THE COST OF NEW DRUG DELIVERY AND DEVELOPMENT – A REVIEW

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ABSTRACT

Drug discovery and development is a complex, high octane, high risk and potentially highly rewarding endeavour. Companies literally burn cash to push through the arduous process, to the tune of $802 million per drug. Why is it so high? Who's paying for it? Can this be sustained? The development of a new drug requires a major investment of capital, human resources, and technological expertise. It also requires strict adherence to regulations on testing and manufacturing standards before a new drug can be used in the general population. All these requirements contribute to the cost increases for a new chemical entity (NCE, i.e., new drug candidate) research and development (R&D). The central question raised by this trend is who will pay for new pharmaceutical R&D?

With this question in mind, this article has three objectives

1) To describe how the environment for pharmaceutical R&D has changed over time and the effect of these changes on the R&D process.

2) To summarize available information on the cost of drug discovery and development for NCEs, and.

3) To consider the societal value of new drugs. The focus is on the United States, as the largest pharmaceutical market, and for which the relevant literature is most comprehensive, but many of the issues discussed are similarly important in the other major markets.

KEYWORDS: Drug discovery, New Drug development, Research and Development.

The Changing Environment for Pharmaceutical R&D

Trends in the type of new drug development. Drug therapy has developed in response to population health care needs to the extent that resources and technology permit. The most recent trend has been to pursue drugs for the treatment of chronic diseases, especially those that most commonly afflict the aged. Of the three leading causes of death — cardiovascular disease (CVD), cancer and stroke — CVD is the biggest killer. In the United States alone, the cost of treating CVD will exceed US $368 billion in 2004, and CVD claims more lives each year than the next seven causes of death combined. As with all health-care technologies, drugs are improved through continued research, without which there would be no advances in treatment.[1]

Although there have been some new uses for older drugs (i.e., thalidomide) and some very old drugs continue to be used today (i.e., digoxin), the drug therapy used today is much improved from even 20 years ago. There have been marked improvements in long-established drug classes (i.e., atypical antipsychotics) and entirely new classes of drugs (i.e., statins) that offer major improvements over previous treatments have emerged. There are now drugs for conditions that were previously without treatment (i.e., Alzheimer's disease), and the emergence of HIV/AIDS in the early 1980s points to the need to expect the unexpected. The new drug approval process. In the United States, as in most countries, there is a formal process by which new drugs are approved for marketing. The standards of evidence for new drug approval are Similar across.
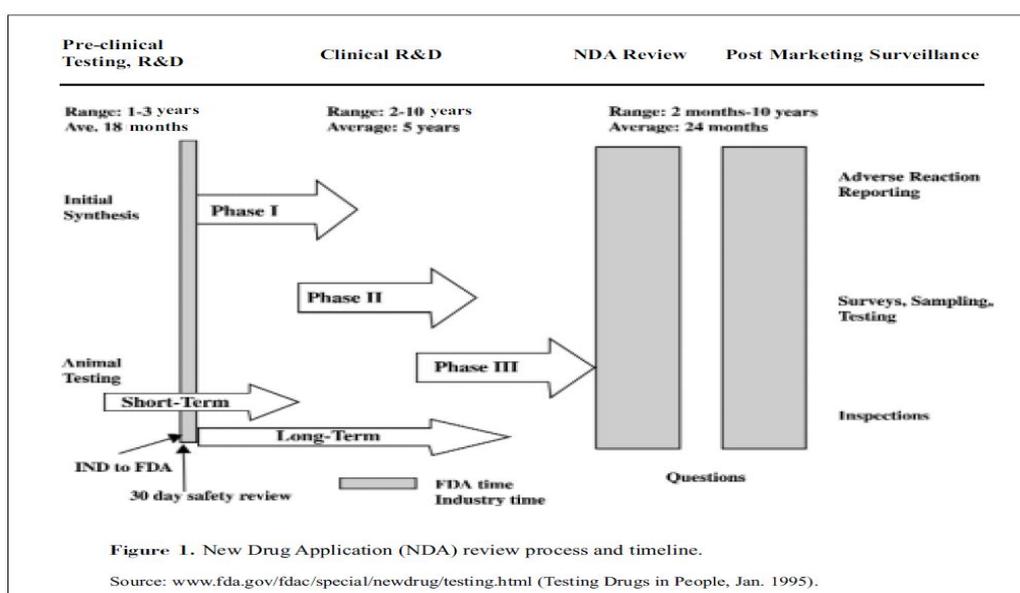

