KEY FACTORS IN THE RISING COST OF NEW DRUG DISCOVERY AND DEVELOPMENT

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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 issue of the rapidly rising cost of new drug development — now thought to be greater than US $800 million — and highlight the necessity for an efficient use of resources. With this in mind, here we review studies on the cost of developing new drugs and consider how this cost has, and could be, affected by the changing environment for pharmaceutical research and development.

During the past twenty years, there have been increasing efforts by payers to constrain expenditure on pharmaceuticals in the United States through legislative means, such as the Hatch–Waxman act. Passed in 1984, this legislation had the dual purpose of increasing generic drug availability, while maintaining some protection for intellectual property. Since its passage, there have been numerous attempts to modify the balance of forces in the Act through legislative means. It is difficult to find an explicit rationale for this behaviour, except in the popular press, where the view is often expressed that 'drugs cost too much'.

In response, pharmaceutical company representatives note that research and development (R&D) costs for new products are greater because of increasing regulatory requirements and restrictions put in place by pricing and reimbursement authorities and managed-care organizations. For example, the ACADEMY OF MANAGED CARE PHARMACY FORMULARY GUIDELINES now cover more than 100 million lives in the United States[1]. The pharmaceutical industry has also spent more to speed up development and improve the accuracy of the research, and without intellectual property protection these costs could not be recovered. In addition, the industry contends that the decreasing time available to recover R&D investment tends to push drug prices higher.

It is clear that the development of a new drug requires a major investment of capital, human resources and technological expertise. It also requires strict compliance with regulations on testing and manufacturing standards before a new compound can be used in the general population. More recently, there has been an emphasis by the US FDA on the development of risk profiles for pharmaceutical products. All these requirements contribute to the cost increases for new chemical entity (NCE) R&D. The central question raised by this trend is: who in the future will pay for new pharmaceutical R&D?

With this question in mind, the objectives of this article are, first, to describe how the environment for pharmaceutical R&D has changed over time, and the effect of these changes on R&D cost, risk and the time invested; second, to review the literature on the cost of drug discovery and development for NCEs; and last, to consider the societal value of new drugs. The focus is on the United States, which is the largest pharmaceutical market and that for which the relevant literature is most comprehensive, but many of the issues discussed are similarly important in the other major markets.

The changing environment for pharma R&D

Trends in the type of new drug development. Drug therapy has developed in response to population healthcare needs to the extent that resources and technology permit. The most recent trend has been to pursue drugs

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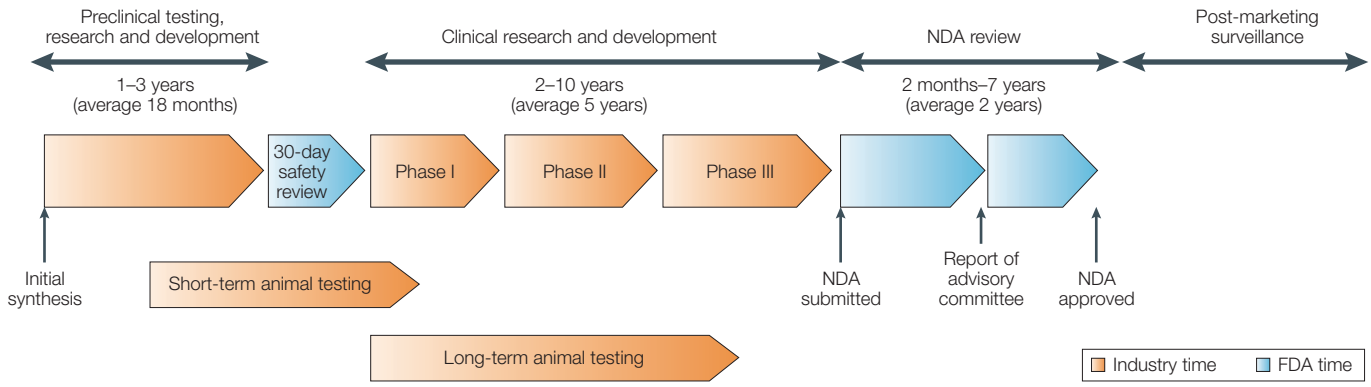


Figure 1 | **The drug approval process in the United States.** To approve a new chemical entity, the FDA requires proof of SAFETY and EFFICACY — generally evidence from at least two well-designed, randomized, double-blind, placebo-controlled clinical trials. As shown, the approval process of a new chemical entity begins with a preclinical stage in which a new compound is tested *in vitro* and then *in vivo* in laboratory animals to evaluate toxic and pharmacological effects[59]. During this period, the developer also investigates the drug's genotoxicity. If the compound is considered promising, the developer will file an Investigational New Drug Application (IND) with the FDA describing the compound's pharmacological profile, and presenting results of short-term toxicity testing in at least two animal species. If the FDA does not place a 'hold' on the application, the sponsor can begin Phase I clinical trials in humans after 30 days. Phase I clinical trials are conducted in a small number of normal, healthy volunteers to determine the safe dosing range and toxicity of a compound. If the compound is still considered promising, it will go on to Phase II testing, in which it is tested in a larger sample of volunteers who have the medical condition the product is intended to treat. If the compound is still considered promising, it will progress to Phase III testing, which uses a larger sample of subjects with the disease of interest and which can test different dosing quantities or schedules than those used in Phase II trials. The primary purpose of a Phase III trial is to demonstrate efficacy; however, because Phase III trials have more subjects than Phase II it is more likely that adverse events will be observed. If, at the end of Phase III, the compound still seems promising, the manufacturer will submit a New Drug Application (NDA) to the FDA. The numbers shown indicate that the time between preclinical testing and NDA approval ranges from an estimated low of 3.2 years to a high of 20 years, with an average of about 8.5 years. In recent testimony, the Pharmaceutical Research and Manufacturers of America (PhRMA) reported an average drug development time of 14.2 years in the 1980s and 1990s[60]. Regardless of the specific estimate adopted, it is clear that drug development is a lengthy process (based on data from REF. 61).

