and commercial perspective is applied; what is the current standard of care and comparator drugs either in the market or under development that the new drug will compete against?
- **Biostatistics**—Statistical processes and methods applied to the collection, analysis, and interpretation of biological data, especially data relating to human biology, health, and medicine; this section evaluates trial design and key efficacy analyses at different doses for different cohorts
- **Regulatory**—Expertise in bringing the drug from pre-IND, IND, and end of Phase 1, 2, or 3 to NDA/BLA submission and meeting post-marketing obligations is addressed in this program; evaluation of the use of accelerated approval programs, simultaneous global filings, and sub-requirements such as pediatrics are addressed
- **Commercial**—“Will the drug be profitable?” is the core impetus for investment in the program; understanding of the competitive landscape for the drug in its class, for assessing the strategy of a precision medicine product versus a blockbuster, and understanding the reimbursement potential is addressed

Areas of Caution

The process of asset evaluation needs to provide focus into four key areas: the scientific and clinical viability of the drug (scientific), the development strategy of bringing that drug to market (go it alone, partnering, licensing, etc. and development speed/costs), the regulatory, and the commercial viability and valuation of that asset.

In our experience, there are some areas of caution that we believe should be highlighted:

- Dose selection continues to be a vexing challenge in establishing POC and in selecting the “right” dose for late phase trials. In early development, dose selection is key as too high a dose can result in unacceptable toxicity and too low a dose can impair efficacy. In our learnings, an understanding of the relationships between the disease, drug characteristics and individual variability is essential. Exposure (of dose)-response analysis can be levered to inform or confirm trial design decisions, such as cohort selection and endpoint criteria as well as dose regimen.
- In the excitement around the scientific and clinical viability analysis, we see a shortchanging of CMC analysis. Drugs can be denied marketing approval if the quality of the product and the manufacturing process cannot be shown to be of a sufficiently high standard to satisfy regulators. Failure to allocate the time and investment in CMC reviews frequently results in delays in drugs’ overall development timelines that could have been avoided.
- While most companies want to sell their drug globally (or in multiple countries), they often develop a regulatory plan that is centered on one location and hope to adapt it later for others. The assumption that the FDA will accept the EMA approval and vice versa is incorrect, and it is wise to understand up front the different requirements and plan accordingly. A simultaneous submittal strategy can be accomplished, but it must be planned (and financially supported).

Challenges to Heed

- Dose selection
- CMC
- Global regulatory strategy
- Competitive viability
- Patent landscape

- Comparative effectiveness and health economics outcomes research (HEOR). As the voice of the payer increases, a metric-driven approach to determine if the evidence supports a case for reimbursement is pivotal to success. Not only must a cost model be developed for the payers, but a model-based analysis of the competitive landscape will determine the value trajectory for the drug.
- Intellectual property. The relative value of composition of matter, method of use, or other IP claims are direct drivers of value of an asset. Failure to understand or address the patent landscape and impact of time has heralded the death of many potential medicines. Development decisions including methods of manufacture or formulation may infringe process patents and impact freedom to operate, which can create expensive settlements.

Moving Forward

The high costs and risks associated with drug asset acquisition require the involvement of an unbiased and cross-functional team. That team should have deep subject matter expertise in early development formulation, clinical pharmacology, translational medicine, and regulatory science strategies to optimize the pre-clinical to clinical proof-of-concept development process. Working with others from the financial and commercial side, they need to look for opportunities to cost-effectively accelerate the clinical development-to-launch process, with a view to increasing the probability of success and cost benefit of the drug. This approach will support interactions with health authorities and payers on innovative development programs.

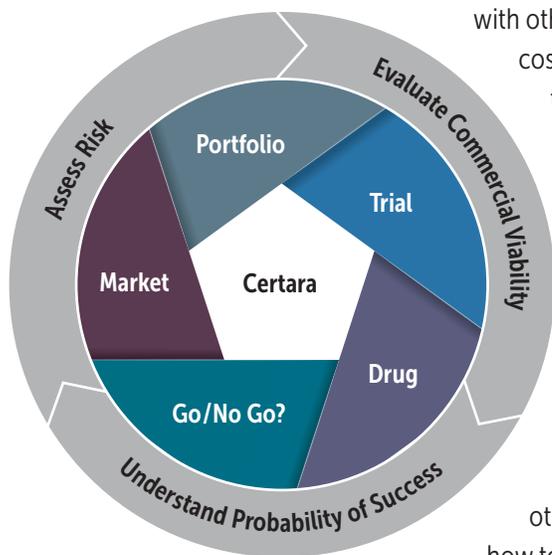
A hallmark to the design of contemporary drug development programs is a strong modeling and simulation (M&S) strategy beginning in early development to improve decision-making and provide a narrative to support proof/reason-to-believe for differentiation, efficacy, and safety to health authorities, payers, investors, and deal-makers. Our definition of M&S includes PBPK (physiologically-based pharmacokinetics), PK/PD (pharmacokinetics/ pharmacodynamics), quantitative pharmacology, model-based meta-analysis, and other relevant quantitative approaches that facilitate differentiation. Understanding how to reduce the clinical trial burden/cost, how to successfully lever accelerated approval approaches, and how to increase the economic feasibility of bringing products to new regions and underserved populations is valuable. Most important, the experience in pressure testing, optimizing, and communicating the value of development and licensing plans to support partnering strategies is key to success.

Summary: Select the Right Team Lead

A technical evaluation team leader must be a highly experienced drug developer who has lead due diligence and development teams, and understands the interplay of the various functions and how to weigh the functional perspectives appropriately, in order to define program POS and other program impacts such as slippage risk. Such a team leader must also be able to articulate how the due diligence findings are incorporated into deal terms in order to stage-gate investment decisions aligned with value creation and be able to support negotiations from both the buyer and seller perspectives.

We believe that Certara—with >200 scientists with expertise in drug development, clinical pharmacology, and M&S—is the right strategic partner to bolster your ability to select the best investment opportunities.

Interdisciplinary Approach to Asset Evaluation



Experience in pressure testing, optimizing, and communicating the value of development and licensing plans is key to success.

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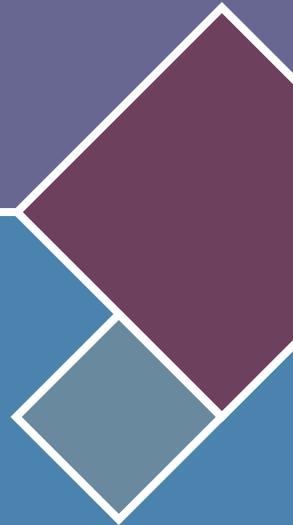
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About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

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