Figure 1. New Drug Application (NDA) review process and timeline.
Source: www.fda.gov/fdac/special/newdrug/testing.html (Testing Drugs in People, Jan. 1995).

Figure 1: New drug application (NDA) review process and timeline.

The average time from synthesis of a self-originated NCE to approval of a new drug application (NDA) has increased significantly, from an average 7.9 years in the 1960s to 12.8 years in the 1990s (see Figure 2). Much of the increase is due to increases in clinical trial length (the time from filing of an Investigational New Drug (IND) application to NDA submission). This can be attributed to a variety of factors, including increased regulatory requirements, the need for more study subjects in clinical trials, an increasing difficulty of recruiting subjects for clinical trials, and the nature of the diseases being investigated. In addition, the average number of procedures performed on patients has increased by 118% in Phase-II and 51% in Phase-III clinical trials.
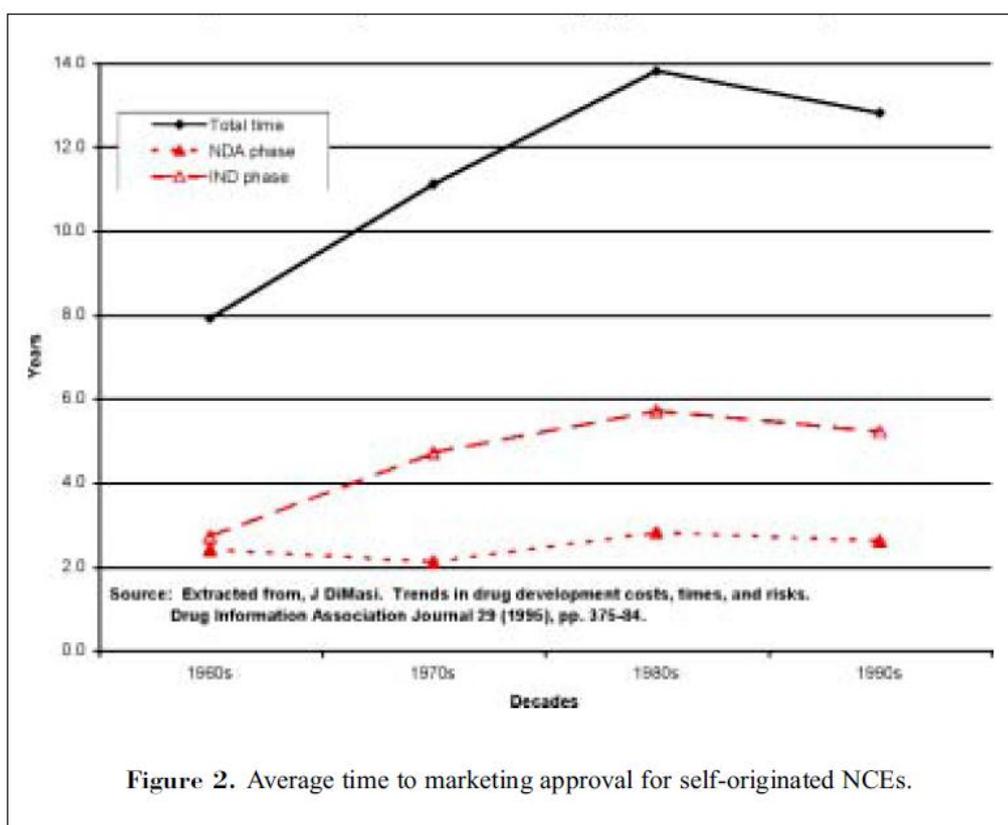

Figure 2. Average time to marketing approval for self-originated NCEs.