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 is expected to exceed US $368 billion for 2004, and CVD claims more lives each year than the next seven causes of death combined[2]. Pharmacotherapy is the main treatment for CVD, cancer and stroke, as well as other chronic diseases. Although surgery is an important intervention, it is generally used to treat an acute condition, and is usually followed by a lifetime of pharmacotherapy to manage the patient's chronic condition. As with all health-care technologies, drugs are improved through continued research, without which there would be no advances in treatment.

Although there have been some new uses for older drugs (for example, thalidomide), and some very old drugs continue to be used today (for example, digoxin), the drug therapies used today are much improved over those from even 20 years ago. There have been marked improvements in long-established drug classes (for example, atypical antipsychotics), and entirely new classes of drugs have emerged (for example, statins) that offer major improvements over previous treatments. There are now drugs for conditions that were previously without treatment (for example, Alzheimer's disease). Finally, the appearance of HIV/AIDS in the early 1980s has taught us to expect the unexpected; since then, several entirely new compound classes for the treatment of this disease have been developed and improved.

ACADEMY OF MANAGED CARE PHARMACY FORMULARY GUIDELINES
The Academy of Managed Care Pharmacy's *Format for Formulary Submissions*, published in October 2000, is a set of guidelines for the evaluation of medications. The *Format* is helping to answer the often-asked question: "which new drugs offer advantages at reasonable costs, thus providing good value?" There are two important goals for the *Format* process: first, to improve the quality, timeliness, scope and relevance of the data and information made available for pharmacy and therapeutics committees to use in their decision-making; and second, to facilitate and streamline the acquisition of data and information and the review process for pharmacists in managed-care organizations.

How are new drugs approved and how long does it take?
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 countries, although the specific process can differ. However, the three largest prescription drug markets in the world (the United States, the European Union and Japan) have taken steps to harmonize their procedures to ensure the timely introduction of new drugs and to reduce the cost of development. An overview of the drug approval process, shown in FIG. 1, demonstrates both its complexity and why it is time-consuming.

The Tufts Center for the Study of Drug Development (CSDD) has conducted several studies of drug development times, which indicate that the total time from synthesis (of a compound) to approval of a New Drug Application (NDA) for self-originated NCEs has increased significantly, from an average of 7.9 years in the 1960s to 12.8 years in the 1990s (see FIG. 2). Much of the increase in drug development time is due to increased time for the clinical trial portion of the process (the time from filing of an Investigational New Drug (IND) application to NDA submission; FIG. 1), as shown in FIG. 2. This can be attributed to a variety of factors, including increased regulatory requirements, the need for more study subjects, the increasing difficulty of recruiting subjects for clinical trials and the nature of the diseases being investigated today, which are more likely to be chronic conditions (BOX 1).

SAFETY
Safety is determined by balancing risk and benefit for a given disease.

EFFICACY
The ability of a drug to work under ideal conditions (for example, in a well-controlled clinical trial).

REVIEW TIME
The FDA defines review time as the time it takes the FDA to review a New Drug Application.

APPROVAL TIME
The FDA defines approval time as the time from the first New Drug Application (NDA) submission to NDA approval. It includes the sum of FDA review time for the first submission of an NDA to the Agency, plus any subsequent time during which a pharmaceutical sponsor addresses deficiencies in the NDA and resubmits the application, plus subsequent FDA review time.

The median time required for the FDA review and approval processes have generally decreased since 1992, when the first Prescription Drug User Fee Act (PDUFA) was passed[3] (BOX 2), although there is concern that REVIEW TIMES could begin to suffer as FDA resources are diverted from the review process to meet other needs, such as closer scrutiny of clinical trials, transfer of biotechnology oversight to the Center for Drug Evaluation and Research (CDER), and addressing possible bioterrorism threats[4]. Recently, there have also been concerns expressed about an increase in the number of safety recalls of previously approved drugs, and a decrease in the number of new drug approvals (especially for NCEs)[5,6]. Although the FDA and the US Government Accounting Office (GAO) differ on interpretation of the data, it is clear that FDA's resources might be inadequate to maintain the recently achieved drug APPROVAL TIMES. Some of the decrease in the number of NDAs submitted to the FDA is, according to one pharmaceutical industry executive[6], due to increased testing requirements imposed by the FDA, which seem to be a result of the more stringent application of approval guidelines following the increased recalls of drugs approved in the 1990s. The additional cost and time required to do the work needed for these NDAs might simply not be worth the potential return. The GAO also cited the loss of FDA personnel as an important factor contributing to increased review and approval times, and if this loss continues this could exacerbate the problem. It seems that the current NDA approval process is at a precarious stage that could adversely affect NDA approval times, depending on the unfolding of events at the FDA.

In summary, data from a variety of sources converge on at least two points. First, new drug development from the synthesis of a compound to NDA approval can take 10–20 years, with an estimated average of about 9–12 years. Second, the length of this process has increased in the past 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. So, although there have been important reductions in the time required for FDA processing of NDAs, the total time and cost of new drug development has increased and seems destined to continue increasing, especially if the problems outlined in the GAO report persist.

