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Nat Rev Drug Discov. 2016 October ; 15(10): 673–674. doi:10.1038/nrd.2016.104.**Investigating investment in biopharmaceutical R&D****Percy H. Carter,**Bristol-Myers Squibb Company, Research & Development, Route 206 and Province Line Road,
Princeton, New Jersey 08543, USA**Ernst R. Berndt,**Sloan School of Management, Massachusetts Institute of Technology, 100 Main Street,
Cambridge, Massachusetts 02139, USA**Joseph A. DiMasi, and**Tufts Center for the Study of Drug Development, Tufts University, 75 Kneeland Street, Boston,
Massachusetts 02111, USA**Mark Trusheim**Sloan School of Management, Massachusetts Institute of Technology, 100 Main Street,
Cambridge, Massachusetts 02139, USA**Abstract**

Recent studies have highlighted a reduction in projected financial returns associated with biopharmaceutical R&D, owing to decreased productivity, increases in costs and flattening revenue per new drug, prompting calls for dramatic revisions to R&D models. On the basis of previous financial modelling, the simplest hypothesis would be that new investment in such R&D should be minimal and focused on biologics in preference to small molecules, as the internal rate of return on investment for biologics projects has been reported to be higher.

We sought to discern how investors have been acting in recent years, and so examined investment trends in nascent public biopharmaceutical companies located in the United States by constructing a database of such companies that had US initial public offerings (IPOs) between 2010 and 2014 (see Supplementary information S1 (box) for details). We then analysed the characteristics of the 113 companies that met our inclusion criteria, including their corporate strategy and therapeutic modality focus. Here, we present the key findings from this analysis and discuss its implications based on our own financial modelling.

Investment trends

Our analysis indicates that investors have still been willing to fund emerging companies focused on small molecules, biologics or non-traditional approaches. Perhaps more

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Supplementary Information: **See online article:** S1 (box) | S2.(box) | S3, (table) | S4 (box) All Links are active in the Online PDF

surprisingly, small-molecule companies comprise the majority of the total IPO pool and its segments focused on R&D on novel molecules, development of novel molecules or delivery of known compounds using novel technologies (Fig. 1). Notably, the importance of small molecules to the IPO cohort remains when the data are re-examined based on aggregate dollars raised or segmented to focus only on companies pursuing oncology and/or autoimmunity indications, for which biologics (largely monoclonal antibodies) have been particularly commercially successful in recent years (Supplementary information S1 (box)).

Financial modelling

Given the apparent disconnect between investor behaviour and previous models, we constructed our own financial model to assess in a quantitative manner the impact of various assumptions on the development of small molecules and biologics (see Supplementary information S2 (box) for details and Supplementary information S3 (table) for the model). We chose a single-molecule framework, beginning at preclinical development (that is, candidate identification to first-in-human) and extending through the initial sales following loss of exclusivity. A month-by-month estimate of pre-tax net revenue in real 2008 dollars was constructed based on 34 model inputs, all of which were derived from published sources. The net present value (NPV) was determined by summing the probability-adjusted, fully discounted cash flow of each of the nine development stages.

Using baseline inputs, the NPVs for an average preclinical small molecule and biologic were US\$37 million and \$104 million, respectively (Fig. 2). These correspond to inflation-adjusted internal rates of return on investment of 15.7% and 18.9%. The NPV increased sharply for both modalities if the valuations were conducted later in the development process (Fig. 2; Supplementary information S2 (box)), because previous costs were sunk.

We used sensitivity analyses in order to probe the importance of each non-rate variable to the estimate of economic value. An improvement of 15% in the input variable yields only a >5% change in NPV for 15 of the non-rate variables (Supplementary information S2 (box)). The most sensitive variables are in the commercial and late clinical phases, with three of the top five most sensitive variables related to the revenues from peak sales: profit fraction, US peak revenue and global multiplier. Critical R&D variables include both the phase III and phase II probability of phase transition. Since these probabilities favour the biologic programme over that of the small molecule, it is not surprising that the percentage difference between these two modalities shrinks dramatically when the analysis begins at a later stage (Fig. 2), by which time more risk has been discharged.

We also probed the sensitivity of the model to three rate variables: discount rate, rate of R&D cost increase and rate of peak sales increase. Perhaps not surprisingly, the model is quite sensitive to both the discount rate and the real rate of increase in peak sales (Supplementary information S2 (box)). Although our financial model is not exceptionally sensitive to R&D cost, persistent changes in the magnitude observed historically (~6–8%) are large enough to meaningfully reduce the NPV.