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Data from a variety of sources converge on at least two points. First, new drug development can take from 10 to 20 years with an estimated average of about 9 to 12 years. Second, this time has increased in the last 20 years, mainly owing to increased regulatory requirements and an increase in the length and complexity of clinical trials necessitated by greater emphasis on chronic conditions.

The Risk Component

Risk in the pharmaceutical industry is the result of scientific, regulatory and economic uncertainty. The first two risks create the lengthy development time and thereby the economic risk.[2] The longer the scientific development time, the greater the likelihood that a competitor will make the discovery first and thereby greatly diminish the possibility for a return on the R&D investment of the innovator. Regulatory uncertainty occurs because the time required for new drug approval further delays product marketing, and because marketing approval is not assured.

Pharmaceutical firms are attempting to reduce risk by making the decision to discontinue work on less promising drugs earlier. A drug may be viewed as less promising for scientific or economic reasons. A part of this rationale is that more payers are demanding evidence of cost effectiveness in their covered populations before agreeing to pay for a drug, thus raising the economic success bar for all drugs entering R&D before they ever reach the market. The trend towards earlier abandonment of marginal drugs indicates a strategy for coping with increased risk. Another measure of risk is the rate at which drugs entering R&D are approved for marketing. By one estimate, the overall success rate for all investigational drugs tested in humans anywhere in the world from 1983 to 1994 was 21.5%. In this study, the highest success rate was for anti-infectives (28.1%), whereas the lowest rate was for central nervous system drugs (14.5%). Again, the message is that the probability of success is small, it is not equally distributed across therapeutic categories, and innovative drug development is a risky endeavour (DiMasi et al., 2001).

Further evidence of risk is found in the highly skewed nature of sales for approved NCEs. For NCEs introduced between 1988 and 1992, the top decile (10%) of drugs (by sales dollars) accounted for 56% of overall sales of the cohort of NCEs studied. In practical terms, it means that unless a company can routinely and frequently develop a "blockbuster" drug, the funds to support additional research will diminish (Grabowski & Verson, 2000a).

In summary, the combination of long lead-times from discovery to NDA approval, the high probability of failure for compounds entering clinical testing, and the unpredictability of sales once a product is marketed creates a risky business environment. Decisions to fund clinical trials are critical to economic success, and the stakes increase substantially as drugs move through each successive clinical phase (Figure 3).
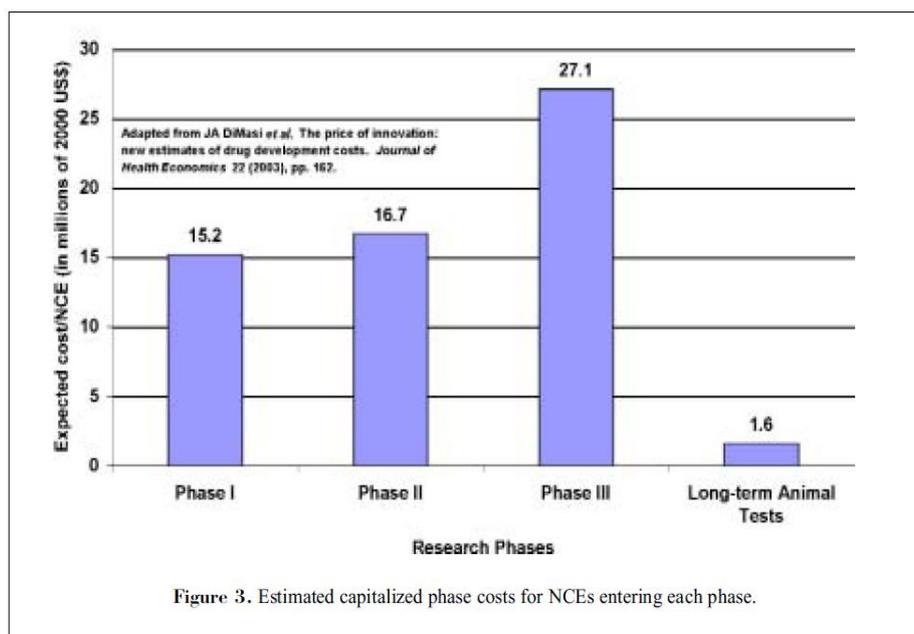
Figure 3. Estimated capitalized phase costs for NCEs entering each phase.