Risk. 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. 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. Regulatory uncertainty occurs because the time required for new drug approval further delays product marketing, and because marketing approval is not assured.

Risk is often assessed in terms of the time from filing an IND application to NDA approval or abandonment of research on an NCE. Taken together, the scientific and regulatory periods account for the majority of elapsed time in drug development (the combined time for clinical testing and NDA review has been labelled "residence time" by DiMasi). Much of the time component in drug development has been discussed above, but some attention is given here to the specific question of residence time.

Only a small percentage of compounds entering clinical testing ultimately obtain marketing approval. In 2001, DiMasi reported on changes in residence time for two cohorts of NCEs: those beginning clinical testing during 1981–1983, and a second cohort that covered 1990–1992 (REF. 7). For NCEs beginning clinical testing between 1981 and 1983, the average time to research abandonment was 4.7 years, whereas it was 3.3 years for the 1990–1992 group. This reduction of ~30% indicates that pharmaceutical firms were attempting to reduce risk by making earlier decisions to discontinue work on less promising compounds. A compound might be viewed as less promising for scientific or economic reasons, or both. The latter is becoming increasingly important, as the cost of drug development continues to increase and the resources for R&D cannot expand sufficiently to cover all possible opportunities. This point has been made by Grabowski[8]: "...there is a strong rationale for integrating pharmacoeconomic analysis directly into strategic decision-making, starting as early as possible in the R&D process." A part of this rationale is that more payers are demanding evidence of cost effectiveness in

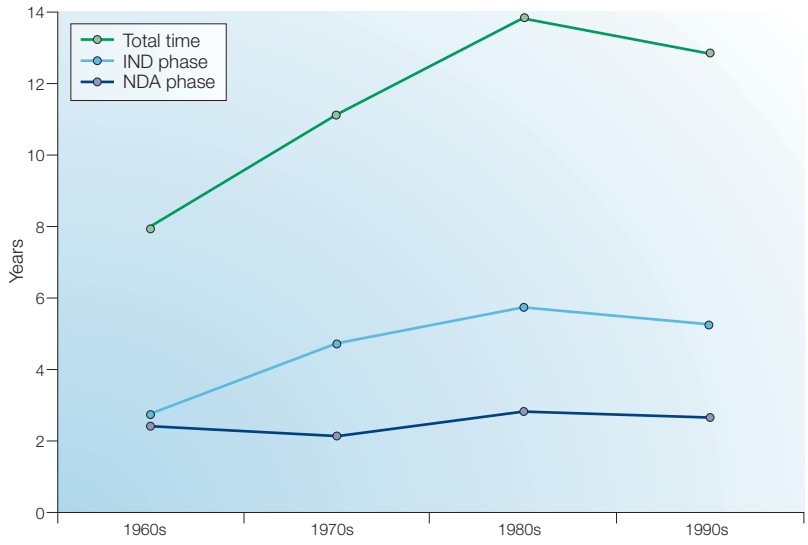


Figure 2 | **Trends in drug approval time.** The total time from synthesis (of a compound) to NDA approval for self-originated NCEs has increased from an average of 7.9 years in the 1960s, to 11.1 years in the 1970s, 13.8 years in the 1980s and 12.8 years in the 1990s[62]. If licensed NCEs are included in the calculation, average approval times for the same time periods are 8.1 years, 11.6 years, 14.2 years and 15.0 years, respectively. Much of the increase in drug development time is due to the increased length of the clinical trial portion of the process. For self-originated NCEs, the clinical phases averaged 2.7 years in the 1960s, 4.7 years in the 1970s, 5.7 years in the 1980s and 5.2 years in the 1990s. If licensed NCEs are included, the comparable times are 2.5 years, 4.4 years, 5.5 years and 6.1 years, respectively. Because the review time at the FDA (labelled the NDA phase) did not change appreciably during the study period (2.4 years in 1960s, 2.1 years in the 1970s, 2.8 years in the 1980s and 2.6 years in the 1990s), the inference is that much of the increase in drug development time occurred during clinical testing (labelled the IND phase). Based on data from REF. 62. IND, Investigational New Drug Application; NCE, new chemical entity; NDA, New Drug Application.

Box 1 | **Increasing regulatory requirements, trial size and trial length**

Increased regulatory requirements can be seen in the new mandates to include women and children in testing, as well as increased concerns about toxicity and patient monitoring. More subjects are needed because many of the drugs being developed require increased numbers to achieve FDA statistical standards for demonstrating safety and efficacy. Using data from several published sources, DiMasi *et al.* reported that clinical-trial sample sizes increased an average of 7.47% per year from the 1970s to 2001 (REF. 9). Finally, chronic conditions tend to require longer time periods of drug use to demonstrate the desired effects, even when surrogate endpoints are used.

It was also noted that even if the length of clinical trials were to remain constant, the investigation process is much more complex today, both in terms of what is done to patients and the record-keeping procedures; an increase in the number of procedures performed on patients in Phases I–III from 1989 to 1993 ranged from 51% in Phase III to 118% in Phase II[9]. The net effect has been to increase the length of the clinical phase of drug testing, which is usually the most expensive part of drug development.

their particular covered populations before agreeing to pay for a drug. The bar for economic success has been raised for all compounds entering R&D before they ever reach the market. Longer residence times delay market access and represent increased risk. The trend towards early abandonment of marginal compounds indicates a strategy for coping with increased risk.