Using published data for inputs and standard financial evaluation methods, our model suggests that a preclinical drug candidate carries a positive NPV and that this value is 2.5-fold higher for a biologic than for a small molecule. Although our financial estimates are not inconsistent with IPO valuations, they explain neither the continued investor preference for small molecules over biologics, nor why there is not a premium for biologics companies (Fig. 1). We explored three categories of possible explanations for the apparent disconnect: investor behaviour, the robustness of financial models, and the relevance of the models to current R&D practice (see Supplementary information S4 (box) for details).

Investor behaviour

The simplest explanation would be that investors are not strictly rational and the efficient market hypothesis does not hold, or that investors may not be sophisticated enough to form an efficient public market for a space as complex as biopharmaceuticals. Although we consider that truly irrational behaviour is an unsatisfactory explanation, we cannot exclude the possibility that behavioural factors may have contributed to the magnitude of investment or the quality threshold applied for investment. In particular, if the private-stage investors that shape IPOs are focused on their ‘exit’ and not on the ultimate marketing of the compound, then other factors (such as time, cost and marketability of the asset) could have more of a role than implied by our end-to-end financial model. Specifically, if a small-molecule programme is believed to proceed more quickly or more economically through discovery and early development than a biologics programme, as has been suggested in earlier research, this could influence project selection.

Robustness of the models

A second simple explanation would be that the investment community did not find the previous investment models to be sufficiently accurate. Given the sensitivity of our model to sales estimates and the inherent difficulty in making commercial projections at an early stage, it may be that the 2.5-fold difference in NPV between small-molecule and biologics projects is simply perceived as being within the margin of error and therefore insufficient to direct corporate strategy. The NPV for a novel small-molecule drug discovery platform is particularly difficult to estimate, both because its value could be substantially larger than a single programme if its inherent promise is realized and because the technical probability of success is uncertain.

Relevance of the models

A final potential explanation is that investors do not view the models, which are based on historical data, as relevant to current pharmaceutical R&D, at least in the biotechnology sector. Few companies come forward with a project portfolio they label as ‘average’, and so historical data on the average success rates for small molecules and biologics may not accurately reflect internal expectations for new projects being pursued by IPO-stage biopharmaceutical companies, given the pace of recent scientific advances. The therapeutic area alone can provide different expectations for probabilities, as well as for costs and sales revenues. Optimization of R&D models could also favourably influence the expected outcome, or at least shift failure to an earlier, less-expensive stage of the process.

Conclusions

Taken together, the IPO data set and our financial model provide the basis for cautious optimism about future investment in biopharmaceutical R&D. The caution stems from the results of our sensitivity analysis, which highlight that relatively small changes in sensitive variables (such as success rates, peak sales, profit margin and cost of capital assumptions) could rapidly result in even IND-ready projects having a negative net NPV. The optimism stems from the clear indication that investors are still willing to back projects and companies that have advanced to the preclinical stage. Furthermore, companies continue to see exciting therapeutic opportunities to pursue in their laboratories. Although these seem to be primarily in small-molecule projects, the rise of non-traditional approaches is also notable and is indicative of the continued evolution of the science underpinning biopharmaceutical research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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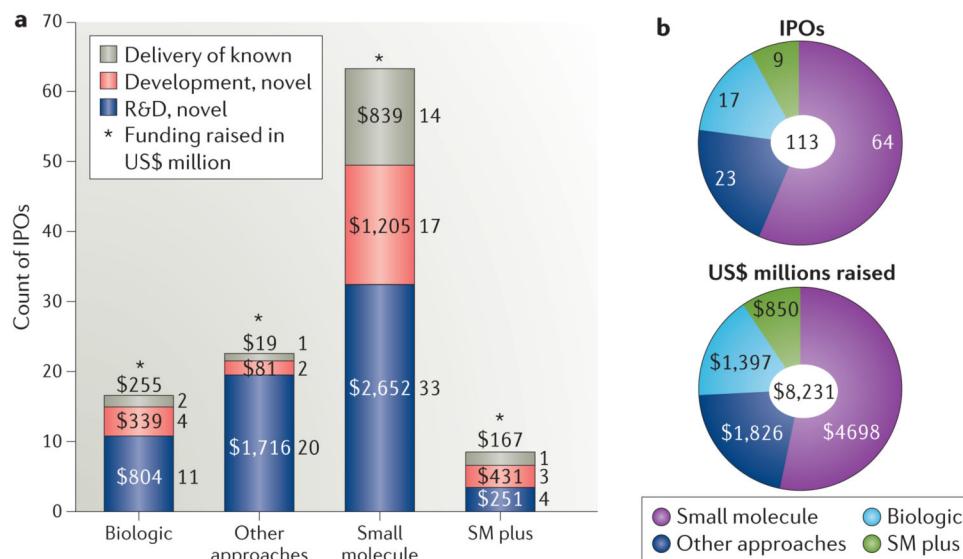