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Protection of Intellectual Property

Nearly all countries have some form of protection for intellectual property. Often this is a patent law that confers a monopoly on the innovator for a specified period of time. For pharmaceuticals, the most common time period is 20 years from the time the sponsor files for the patent.[3] Intellectual property protection (in this case by patents) is important, because the cost of innovation is high, whereas the cost of imitation is low. The development costs for a new drug are essentially an investment in knowledge, whereas duplication of the new compound is a simple technical matter. This is an especially important issue in pharmaceutical research because of the long lag time from discovery of a novel compound to marketing. Although recent changes in patent law have increased the period of protection, the effective patent life was estimated to be 11.4 years for NDAs approved in 1995 (Grabowski and Vernon, 200b).

Therapeutic Competition

The market for innovative new pharmaceuticals has become so competitive that patent life no longer confers a significant monopoly, because more than one company may be developing compounds with similar mechanisms of action, even though the chemical compounds are different and can each therefore be patented. Two recent examples illustrate this trend.[4] Fluoxetine (Prozac, Eli Lilly), an antidepressant, was the first drug in the selective serotonin reuptake inhibitor (SSRI) therapeutic class and was approved in

December 1987. The next SSRI product was sertraline (Zoloft, Pfizer), which did not receive marketing approval until four years later, but still well within the patent protection period for Prozac. On the other hand, Celecoxib (Celebrex, Pfizer) and rofecoxib (Vioxx, Merck) were the first two COX2 inhibitors to be approved (in December 1998 and May 1999, respectively), only five months apart.

Generic competition. Competition from generic products is rising throughout the world. It was given a major enhancement in the US market with the 1984 passage of the Hatch-Waxman Act (also known as the Drug Price Competition and Patent Term Restoration Act). The Act had the dual purpose of restoring some of the patent erosion that occurs during clinical trials and regulatory review, while increasing price competition for pharmaceuticals by significantly reducing barriers to the entry of generic drugs following patent expiration.

Public policy issues. As well as the regulatory and market forces described above, there have also been significant public policy changes (in addition to the Hatch-Waxman Act) that have shaped the pharmaceutical R&D environment. The impact of these changes may be difficult to quantify, but the direction of their effects can be easily discerned.

When the Medicare Prescription Drug Improvement and Modernization Act of 2003 becomes fully implemented in 2006, pharmaceutical industry revenues will be challenged again, and consequently so will the pharmaceutical industry's ability to fund R&D (P.L. 108-173). This new Act will increase the federal control over drug use to a minimum of 29% of the population up to 36%, depending on the method of calculation. As these programs tend to cover people with greater health care needs than the general population, we can expect the federal presence to affect an even higher percentage of total expenditure than the percentage of population covered and program managers to aggressively pursue expense controls.

State Medicaid programs have restricted drug prices for many years, but recent reductions in state budgets have given rise to increased reimbursement and expenditure restrictions (e.g., higher co-payments to patients, lower provider reimbursement) and constraints on manufacturer prices. Many of these methods are not new, but their intensified uses have the net effect of reducing the sales potential for innovative new products.

In the private sector also, there are changes that are likely to reduce pharmaceutical company revenue. Direct effects include more limited drug benefit programs by insurance companies

and employers and increased patient co-payments. More restrictive formularies will impose new hurdles to the adoption of innovative new drugs and will reduce reimbursement levels, especially for newer drugs.