In one sense, the most definitive measure of risk is the rate at which drugs entering R&D are approved. In this context, risk can be assessed by measuring the proportion of NCEs that go from IND to NDA approval. Because of the many differences in timing from discovery to NDA approval, success rates can be difficult to calculate; however, a few different types of success rate have been reported in a group of CSDD studies[9–16]. Perhaps the best estimate is provided in the 2003 DiMasi paper[9] in which the authors estimate the overall success rate for all investigational drugs tested in humans anywhere in the world from 1983 to 1994 with information on their current status obtained through to early 2001. A statistical model was used to estimate the probability of success for the small number of products still in active testing (described in REF. 7). On the basis of these criteria, the authors predicted an overall final clinical success rate of 21.5% (REF. 9). Again, the message is that the probability of success is fairly small and the business of innovative drug development remains risky.

In this same study[9], NCEs from the entire time period (1981–1992) were grouped by therapeutic class to assess differences in success rates across classes. The highest success rate was for anti-infectives (28.1%), whereas the lowest rate was for central nervous system drugs (14.5%). Low rates were also found for antineoplastics (15.8%) and immunological drugs (15.4%), suggesting that development of drugs for chronic conditions is more problematic than for acute conditions.

A further element of risk is the highly skewed nature of sales for approved NCEs. Grabowski and Vernon have demonstrated that for NCEs introduced between 1988 and 1992, the top decile of drugs (by sales dollars) accounted for 56% of overall sales of the cohort of NCEs studied[17]. When compared with an earlier cohort of NCEs approved in 1980–1984, the more recent group showed more rapid sales growth following product launch and higher peak sales, but a much faster rate of decline following patent expiration. The consequence of this trend is to increase the uncertainty of economic success of R&D in the aggregate, because sales are concentrated on a few products over a decreasing period of time. 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.

Concentration of sales on a few products is also demonstrated by the number of marketed NCEs that yield a positive return on the average research investment. Grabowski and Vernon found that for a cohort of NCEs introduced between 1970 and 1979, only the top three deciles of drugs (by sales) gave an after-tax return that exceeded the average R&D investment[18]. Because much of R&D expenditure is fixed cost (for example, facilities and personnel), the risk of not covering costs is clear and real. Joglekar and Paterson[19] reported a similar finding in their study of NCEs introduced between 1962 and 1977: after 24 years of sales, some two-thirds of NCEs returned no more than bonds.

Grabowski and colleagues recently examined returns on R&D for NCEs introduced from 1990 to 1994 (REF. 20). The methods used were similar to those in their earlier work, but the sample of 118 products for this study was larger than the previous study, and included biotech drugs (unlike the previous study) as well as 'conventional' molecules. As in their previous work, the authors constructed 20-year-sales life cycles for each drug, and converted sales to after-tax profits (and cash flow) using industry-level data. These data were combined with DiMasi's results on R&D expenditure to determine the net present value and internal rates of return. Results from this study confirm the findings of the earlier work and show that the trend of concentration of returns on a small number of products has continued into the 1990s. Results for biotech products suggest that their returns to R&D are similar to those of the pharmaceutical industry in general.

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 create a risky business environment. Pharmaceutical companies have attempted to manage risk by making 'go/no-go' decisions at earlier stages in the development and clinical testing process. These are crucial decisions, because R&D costs increase substantially as compounds move through each successive clinical phase (FIG. 3).

The competitive environment. The competitive environment for pharmaceuticals has a profound influence on new drug development. Because the development of an NCE is costly, takes many years and is inherently risky, a company will pursue only those compounds for which there is a reasonable expectation that a market will exist once a product receives NDA approval. If, because of competition, there is an insufficient market for a compound in development there is often little

incentive to continue work on it. Clearly, this involves an assessment of the clinical value of the product, but it must be in the context of expected competition.

The competitive environment is likely to be different across countries. Where government is the only payer, price competition among pharmaceutical products is constrained, whereas markets with several payers are likely to be more price-competitive. Even within single-payer markets, the competitive environment will vary on the basis of such factors as cost-sharing between the payer and the patient, the mechanisms by which prices are determined and the level of reimbursement set by the payer. However, two trends have emerged in recent years that are consistent across all countries: market share erosion of newly marketed NCEs through therapeutic competition, and an intensification of generic competition following patent expiration. These are not the only competitive forces affecting prescription drug markets, but they are now universal, whereas pricing and reimbursement mechanisms tend to differ across countries.

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. 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 typically a simple technical matter. This is an especially important issue in pharmaceutical research because of the long lag time between the discovery of a novel compound and marketing. Although recent changes in patent law have increased the period of protection, the EFFECTIVE PATENT LIFE (EPL) is nowhere near the maximum. Grabowski and Vernon[21] have estimated EPL to be 11.4 years for NDAs approved in 1995.

