Editorial

New estimates of drug development costs[☆]

1. Introduction

DiMasi et al. (2003) (hereafter DHG) have estimated the average costs of bringing a new drug (or more precisely a new chemical entity (NCE)) to market to be US$ 403 million in 2000 dollars. Accounting for the time between investment and marketing raises the cost to US$ 802 million. These are impressively large numbers, usually associated with purchase of a squadron of jet fighters (40 F16s in fact). The estimates have been a matter of heated debate since they were first made public in 2001. The Public Citizen (2002) referred to the "US$ 802 million myth" prompting the Pharmaceutical Research and Manufacturers Association (PhRMA, 2001) to respond that the estimate of US$ 802 million was likely to be conservative.[1]

Critics of the pharmaceutical industry, and of current public policy towards pharmaceuticals, believe that prices and rates of return in the prescription drug market are supra competitive. They refer to accounting rates of return on the order of 18% in the late 1990s as evidence. The industry in contrast claims that rates of return in the industry, when research and development (R&D) costs are appropriately accounted for, are approximately competitive. Estimates of high costs for developing drugs play into this debate by reducing the estimated profitability of the drug industry.

In this Editorial, I discuss how economists and economic policy makers might interpret the estimates offered by DHG. My aim is not to critique the cost-finding methods nor to take sides in the profitability debate, but to place the results of a very carefully conducted empirical investigation into context. The remarks I will make below are organized into three sections. First, I will note some clear lessons from the DHG paper. Then, I present some facts and background on pharmaceutical research and development (R&D) spending that are helpful in interpreting the DHG estimates. Finally, I consider the cost estimates in context of economic choices in the industry.

[1] See statement of Christopher Mollineaux of PhRMA, July 23, 2001 available at: www.phrma.org/mediaroom/press/index.

2. Some lessons

DHG carefully assess the average costs of developing a new chemical entity (NCE). An NCE is a new therapeutic molecule or compound that has not previously been tested on humans. The unit of observation in terms of the product is the NCE developed "in-house" by prescription drug manufacturers. The analysis is built on a cost survey of 10 large pharmaceutical manufacturers. The survey results represent self-reports from the 10 manufacturers about the various types of costs they incurred in developing different drug products during the 1980–1999 period. The surveyed manufacturers allocated R&D costs according to those drugs developed in house, those licensed or acquired and products that were already approved. Thus, the cost estimates are made for the segment of total R&D costs that are attributed to in-house developed NCEs.[2] Sixty-eight drugs were studied. They include drugs that made it to market, drugs that were not brought to market, and some that are still in development. Building on methods developed in a previous paper (DiMasi et al., 1991) and by the Office of Technology Assessment (1993) the estimates are meticulously built up for both the average out-of-pocket cost estimates and the average economic cost estimate, which takes into account the opportunity cost of capital.

The detailed construction of the estimates serves as a primer on the economics and industrial process of drug development. As a result, it contains a wealth of useful facts and explanations regarding how drugs are tested and evaluated during the multi-stage process of drug development. By analyzing the drug development process in such detail DHG remind policy makers of some important features of the prescription drug market. First, the drug development process is risky. The paper contains an analysis of the transition probabilities of moving from the pre-clinical phase of testing through the three phases of human testing that are part of the FDA regulatory process. Based on a data analysis of a panel of drugs they estimate that only 21.5% of drugs that began the Phase I human trials are eventually brought to market. Second, DHG show that the development process is time-consuming, 90.3 months on average span the start of clinical testing to marketing approval, a number that is lower for the 1980–1999 period than for the earlier period covered by DiMasi et al. (1991). This delay relates to the third key feature: regulations can matter a lot to the cost of drug development. Improvement in FDA approval times has been central to reducing development time. DHG report a decline in the duration of the FDA approval period from 30.3 months in their earlier study to 18.2 months in this study.

Most importantly, the study highlights the point that regardless of the exact cost figure estimated, if we are not cognizant of the complex, risky and costly process of drug development, public policy can damage an industry that has over the past generation bestowed enormous benefits on society by improving the effectiveness of health care.

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[2] The self-report data have been viewed with skepticism by some critics. DHG have made an effort to obtain data from other sources as crosschecks of the self report information. It should be noted that the OTA (1993) study found variation in how firms measure and report R&D costs. Some specific issues including the timing of when capital expenditures are counted and how and when R&D costs are attributed to individual drugs. Gluck (2002) discusses these and other issues in cost reporting.

3. R&D spending in context

In order to understand the meaning of the average economic cost of an NCE, it is useful to consider the various types of new products that pharmaceutical manufacturers introduce and the role that R&D plays in bringing each type to market. In 2000, the FDA approved 98 new drug applications (NDA). Among the 98 new drugs approved, 27 were new molecular entities (NME).[3] The balance are products that represent new formulations and new methods of delivering existing drugs. This second type of new drug product is excluded from the DHG analysis. These drugs are of course "less new" than NCEs, but they often account for substantial sales and offer therapeutic advantages in terms of efficacy, administration and patient compliance. CMR International (2002) estimates that about 30% of R&D spending is devoted to bringing "line extensions" to market.[4]

The average cost of an NCE is therefore an important component of the average cost of all potential new drug products that were assessed and or marketed during the 1980–1999 period, but it is not the whole story. The costs per NCE and per new product of any type are different. The cost data for estimating the cost per new product would include R&D spending for line extensions in the numerator. The denominator would include the number of marketed new products. Such an alternative average cost figure would reflect the average cost of bringing a new drug to market across the entire spectrum of new products sold by pharmaceutical manufacturers. My guess is that number would be much lower than the average cost per NCE.