Indirect factors are likely to be just as important. Primary among these is the dwindling number of people with adequate retirement health benefits. Many employers are reducing their retirement plans and others are opting for defined contribution plans rather than defined benefit plans. Some of them are also eliminating their retiree health care coverage programs. A consequence of this will be an increase in the number of people who reach retirement with little or no health insurance, including no drug benefit. As the "baby boomers" advance toward retirement, they will create political pressure to expand the Medicare outpatient drug benefit (without increasing the total cost of health care). Finally, the rising numbers of on-line pharmacies (Canadian and elsewhere) will add weight to the government and private sector efforts to reduce pharmaceutical sales.

Cost of New Drug R&D

The costs of pharmaceutical R&D have been studied using several conceptual models and measurement methods. In this section, we summarize almost exclusively the results from studies of R&D associated with NCEs. The studies given the most attention are based on empirical work that attempts to estimate the resource costs of new drug development.

Review of drug development cost studies. Each study reviewed here included the cost of failed products along with the cost of those that received approval, and R&D expenditures were capitalized to the point of marketing approval or abandonment of research. Finally, each of the reviewed studies is limited to self-originated NCEs. NCEs acquired through licensing were not included because their total cost of development is unknown, and would be understated in any event (Dickson & Gagnon, 2004).

In 1979 Hansen reported on a sample of NCEs first tested in humans between 1963 and 1975 and obtained from 14 pharmaceutical firms.[5] Using firm-level data for costs and development times for each NCE, and capitalizing expenditure to the appropriate point (NDA approval or abandonment of research), Hansen estimated the average development cost to be US $54 million in 1976 dollars.

In 1987 Wiggins modified the Hansen methodology by aggregating drugs into therapeutic classes and then by using regression techniques, estimated the average cost of new drug development to be US $125 in 1987 dollars. However, he included licensed NCEs in his estimate, which would tend to give a lower average cost than including only self-originated NCEs. Woltman adjusted the Wiggins estimate in an attempt to more completely reflect the Hansen methodology and reported an estimated average cost of US $108 million in 1987 dollars.

In 1991 DiMasi used the Hansen methodology on a sample of self-originated NCEs for 1970 to 1982 provided by 12 US-owned pharmaceutical firms to estimate the average NCE development cost at US $231 million in 1987 dollars. He replicated this study in 2003, with a few changes in the methods and estimated the cost of drug development for self-originated NCEs at US $802 million in 2000 dollars.

The US Office of Technology Assessment (OTA) conducted its own investigation into the cost of drug development for NCEs by doing a reanalysis of the 1991 DiMasi study rather than using original data. Briefly, they concluded, "…from the corroborative evidence available at the aggregate spending level that the estimates of cash outlays per successful NCE made by DiMasi are reasonably accurate." OTA also adjusted for tax deductions and R&D tax credits, which gave an estimated average cost of developing a new drug to be no more than US $237 million (in 1990 US dollars) or US $293 in 2000 US dollars (Office of Technology Assessment, 1993).

Table 1. Projected Costs of NCE Development in Millions of U.S. $

Study, Year	Years Covered by NCEs	Average Cost (millions)	Average Cost 2000 $ (millions)
Hansen, 1979	1963 – 1975	$54 in 1976 $	$137
Wiggins, 1987	1970 – 1985	*$125 in 1987 $	$173
Woltman, 1987	1970 – 1985	*$108 in 1987 $	$149
DiMasi, 1991	1970 – 1982	$231 in 1987 $	$319
DiMasi, 2003	1983 – 1994	$802 in 2000 $	$802
OTA pre-tax, 1993	**	$359 in 1990 $	$445
OTA post-tax, 1993	**	$237 in 1990 $	$293
Public Citizen, 2001	#	n/a	$110

Note:
* These are marginal cost estimates while all the others are average cost estimates. Marginal cost estimates are expected to be lower than average costs.
** Did not analyze NCEs, but did a reanalysis of the DiMasi, 1991 data.
# Reanalysis of the DiMasi, 1991 study. The estimate is after-tax and does not include the cost of capital (cash outlay only is included).
NCE, new chemical entity; OTA, US Office of Technology and Assessment.