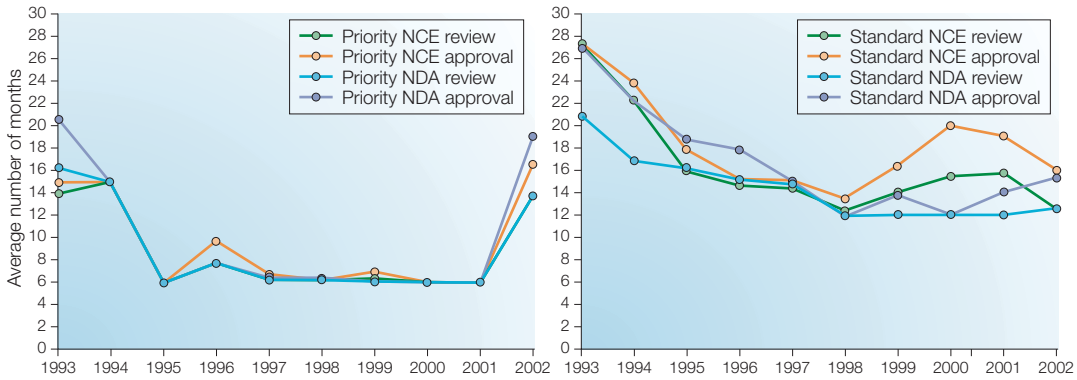
Evidence on the social value of a patent protection system for the development of new pharmaceutical therapies has been summarized by Grabowski in a more recent paper that examined eleven major national pharmaceutical markets[22]. Countries with significant patent protection systems for new drugs had the greatest percentage of new drugs approved for marketing in six of the eleven markets examined. The evidence also indicates that countries that strengthen their patent policies for new pharmaceuticals show a marked increase in pharmaceutical R&D activity (for example, Canada and Japan). As will be demonstrated later, access to newer pharmaceutical technology yields positive returns to society. However, it should be clear that patent protection does not ensure market exclusivity, because there is intense competition from other products in the same therapeutic market, often long before expiration of a patent.

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 might be developing compounds with similar mechanisms of action, even though the chemical compounds are different and can

Box 2 | **The Prescription Drug User Fee Act and approval times**

The first Prescription Drug User Fee Act (PDUFA) was enacted in 1992 in response to lengthening drug approval times. The act linked the payment of fees by drug developers to increases in the efficiency of the FDA review and approval process. Since PDUFA was introduced, the median approval time for priority new chemical entities (NCEs) and New Drug Applications (NDAs) have both been reduced substantially and remained relatively constant at about six months for 2000 and 2001 (see figure; left). However, there was a sharp increase in the review and approval times for priority NCEs and NDAs in 2002; whether this is an aberration or the beginning of a trend is not clear.

The median review and approval times have also been reduced for standard NCEs and NDAs; however, there has recently been an increase in median approval times for standard NCEs and NDAs (see figure; right). In addition, it seems that some of the reductions in review and approval times might be an artefact of the way the system operates. For example, when the FDA identifies a problem late in the review cycle, it can issue an 'approvable letter' which allows the FDA to meet its PDUFA performance goals without making a final decision on the application[4]. Counting this as an approval clearly reduces the median time.



EFFECTIVE PATENT LIFE
EPL is defined as the number of years of market exclusivity for a product once it has received marketing approval. EPL will always be less than the nominal patent life because drug entities are patented long before they receive marketing approval.

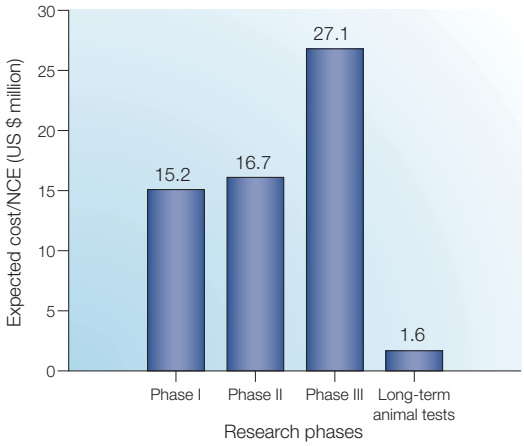


Figure 3 | **Estimated capitalized out-of-pocket costs for NCEs entering each phase.** Clinical testing is the most costly component of drug discovery, with the costs increasing in each successive phase (note that Phase III expected costs are 44% higher than Phase I). Although animal testing costs are less than those for clinical trials, the total cost of these tests is not trivial (adapted from REF. 9). NCE, new chemical entity.

each therefore be patented. Two recent examples illustrate this trend. 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 product in the SSRI class was sertraline (Zoloft; Pfizer), which received marketing approval in December 1991, four years after fluoxetine and well within the patent protection period for fluoxetine. Celecoxib (Celebrex; Pfizer) and rofecoxib (Vioxx; Merck) were the first two COX2 inhibitors to be approved (in December 1998 and May 1999, respectively). So, in this case, the time from market entry of the first product, celecoxib, to the first competitor, rofecoxib, was only five months. The result of therapeutic competition is to discipline pricing in a multi-payer market because there is competition for market share. From the innovator's perspective, there is a significant reduction in market share from the potential that would exist without therapeutic competition. The opportunity for competition can also exist in single-payer markets, but it is generally less direct and not as intense.

Generic competition. Competition from generic products is rising throughout the world, and 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. Grabowski and Vernon reported that within six months of a generic entry to the market, for a cohort of drugs encountering generic entry in 1993, the average generic price was 46% of the brand price (a 54% price cut)[23]. And after 42 months following generic entry for seven major drugs in 1989 to 1990, the average generic price was 34% of the brand price and generics had 71% of market share[23]. Clearly, therapeutic and generic competition has created increased pressure for innovative products. Competition begins during the patent protection period and intensifies following patent expiration with the entry of generic competitors.

The rationale for protection of intellectual property is that the public will benefit from innovative new products and that these innovations are more likely to occur when there is temporary protection for the purpose of ensuring an adequate return for the financial risk incurred. The innovator is not given a grant of funds, only a window of time during which to seek recovery of the investment. Erosion of the exclusivity period through therapeutic competition makes it more difficult to earn an adequate return on investment commensurate with the risk incurred. More competition following patent expiration only intensifies the competitive environment and quickly erodes the innovator's product sales.

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 is difficult to quantify, but the direction of their effects can easily be discerned. Recently adopted or proposed policy issues of major importance for pharmaceutical R&D are examined briefly.

