Supplementary box S2 | R&D productivity model and cost of drug development estimates

Our model is intended to introduce a framework for evaluation and discussion of how to improve R&D productivity. It is also intended to form the basis of a prototype model that can be used by others in the pharmaceutical industry to examine their own model of R&D performance and productivity efforts.

Although our model is not intended to provide a definitive statement of the industry's cost of drug development, we consider that the model, assumptions and the resulting estimated cost of drug development do approximate current industry R&D performance. The key parameters of our model (success rates, cycle times, phase costs and cost of capital) derive from industry benchmarking data, including very recent data from the Pharmaceutical Benchmarking Forum[1] (see supplementary box S3 for further details), as well as our internal portfolio metrics, comprising over 15 years of project-level data from Lilly's R&D portfolio.

Numerous efforts have been made to estimate the cost of drug development using different methods, assumptions and data sources. The table below summarizes recently published estimates[3,4,8,9]. These models and estimates are useful in analysing returns on R&D investment and productivity, and have frequently been used in public policy debates[4], including the current debate on follow-on biologics[5]. Although we do not intend to exhaustively examine these prior efforts in this discussion, it is important to understand the key differences in the methods and assumptions used to guide these estimates; that is, in order to place our model in context as others use such models to examine their own R&D productivity efforts.

	Model used in this paper	DiMasi[4] 2003	DiMasi[8] 2007 pharma	DiMasi[8] 2007 biopharm	Gilbert[3] 2003	Adams[9] 2006
MODEL OUTPUTS						
Out of pocket	$873	$403	$672	$559	n/a	n/a
Capitalized	**$1,778**	**$802**	**$1,318**	**$1,241**	**$1,700**	**$868**
KEY ASSUMPTIONS						
P(TS) - FHD to Launch ("clinical approval success rate")	11.7%	21.5%	21.5%	30.2%	11-12%	24%
Cost of Capital	11%	11%	11%	11.5%		11%

Methods

The method set forth in DiMasi 1991[6] has formed the basis for many recent efforts to calculate the cost of drug development[4,7–9]. From here on, when we refer to DiMasi without a specific reference, we refer to the model and approach set forth in 1991[6]. This method calculates the pre-tax cost to get a compound to marketing approval using survey data on actual drugs to estimate clinical parameters, as well as statistical modelling to estimate approximate spend on preclinical phases. The method starts with 'out-of-pocket' costs that include the cost of failures and 'capitalizes' these costs to include the returns required by shareholders to use their money during development[4]. The importance of DiMasi's estimates to public policy[10] has led to additional discussion of both the methodology and assumptions, including challenges from Public Citizen[12], Love[13] and Light and Warburton[10.11] and responses by DiMasi[14–16].

Like the DiMasi model, our model utilizes a set of key parameters: success rates, cycle times (phase duration or length), phase costs and cost of capital. Although there are differences between the approach set forth in DiMasi and the approach used in our analysis, differences in approach are less important than the differences in several key assumptions. It may be useful however to further delineate differences in both our approach and model assumptions.

Our model (shown in Figure 2) essentially calculates the number of assets needed in each phase of R&D to generate one approved compound based on assumptions for success rates (p(TS)). We then calculate 'out-of-pocket' costs using assumptions for the cost per asset for each phase and 'capitalized' costs by taking into account cycle times for each phase. Unlike DiMasi, our model also includes separate assumptions for the phases of drug discovery prior to Phase I. Including these phases allows us to explicitly model the impact of productivity efforts in the earliest phases of discovery. Our assumptions for those phases, while based on

internal and benchmarking data, were set to approximate DiMasi's assumption that 30% of 'out-of-pocket' costs come from these early phases.

Our model does not include 'exploratory' and 'post-launch' costs, which are inherent parts of drug discovery and development costs. DiMasi does separately estimate post-approval costs[4]. Our cost assumptions do not incorporate non-molecule-related costs (for example, overheads such as technology licenses) required to support an R&D organization. Including these costs would increase our estimated cost of drug development by approximately 30%. DiMasi's phase cost assumptions come from cost surveys requesting aggregate costs that should include allocations of non-molecule expenses[4]. An issue with using cost of development models to evaluate performance is that they do not include value in the analysis. We have therefore created additional models that we use in some productivity analyses to ensure value is incorporated as a critical parameter.