Public Citizen (a national consumer group) has raised numerous concerns about the 1991 DiMasi study. They argue that the cost of capital should not be included in the cost of drug development and they also removed their own estimates of tax credits and deductions to give an estimated cost for drug development of US $110.2 million in 2000 dollars. Public Citizen removed the opportunity cost of capital, because in their words, it is a "…theoretical calculation of what R&D expenditures might be worth if they were invested elsewhere" (Public Citizen, 2001). Virtually all economists would argue there is nothing theoretical about the cost of capital. Public Citizen raised similar concerns about the 2003 DiMasi study, but did not offer any additional analysis. DiMasi and others have repudiated their assessment, arguing that the aim of the 2003 study was to estimate resource costs, not effective cost to firms. Finally, they characterize exclusion of the cost of capital by Public Citizen as a major methodological flaw Summary of cost studies. This discussion documents that the rapidly rising cost of pharmaceutical R&D is due mainly to the increased cost of animal testing and conducting clinical trials. The best estimate of the costs of drug R&D today is likely to be that from the most recently available well-designed study; that is, US $802 million.[6]

We also should note that improvements in the drug development process would yield significant improvements in this picture. DiMasi has calculated that a 25% reduction in clinical phase lengths would reduce total capitalized drug development costs by 16% (approximately US $129 million). He also reports that improving success rates from the current 21.5% to 33.3% would yield a reduction of US $221 million in capitalized cost per NCE.[11-14]

The Societal Value of Pharmaceutical R&D Investment

A theoretical model demonstrating the connections between pharmaceutical R&D and societal value is shown in below figure.
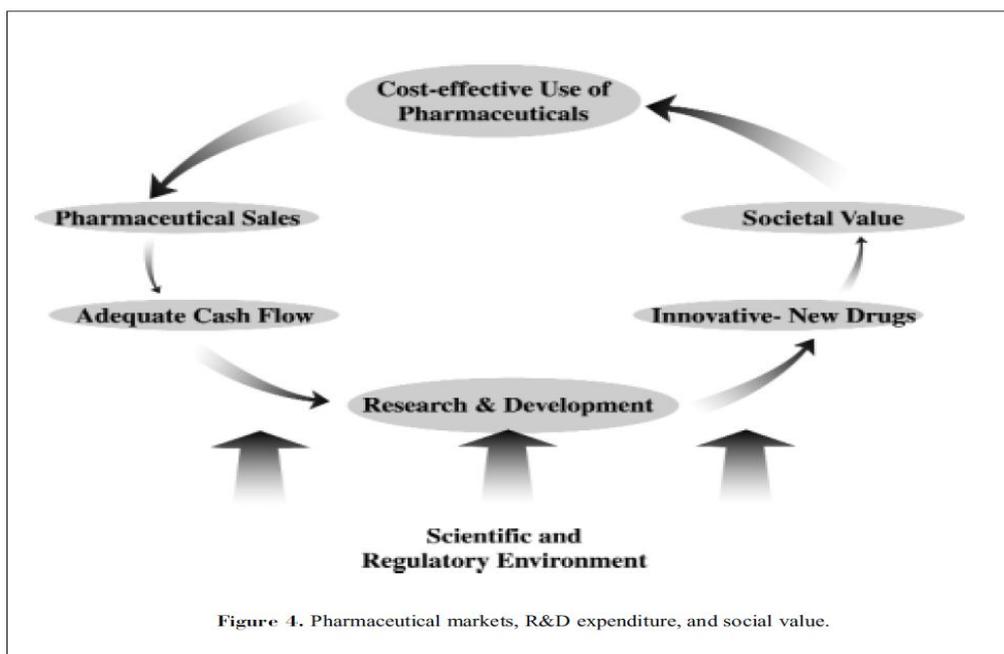
Figure 4. Pharmaceutical markets, R&D expenditure, and social value.