Currently, the issue with the greatest likelihood of adversely affecting pharmaceutical revenue is the Medicare Hospital Outpatient Prospective Payment System rule[24]. The new Centers for Medicare and Medicaid Services (CMS) rules that took effect in 2004 have the potential to significantly reduce payment for pharmaceuticals (drugs and biologicals) typically provided in hospital outpatient departments. Until December 2003, MEDICARE did not include an outpatient prescription drug benefit. Passage of the Medicare Prescription Drug, Improvement and Modernization Act[25] of 2003 will provide a voluntary drug benefit beginning in 2006, with a discount card and subsidies for low-income people beginning in 2004. When this act becomes fully implemented in 2006, pharmaceutical industry revenues will be challenged, and consequently so will the pharmaceutical industry's ability to fund R&D. Now that Medicare has an outpatient drug benefit, there will be a strong connection between reimbursement and pharmaceutical company revenue. Programme managers will demand economic concessions from all involved: patient, provider and manufacturer. The new Medicare drug benefit gives the federal government control over drug use by a significant segment of the population (29–36%, depending on the method of calculation[26–28]). Equally as important is the fact that this would represent an increase of potential drug-benefit recipients of between 60.6% (low estimate) to 92.2% (high estimate). As these

MEDICARE
The federal health insurance programme for people 65 years of age or older, certain younger people with disabilities and people with end-stage renal disease.

programmes tend to cover people with greater healthcare 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.

MEDICAID programmes raise other issues. State Medicaid programmes have used reference pricing (Maximum Allowable Cost) and other forms of cost containment for many years. Recent reductions in state budgets have had an adverse impact on Medicaid programmes in many states and given rise to the introduction of various new reimbursement and expenditure restrictions applied to all levels of the benefit programme, including patients (for example, higher co-payments), providers (for example, lower provider reimbursement) and manufacturers (for example, prior authorization programmes, reduced reference price levels and higher rebate rates). Although many of these methods are not new, their intensified use and more restrictive provisions have the net effect of reducing the sales potential for innovative new products. In addition to actions to reduce Medicaid prescription drug expenditure, many states are actively pursuing strategies to "lower prescription costs to broader segments of residents through discount programs, bulk purchasing programs, expanded manufacturer rebates, as well as forms of price negotiations or price controls."[29] In the same report, the National Council of State Legislatures (NCSL) noted that by December 2002 there were 34 states that had enacted or authorized some type of programme.

In the private sector, there are direct and indirect factors that are likely to reduce pharmaceutical company revenue. The direct effects include more limited drug benefit programmes by insurance companies and employers that use more restrictive formularies and increased patient co-payments. Pharmacoeconomic guidelines (for example, formulary approval dossiers) have imposed new hurdles to the adoption of innovative new drugs and are used to reduce reimbursement levels. Although guidelines are ostensibly mechanisms for establishing value for money, in general the outcome is to set lower levels of subsidy for new drugs than those requested by the product sponsor.

Indirect factors are likely to be just as important. Primary among these is the dwindling number of people with adequate retirement benefits, including health benefits. Many employers are reducing their retirement plans and others are opting for defined contribution plans rather than defined benefit plans. Some employers are also eliminating their retiree health-care coverage programmes. One consequence of this change will be an increase in the number of people who reach retirement with little or no health insurance, including no drug benefit. A recent study commenting on corporate health benefits reported that 17% have virtually eliminated their retiree health liabilities by requiring retirees to pay the full premium[30]. Among the key findings is that companies that continue to offer retiree health benefits to future retirees and new hires are reducing their financial obligations by reducing the company contribution toward premiums (now less than 60%), imposing more stringent minimum service requirements to qualify for the benefit, tying the amount of the benefit to the length of service, and placing caps on the benefit (median contribution cap for post-1965 retirees is now US $1,740, down from US $3,900 for pre-1965 retirees). As the 'baby boomers' (age 26–44 in 1990 using US Census Bureau definition[31]) advance towards retirement, this cohort will increase the sense of urgency. This shift is already evident in the change observed between the 1990 and 2000 census figures. The highest growth rates in age cohorts were found in the baby-boomer group; for example, the growth rate of the 50–54-year-old group increased by 55%, whereas the average growth rate for the whole population was 13%[32]. Finally, the Census Bureau estimates that the percentage of the population aged 65 and older will increase from the current 12.6% to 16.5% by 2020 (REF. 33). This will increase political pressure to expand the Medicare outpatient drug benefit and otherwise constrain the cost of health care.

The rising numbers of online pharmacies (Canadian and Mexican), as well as other patient-initiated efforts to minimize their prescription expenditure, add weight to the government and private sector efforts. The new Medicare Prescription Drug, Improvement and Modernization Act of 2003 also proposes to allow re-importation of prescription drugs from Canada[34]. The purpose is to reduce prescription costs to American consumers by permitting re-importation of drugs marketed by US pharmaceutical companies in other countries at lower prices. The act would allow pharmacists, wholesalers and qualifying individuals to engage in re-importation of drugs from Canada if the Secretary of Health and Human Services certifies the safety of the drugs. In 2004, bills have been introduced in the House of Representatives to lift the current ban on drug imports. It seems clear that reimportation, if allowed, is one more action that will reduce pharmaceutical company revenue.

In summary, there are several policy and demographic changes in progress that will adversely affect the funds available for pharmaceutical R&D. An overview of the current cost of R&D and research productivity illustrates another dimension to the industry's problems.