DHG analyze the probability that an NCE that enters the human testing phase will eventually be brought to market. As noted above, about 78% of NCEs are never marketed. Pharmaceutical manufacturers terminate development of NCEs for a variety of reasons. Walker (2002) reports the reasons for termination of development of new products among a group of 28 pharmaceutical manufacturers, estimating that clinical safety issues accounted for 20.2% of terminations in 2000. In addition, 19.4% of terminations involved toxicology concerns, 22.5% were due to disappointing clinical efficacy results, 16.2% were due to various other factors and 21.7% were based on "portfolio considerations".[5] Risk of failure stems from both "exogenous" factors such as unanticipated safety problems, but also from business decisions, grouped under the "portfolio considerations" in the Walker study. The implication is that the cost of drug development should not be taken as a given number against which to compare revenue expectations. Changes on the revenue side would lead to different decisions about which drugs to carry forward in the development process, and would thus change the average cost picture.

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[3] The distinction between an NCE and an NME is small. NCE are new molecules or compounds that have not been tested in humans before. NME is an FDA term used to describe new compounds. Data cited are from FDA (2001).

[4] It should be noted that in 1999 PhRMA estimated the share of R&D devoted to line extension to be about 18% (PhRMA, 2001).

[5] DHG also discuss how the costs at each stage of development are partly made by strategic concerns and are not just the result of regulatory dictates. For example, they note that one reason that the costs of clinical trials may have been increasing is because of a desire to make efficacy claims against other drugs in addition to placebo. This competitive motivation would result in larger clinical trials in order to have sufficient power to detect differences in efficacy against other drugs.

4. Development costs and economic decisions

I would like to consider two issues concerning how we might make use of DHG's average cost estimate for purposes of economic analysis or policy assessment. The first is the implications of the average cost estimates for informing us about the revenues that are required to cover development costs in order to sustain investment in drug R&D. The second concerns how we might view the estimates made by DHG in the context of development decisions for the marginal NCE.

If the average net revenues (revenues minus production costs) from sales of new drugs brought to market do not cover the average costs of developing, new drugs capital would tend to migrate away from drug development. The average cost of developing an NCE is a major component of the average cost of developing a new drug, and is important for assessing the ability of sales to cover development costs.

DHG characterize the drug development process as a multi-stage, multi-period set of choices. It may, therefore be useful to interpret R&D costs as the result of a multi-period set of decisions. Development costs are incurred sequentially. Learning occurs within each stage of testing and evaluation. Lessons are learned about the expected costs of the next stage of research, the likelihood of achieving FDA approval, and the expected revenues following launch (Wiggins, 1981). The speed and the amount of learning that takes place depend in part on the resources allocated to the development process. Profit maximization implies that investment projects will be evaluated according to the net present value to the firm of the investment.[6] The profit-maximizing pharmaceutical company considering development of an NCE must only consider the investment to be made at a particular stage in the development process given what it knows about expected costs of development and expected net revenues at the time. Learning permits the firm to update its assessment of the net present value of making an additional investment in the development of a specific NCE. At each stage of development, the firm also has the opportunity to choose the level of resources to be invested which will affect the speed and the learning in the subsequent stage. Some development costs will have already been sunk. Applying the NPV standard to future streams of revenue and cost will lead profit-maximizing firms to continue any project where the expected NPV of the investment is positive. The average economic value of R&D resources across projects does not directly enter into the optimizing choice for the individual or marginal NCE.

It is worth recalling that the multi-stage nature of the choices is reflected in the DHG analysis. NCE development is halted for strategic reasons at different rates across the phases of development. The size of clinical trials has increased dramatically overtime.[7] The time taken in each stage differs and has changed since their earlier study. The data presented

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[6] There is an extensive literature that examines the net present value criteria in the context of uncertainty and irreversibility in investment. Much of that literature holds important lessons for modeling pharmaceutical R&D. I, however, limit my comments to a very simplified conception of a multi-period investment model. For an excellent review see Pindyck (1991).

[7] Critics (Public Citizen, 2001) of the DHG study suggest that the costs of clinical trials estimated by DHG are larger than that of NIH trials, which they contend, suggests bias. The fact that the trials are conducted for different purposes makes the comparison to NIH trials as a type of gold standard misleading.

by DHG offers a rich source of information that informs us about both economic parameters governing the net present value assessment at each stage of the development process as well as the outcomes of those choices. Information about the cost of capital, and the structure of drug investigation required at different stages by the FDA are economic parameters that are given to decision-makers. Investment intensity, durations of testing at each stage and project abandonment rates are each at least partly matters of choice to economic decision-makers. The average costs of drug development are therefore reflections of the choices made by prescription drug manufacturers in response to economic parameters such as the user cost of capital, prescription drug prices and formulary designs. These cost estimates will necessarily change as revenue; input cost and procurement parameters change.

The average out-of-pocket costs of an NCE estimate of US$ 403 million and the average economic cost of an NCE of US$ 802 million are not cost parameters that decision-makers use to evaluate the value of investing in development of a new product. They reflect the outcomes of profit-maximizing choices given a complex set of economic, institutional and technological circumstances.

DHG provide carefully constructed estimates of the average cost implications of profit-maximizing choices about developing NCEs overall. This is significant because NCEs are generally considered the source of major therapeutic advances. The estimates provide useful lessons about drug development. The previous study by DiMasi et al. (1991) has been extremely influential in educating the field on the economics of developing prescription drugs. That study has been widely cited and debated, and DHG have expanded and improved upon the earlier work. This new and valuable effort is already the subject of intense interest. This research group continues to advance our understanding about the complexity, risk and cost of the R&D process for new drug products.

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