Assumptions

The key differences between most of the recently published estimates of the cost of drug development come from the assumptions used in the analyses. DiMasi leverages a proprietary Tufts database of drug development information from recently launched compounds to develop assumptions and thus drug development cost estimates at different time periods, for different types of compounds (pharmaceutical vs. biopharmaceutical) and for different therapeutic categories[4,6–8]. Adams[9] duplicated the DiMasi approach but used a different data source (Pharmaprojects database) for success rates and phase lengths. Adams also leveraged their data source to estimate the cost of drug development for different firms and for different therapeutic areas and indications. In our paper, we use success rates and cycle times from a very recent industry benchmarking study (PBF/KMR)[1] and other approximations based on internal data and other public sources[3,4,8].

Success rates

The primary differences between our assumptions and other recent estimates by DiMasi[4] and Adams[9] are in the estimates of success rates. DiMasi's assumptions yield a cumulative probability of 21.5% from the start of Phase I to approval[4], although the recent Tufts estimate has been revised downward to 16%[17]. Our model leads to a lower cumulative probability of 11.7% based on the success rates from the PBF/KMR benchmarking study[1], which also approximates our own internal estimates. The assumptions from our model also closely approximate the Bain drug economics model[3]. Because of the enormous impact of even small differences in p(TS), this is also a major focus of the productivity efforts described in our paper.

Phase costs

Reliable estimates of phase costs have traditionally been the most difficult to obtain, particularly for later stages of development. DiMasi[4] establishes the latest set of commonly used pharmaceutical estimates of phase costs in year 2000 dollars, with a more recent paper[8] inflating these costs to 2005 dollars. Our estimates are based on internal data and industry benchmarking data and are in 2008 dollars.

Cycle times/phase durations

DiMasi[4] and our model differ slightly in cycle time assumptions, with our model assuming slightly longer overall times in both pre-Phase I and clinical phase durations. Cycle times do not factor into "out-of-pocket" estimates, but the differences in assumptions do have an impact on estimates of "capitalized" costs.

Cost of capital

We utilize an 11% cost of capital in our paper, which is the same as the base value used by DiMasi[4] for pharmaceutical companies.

Additional considerations for costs models

As noted above, it is very important for each company to build a cost model that takes into account its own particular circumstances, strategic needs, and assumptions. The process of creating an appropriate cost model should comprise three steps: framing of the decision(s) for which the model will be used; developing a model framework that has commensurate breadth and detail; and populating the model with relevant assumptions.

Depending on the decision context, the model might be expanded or simplified from the model discussed in this paper. For example, the model might only cover clinical development, or it might include various additional components of the molecule life cycle, such as discovery research or post-launch development (potentially including FDA-mandated studies, efforts to expand to additional regions, or clinical studies to add new indications or line extensions). In addition, other financial components can be included, such as overhead costs and measures of value for launched products. DiMasi[2] details the significant impacts of these factors, which could cumulatively lead to substantial changes in overall cost per NME[17].

Finally, we would like to emphasize how important it is for a company to use assumptions that represent its particular circumstances rather than industry averages. A company that has a different risk profile or therapeutic focus, or one that is going through major organizational change (such as a merger) might find different opportunities for productivity improvement, or might find that areas that would otherwise be opportunities to be off-limits for strategic reasons. In this regard, a recent analysis indicates most mergers have had little to no beneficial impact on R&D productivity[18].

Using models of R&D performance in the pharmaceutical industry

We are continuing to create, use and adapt these types of models to inform our R&D strategy and productivity efforts, as well as many of the initiatives mentioned in the paper (for example, FIPNet, Tailored Therapeutics, and so on). We suggest that others in the industry develop and utilize similar models to help inform and direct their efforts to improve R&D performance. This requires an understanding of the underlying model and utilizing assumptions appropriate to each company's own business model, as results can vary significantly depending on the R&D model and therapeutic area focus of a given company[7,9].

Ranges of the cost/NME from about $500 million to $2 billion have been proposed based on therapeutic and individual firm models[9]. A recent analysis that employs a model that is not compatible in structure or approach to the other reported models has even reported estimates as high as $2.6 billion to $8 billion for individual companies[19]. We have shown that even the base model used in this paper does not incorporate many of the elements of R&D performance (such as value, post-launch commitments and strategies, and overheads). Not recognizing the scope limitations of any models can lead to inappropriate conclusions and missed opportunities to improve R&D productivity in areas not modelled. Regardless of these challenges, developing and leveraging such models can provide valuable insights into the return on R&D investments and areas of focus for the important and necessary performance improvements that are required of the industry by our patients, shareholders and other stakeholders.

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