Cost of new drug R&D

The costs of pharmaceutical R&D have been studied using several conceptual models and measurement methods. In some cases, investigators have used the average cost of developing a new drug, and others have focused on selected components of the process (for example, animal studies or clinical trials). 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. There are other perspectives on cost, but an examination of resource costs is the most comprehensive and economically appropriate approach for understanding the economics of new drug development.

MEDICAID
A joint federal and state programme that helps with medical costs for some people with low incomes and limited resources. Medicaid programmes vary from state to state, but most healthcare costs are covered if you qualify for Medicare and Medicaid.

STUDY PARAMETER CHANGES
The methodological differences between the 1991 and the 2003 DiMasi studies can be briefly summarized as: first, the 1991 study examined 93 self-originated NCEs from 12 companies, whereas the 2003 study was based on 68 self-originated NCEs from 10 companies; second, the cost of capital was 9% in the 1991 study and 11% in the 2003 study; third, the average time from beginning clinical trials to marketing approval in the 1991 study was 98.9 months, but 90.3 months in the 2003 study; and last, the average clinical success rate for the 1991 study was 23%, compared with 21.5% in the 2003 study.

Review of drug development cost studies. An understanding of this area requires consideration of at least three factors: first, the different times at which studies were done; second, the methodologies used by investigators; and third, the changes in the environment in which drug development has occurred (see above). The third issue is resolved only by a qualitative description of the changing environment and the logical appeal of the time-ordered events. For example, we might expect longer approval times, and therefore higher costs, in more recent years because of increased regulatory requirements. To resolve the first two points, it is necessary to choose studies that use similar economic methodologies. As the studies were conducted at various times during a 20-year period, it is necessary to use standard economic methods to adjust the various cost estimates to a single point in time for comparative purposes.

The main studies reviewed here used similar methods. In each case, the investigators used micro-level cost and timing data developed over a well-defined time period. Each study 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. Finally, each of the reviewed studies is limited to a sample of self-originated NCEs. That is, NCEs acquired through licensing were not included because their total cost of development might not be known, and would be understated in any event. Other studies have been conducted, but do not use this 'full cost' method that is an important component of study design. Only studies based on the full-cost method will be reviewed here (in chronological order), although some others are mentioned in passing.

Hansen (1979) obtained data from 14 pharmaceutical firms for a sample of NCEs first tested in humans between 1963 and 1975. Firm-level data for costs and development times for each NCE project were used to calculate average drug study clinical phase lengths and associated costs. The cost for each NCE, whether dropped from development or going on to receive an approved NDA, was capitalized to the appropriate point with respect to each NCE. Using this approach, the average cost of new drug development for an NCE was estimated to be US $54 million in 1976 dollars[35].

Wiggins (1987) modified the Hansen methodology by aggregating drugs into therapeutic classes for the analysis and computing the cost estimate for NCEs approved from 1970 to 1985 using a regression analysis approach[36]. He estimated the average cost of new drug development for an NCE to be US $125 million in 1986 dollars. However, Wiggins included licensed NCEs in his estimate, whereas the Hansen sample included only self-originated NCEs. The net effect of including licensed NCEs is to lower the estimated cost. The Wiggins estimate was adjusted by Woltman in an attempt to more completely reflect the Hansen methodology; this gave a revised estimated average cost of US $108 million in 1986 dollars[37]. DiMasi and colleagues reviewed the Wiggins study and judged it to be an estimate of marginal cost of NCE development, whereas the Hansen figure is average cost. Because of the large fixed cost component in pharmaceutical R&D, marginal cost will be lower than average cost (see review of DiMasi below).

DiMasi (1991) used the Hansen methodology for a sample of self-originated NCEs provided by 12 US-owned pharmaceutical firms between 1970 and 1982 to estimate the average NCE development cost at US $231 million in 1987 dollars[38]. The most recent DiMasi study (2003) is an update of the 1991 study, with a few changes in some of the STUDY ESTIMATION PARAMETERS[9]. Here, DiMasi and colleagues estimated the cost of drug development for self-originated NCEs at US $802 million in 2000 dollars[9]. The authors note that if the only change in new drug development cost was the pace of inflation, the US $231 million estimate in 1987 dollars would have been US $318 million in 2000 dollars. They attribute much of the increase in the cost of drug development beyond inflation to the rising cost of clinical trials, which increased five-fold since 1991, and to some extent, the cost of animal studies (increase estimated at 60%)[9].

For purposes of updating the previous estimates and placing them all at a common point in time, each estimate described above is converted to 2000 US dollars using the seasonally adjusted Gross Domestic Product (GDP) Implicit Price Deflator[39] (TABLE 1). In all cases, the values for the earlier studies are lower than for the 2003 DiMasi estimate. As the study methods used are similar, the most reasonable explanation for the differences is a difference in the environment for drug development over time. These changes include the regulatory environment as well as the nature of the drugs being developed.

The Office of Technology Assessment (OTA) in the United States conducted its own investigation into the cost of drug development for NCEs by doing a re-analysis of the 1991 DiMasi study[40]. They acknowledged that an investigation of pharmaceutical development cost must adopt the methods employed by Hansen and DiMasi, and agreed with the previous studies that the three most important components of pharmaceutical R&D investment are money, time and risk. Therefore, their evaluation relied on a detailed analysis of the validity of the Hansen and DiMasi studies.

