Title
The Pharmaceutical Research and Development Process, and its Costs

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Publication Date
1999

Introduction

What are the research and development costs required to find new drugs for tropical diseases? That question is the subject of this paper, which explores the current state of knowledge on how much it would cost to develop new medicines specifically for use in low- and medium-income countries.

The question's relevance follows from the recognition that "despite the fact that 90 percent of the global disease burden occurs in the tropics, only about 5 percent of global health research and development investment is directed at reducing that burden." (Godal, p. 1864) But of course what is required are not merely expenditures on research and development but rather new drugs to reduce the burden of disease. The essential question is how much additional research and development expenditures are needed for that objective.

This issue is critical for the question of costs: imitative or "me too" drugs generally cost much less to develop than major breakthroughs. While new drugs are needed, they are not all the same. It is therefore not sufficient simply to examine average costs per new drug without considering their therapeutic benefits.

The Concept of Research Costs

The cost of any activity is the minimum level of expenditures required to achieve a particular result. They represent non-discretionary expenditures that are incurred to achieve a certain result. When this definition is applied to the production of a specific product, the concept is clear; but unfortunately, the clarity dissipates when applied to activities that have a large discretionary component, such as research and development. Because uncertainty levels are particularly high in research efforts, there is considerable discretion as to how much should be spent on particular activities. It is therefore

especially difficult to determine what are the minimum level of expenditures needed to achieve a certain result.

Equally important is defining the objective to be sought. How much therapeutic advance is required of the new product, and when should one push forward on a drug that embodies a minor advance rather than continuing to work towards a major advance? It is far easier to introduce a new pharmaceutical whose therapeutic properties and chemical structure are similar to those of existing products than to find a new product which is both different and superior to what has gone before. As a result, research costs per product should be quite different depending on its ultimate purpose.

In that case, however, there is the problem of how therapeutic gains should be measured. For example, how should improved side effects be compared with therapeutic benefits that apply now to an increased proportion of patients? Such questions are exceedingly difficult and no simple answers exist. Yet, the various dimensions of therapeutic benefit are surely related to the expenditures required to introduce an individual product. What all this means is that there is no unambiguous way to determine the research costs needed to introduce a new pharmaceutical agent.

Finally, there is the matter of which concept of costs should be considered, even if the appropriate measure of output could be defined. I refer here to the distinction between average and marginal (or additional) costs. If each research project and prospective product were a unique enterprise, with few overlapping activities, then these two concepts might coincide. However, that is not the case. Especially in the realm of drug discovery, as contrasted with drug development, there appear to be substantial spillovers such that research projects are linked. (Cockburn and Henderson, 1994; and Henderson and Cockburn, 1996) Another way of looking at this issue is that there are common overheads which influence the productivity of individual projects. As a result,

there is little reason to believe that average and marginal research costs for new pharmaceuticals coincide. Instead, marginal costs can be much lower.

In such circumstances, which concept is the appropriate measure of costs? The answer depends on the circumstances in which the proposed research is to be carried out. If particular research projects are to be carried out through the establishment of an entirely new facility, then average costs are the appropriate concept; although marginal costs are the appropriate measure if these projects are to be embodied in an ongoing facility.

Current Estimates of Pharmaceutical Research Costs

There are no studies, to my knowledge, of research costs specifically of drugs designed for low- and middle-income countries. In this section, therefore, we review current estimates of research costs for all new pharmaceuticals.

Two recent reviews of this economic literature accurately describe the current state of knowledge. (OTA, Ch. 3, 1993; and Kettler, 1999) However, neither this literature or these reviews account for differences in the therapeutic advance embodied in new drugs; and both effectively deal with the research costs associated with an *average* new product.

The study by DiMasi et al. in 1991 set the stage for much of this work, although it built on Hansen's earlier 1979 paper; and the former provides the basis for current estimates of research costs. For a sample of 93 self-originated New Chemical Entities (NCE) introduced by twelve companies in the latter 1970s and through the 1980s, these authors report average cash outlays of $114 million per approved product in 1987 dollars, leading to fully capitalized costs of $231 million. Because the research and development process in that era was so lengthy, actual research and development expenditures represented just under half of the total, the rest being the cost of the time to approval.

In her current review of pharmaceutical research costs, Kettler updates DiMasi's estimates to 1997 values on the basis of the GDP implicit price deflator. Her resulting figure is $312 million, (pp. 14-15) which is the most accurate current estimate of average research and development costs per new product.

DiMasi's study emphasizes the distinction between drug discovery and drug development, where the latter pertains largely to carrying out a substantial volumes of clinical trials. While these trials can be quite expensive, still on an uncapitalized basis, they account for less than half of total research costs. Kettler estimates their share at between 42 and 46 percent of the total. (p. 18) The importance of discovery costs in this total suggests the importance of spillover effects.

Because project-level data were available only for clinical costs for investigational NCEs, DiMasi's estimates necessarily depended on various other parameters derived from other sources. These included: (1) an estimated success rate of 23% at which investigational NCEs gain approval; (2) an estimated ratio of 55.7% between pre-clinical and total R&D costs; (3) an estimated lag structure of 98.9 month between the initiation of clinical testing and NDA approval; and (4) an appropriate discount rate of 9%. (DiMasi, pp. 121-126) All of these factors are essential components in reaching his estimated cost figures, and all are subject to considerable uncertainty. Moreover, all could assume different values in different settings.