Figure 4: Pharmaceutical markets,R&D expenditure ,and social value.

Any adverse disturbance to the scientific research, regulation or use of pharmaceuticals will have detrimental effects on social value.[7] Likewise, any disruption in the flow of funding from sales to R&D will lead to diminished social returns. Figure 4 also shows that opportunities to improve societal benefits can come from multiple pathways, including a more efficient development process, a favourable regulatory environment, and improved use of drugs and Value of new drugs. At a time when pharmaceutical expenditure is rising and the cost of pharmaceutical R&D is being criticized, it is appropriate to ask whether innovative drugs provide value for money. This is a germane question, as attempts to reduce pharmaceutical expenditure generally focus on constraining the use of newer drugs. Does such a strategy have adverse consequences for today's pharmacotherapy and tomorrow's innovations?

As just one example, Fuchs examined inflation-adjusted Medicare expenditure and found that it increased at 4-5% per recipient per year at the same time that GDP was increasing at 1.2% annually (Fuchs, 1999). He attributed the increase to the use of new medical technologies (including drugs) and suggested that there was a positive effect on life expectancy and the health status of the elderly. Other investigators have made similar observations and noted that improvements in life expectancy rarely translate into a lower cost of care over a person's lifetime. For example, use of antibiotics to prevent deaths from infections can cause people to live longer and hence to die from heart disease and cancer, which typically entail even greater

costs. This is the dilemma and the lesson; the value of pharmaceutical innovations often cannot be captured in conventional accounting calculations.[11-14]

Value and cost summary. Pharmaceuticals create value in terms of reduced non-drug healthcare expenditure as well as contributing to improvements in patient quality-of-life that often defy quantification. But what about the cost of these benefits in terms of R&D investment and payments for using the products? In addressing this issue, we assume that few would want to turn back the medical care clock to the time when mercurial diuretics and sulphonamides were standards of care. The more pertinent question then is, how to adequately finance pharmaceutical R&D?

SUMMARY AND CONCLUSIONS

The task of discovering and developing novel NCEs is unusual, if not unique, among business enterprises because it is financed almost entirely by the private sector although many regard the results, such as improved health, as a public benefit. The private sector status of pharmaceutical research means that the industry must generate sufficient income (and make a sufficient return on investment) to cover the cost of developing the next generation of NCEs. Since health care is viewed differently than consumer products, the drug development activities of the pharmaceutical industry are examined closely and subjected to a higher standard of performance than other private sector businesses.[8] There is an expectation that pharmaceuticals will be generally affordable, and that industry resources will be used to develop needed therapies.

This situation begs the question: what is the most efficient means of moving NCEs from the laboratory to the consumer? Is it the current model dominated by large pharmaceutical companies engaged in the complete range of activities from research to marketing? Or has research become so specialized that it is more efficient to foster the growth of smaller, more specialized research-only companies, as some have suggested? Regardless of the answer, it is clear that drug development will remain in the private sector rather than being nationalized or funded by the government. However, government is assuming a larger role in paying for innovative new drugs and therefore has a stake in the efficiency of the development process.[9]

Traditionally, the cost of drug therapy has been principally the concern of patients, because lower efficiency translated into higher prices for them. However, Redwood has postulated a

"progressive fragmentation" of power in health care that presents new opportunities for pharmaceutical companies and shifts industry alliances (Redwood, 2002). He argues that as government pays more of the cost of pharmaceuticals, they see innovative new products as a threat, whereas patients are more likely to have a positive attitude towards innovation, especially where the drug benefit is subsidized.[10] The public desire for new therapies, their increasing cost, and the increased role of government as a payer for innovative new drugs, all converge on the question of the cost of new drug development and argue for an efficient use of resources. The issue of drug development cost is therefore woven into many aspects of health care policy.

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