Figure 1. Characteristics of US-located biopharmaceutical companies with US initial public offerings between 2010 and 2014

The data set ($n = 113$) was segmented by both the companies' strategic focus and the primary modality pursued: traditional small-molecule compounds; biologics (antibodies and protein therapeutics); other approaches (including aptamers, small interfering RNA (siRNA), genetic manipulation and cellular therapy). 'SM plus' refers to companies pursuing multiple modalities, one of which was small molecules. The number of initial public offerings (IPOs) is shown on the y axis and adjacent to the graph segments in panel **a**, with the aggregate dollars raised shown in each segment. The total number of IPOs and the dollars raised for each modality are shown in the pie charts in panel **b**. See Supplementary information S1 (box) for details.

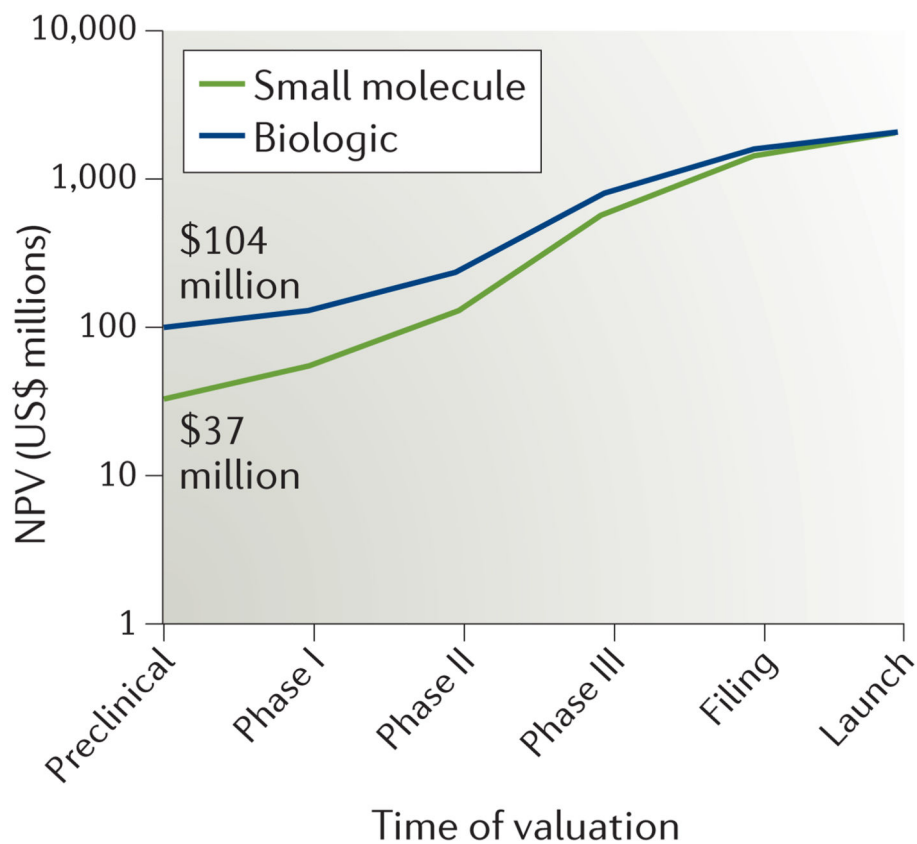


Figure 2. Comparison of the value of small-molecule and biologics projects

The graph shows the probability-adjusted, fully discounted net present value (NPV) based on the time of valuation for an average small-molecule (green) and biologic (blue) programme using our financial model. See Supplementary information S2 (box) for details.