In her review, Kettler considers these factors in some detail. The first such factor is the success rate, and she observes that "the cost of new drug development is critically dependent on the proportion of drugs that fail in clinical testing." (p. 26) If recent scientific advances could reduce the proportion of failures, then overall research costs would decline substantially. A second factor is the level of discovery costs, in contrast to development costs. Because the former were not allocated to particular products, DiMasi estimated them from overall ratios between the two sets of expenditures. Yet, such costs respond to different considerations so past ratios could be quite different in the future.

For example, Henderson and Cockburn, 1996, report that "research programs located within larger firms are significantly more productive than rival programs located within smaller firms." (p. 55) In that case, the continuing consolidation of the world-wide pharmaceutical industry could possibly lead to lower unit discovery costs per new product. Finally, there is the possible effect of important new technologies on both discovery and development costs. In this realm, Kettler notes the recent new advances in biotechnology, combinatorial chemistry, and genomics; and observes that analysts from Lehman Brothers predict a fall in total research costs per new product on this account. (pp. 34-36)

The final two factors relate to the importance of the opportunity costs of research expenditures and thus are directly related to the time pattern of outlays and benefits. While the specific discount rate that is used may be fully correct for the private firms making investments in new products, that figure may be higher than appropriate for public decision-making. Fuchs and Zeckhauser, 1987, write that so long as future citizens are given equal weight with current ones, "the value of life-years to future generations should be discounted at the time-value-of-money rate." (p. 265) And Vicussi observes that "many cost-effectiveness studies currently use a real rate of discount of 5 percent,...[and that] real rates of return of 3 percent, or even less, appear more in line with U.S. economic performance in the past decade." (1995, p. 144) At lower discount rates, total research costs per new drug would be much lower.

In a second study, DiMasi et al., 1995, estimate average development costs for drugs in four different therapeutic categories, and find there to be substantial differences between categories. Out-of-pocket clinical period costs per approved NCE in 1993 prices varied from $50 million among anti-infective drugs to $99 million for nonsteroidal anti-inflammatory drugs. (p.165) The authors attribute these differences largely to different attrition and clinical success rates. (p. 168)

This brief review suggests is that existing estimates of research costs for new pharmaceuticals provide general parameters but not very precise estimates of the cost of finding and developing specific new pharmaceuticals. There are too many unknowns in the research process to reach very precise estimates, which may not be a surprising conclusion.

A Recent Controversy

Before ending this discussion, it is interesting to consider the critique of Love, 1997, on these cost figures. He questions whether the estimates described above are accurate in light of some very different figures he compiles from the Orphan Drug Tax Credit. Love notes that "in order to obtain these credits, companies reported direct expenditures on clinical trials [for drugs approved between 1983 and 1993] of $213.8 million, or $2.3 million per approved drug.... In 1995 dollars, the amount expended on human-use clinical trials was $3.2 million per approved drug, from 1989 to 1993." (p. 2) To be sure, Love's figures ignore discovery costs which, as noted above, represent slightly more than half the total; and they also reflect only successful new drugs. However, even doubling the above figure to account for the first omission, and multiplying the resulting figure by four to account approximately for the second, there are estimated research costs per approved new drug of only about $28 million, which remains much less than the previous figures.

The discrepancy between Love's values and the previous estimates is explained by a pharmaceutical industry representative on the basis of both "lower regulatory requirements and smaller clinical studies." He responds that "clinical trials for orphan drug candidates nearly always involve far fewer patients; ... [and] also, it is clear that FDA applies a more lenient standard to approval of orphan drugs." (Warren, 1997) While there is some validity to these explanations, there is another factor as well which may be even more important. As noted above, the earlier estimates describe the full costs

of discovering and developing new pharmaceuticals, and therefore represent average costs. In contrast, the orphan drug tax credits relate specifically to a particular product and probably include very little of the research and development overheads that currently exist. For that reason, Love's figures may come closer to representing marginal costs; and we should not be surprised when marginal costs are substantially lower than average costs.

Some Conclusions

The purpose of pharmaceutical research spending for tropical diseases is not merely to see the introduction of new pharmaceutical agents but rather to reduce the burden of these diseases in lower- and middle-income countries. While new drugs can be the source of achieving this objective, we should focus on that objective and not merely on the intermediate step of new drugs. What this means is that we should employ a measure of costs that is appropriate to the task.

One implication of this approach is that how a research program is structured is critically important, since in this realm, marginal costs are likely to be far below average costs. Research contracts placed with major pharmaceutical firms would need to cover marginal costs but not necessarily average costs. This consideration holds forth the possibility that the required expenditures may be far less than suggested by the studies reviewed above.

To achieve lower expected costs, however, it is critically important how the research is structured. To the maximum extent possible, one should take advantage of existing research overheads. In regard to pharmaceutical research and development, there is considerable evidence that spillovers across research projects are a critically important factor affecting both prospects for success and costs to be borne. One should therefore expect better results when these activities are integrated to the largest extent possible within the existing structure of pharmaceutical research and development.

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