Table 1 | **Projected costs of NCE development in millions of 2000 US$**

Study (year)	Years covered by NCEs	Average cost (US $ million)	Average cost (2000 US $ million)	References
Hansen (1979)	1963–1975	54 in 1976 $	137	35
Wiggins (1987)	1970–1985	*125 in 1987 $	173	36
Woltman (1987)	1970–1985	*108 in 1987 $	149	37
DiMasi (1991)	1970–1982	231 in 1987 $	319	38
DiMasi (2003)	1983–1994	802 in 2000 $	802	9
OTA pre-tax (1993)	‡	359 in 1990 $	445	40
OTA-post tax (1993)	‡	237 in 1990 $	293	40
Public Citizen (2001)	§		110	41

*These are regarded as marginal cost estimates, whereas all the others are average cost estimates. Marginal cost estimates are expected to be lower than average costs. ‡Did not analyse 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).

The OTA first examined the validity of the methods used to estimate the component R&D costs, and then tested the consistency of the estimates by corroborating them with other studies. Finally, they examined the rate of increase in real R&D cost, implied by the two studies, for consistency with trends in major cost drivers of pharmaceutical R&D, including the number of subjects in clinical trials, research personnel costs and animal research costs. The OTA study suggests that there were two major threats to validity implicit in the methods used by Hansen and DiMasi: first, the small number of NCEs in the samples; and second, reliance on pharmaceutical company self-reported data that OTA could not verify. To confirm or deny the validity of the methods used by Hansen and DiMasi, OTA sought corroborating evidence from the Wiggins study and also used publicly available data on the operation of the US pharmaceutical industry. Regarding the Hansen study, OTA concluded that "the Hansen estimate of $65.6 million in cash outlays per successful drug is reasonably accurate and perhaps even slightly low."[40] On the DiMasi study, they reported "substantial consistency between aggregate R&D spending estimates and the cash outlays per NCE estimated by the DiMasi study."[40]

The final piece of corroboration is that the number of subjects enrolled in clinical trials has increased substantially over time. Some of this is due to the types of drugs and diseases being studied, but there was an increase in subject enrollment across all trials regardless of the drug or disease. There is some evidence to suggest that this trend is also due in part to increased regulatory requirements in other industrialized countries where clinical trial enrollment increased faster than in the United States. However, OTA argued that increases in clinical trial enrollment could not explain the increased cost associated with Phase III clinical trials. In summary, the OTA 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."[40]

The OTA also made two additional analyses of the Hansen and DiMasi studies to examine their calculation of present values of the cash outlays, and to comment on the after-tax cost of R&D. To capture the full cost of R&D investment, it is necessary to capitalize R&D cash outlays from the time of expenditure to the point at which the investment begins to provide a return or the time at which investment ceases; in this case, when an NDA is filed or research on a compound is stopped. This approach is widely accepted, but there can be differences of opinion on what discount rate to use for the present value calculation. Significantly, OTA regarded the DiMasi CAPITALIZATION procedure as fairly conservative, and reported that a reasonable upper bound on the fully capitalized cost of R&D per successful NCE at the time of market approval is US $359 million or US $100 million more than the DiMasi estimate (in 1990 US dollars)[40]. If this is projected to 2000 US dollars using the same GDP deflators, the equivalent amount is US $445 million (TABLE 1).

The OTA's final assessment was to make an adjustment for tax deductions and credits on the basis of the argument that Hansen and DiMasi did not account for taxes the company did not pay because they invested in R&D. OTA acknowledged that revenues must also be reduced by the amount of new taxes a company pays when a product is marketed and has sales. By making these adjustments, OTA estimated that the average cost of developing a new drug would be no more than US $237 million (in 1990 US dollars)[40]. If this estimate is expressed in 2000 US dollars using the previously described GDP deflator, this would be US $293 million (TABLE 1).

Public Citizen (a national consumer group) has also criticized the 1991 DiMasi study. They raise numerous concerns, but their quantitative re-analysis focuses on two points. First, they argue that the cost of capital should not be included in the cost of drug development. Second, they re-calculate the cost of drug development by removing Public Citizen's estimates of tax credits and tax deductions available to pharmaceutical companies. These changes to the 1991 DiMasi results give an out-of-pocket, before-tax estimated cost for drug development of US $110.2 million in year 2000 dollars, which they compare to US $341 million for the 1991 DiMasi study expressed in 2000 dollars[41]. 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."[42] Virtually all economists would argue there is nothing theoretical about the cost of investing capital in one option compared to another. Once an investment decision has been made, the money cannot be invested a second time in an alternative choice.

Public Citizen raised similar concerns about the 2003 DiMasi study, but did not offer any additional analysis[42]. Their most recent critique of R&D cost estimates asserts that all DiMasi estimates should be further reduced because some of the research that contributes to the development of new drugs is publicly funded. It is very difficult to establish an exact figure, but the report suggests that between 77% and 95% of the research projects (not expenditure) were funded by US taxpayers or foreign academic institutions[41,43]. Ernst & Young repudiated the most recent Public Citizen assessment, as did DiMasi[44,45], arguing that the aim of the 2003 DiMasi study was to estimate resource costs, not effective cost to firms. They also characterized Public Citizen's understanding of the tax structure as faulty and suggested that using data from the Pharmaceutical Research and Manufacturers of America (PhRMA) to estimate total R&D spending is inappropriate, because it includes only PhRMA members, which understates the cost of drug development[46]. Finally, they regarded the exclusion of the cost of capital by Public Citizen as a major methodological error. In his response to the Public Citizen comments, DiMasi made many of the above points and also noted that deducting the costs of research is allowed and not a 'tax break'. Additionally, DiMasi noted that tax credits for R&D and orphan drugs are a small percentage of R&D costs — an estimated 2% of R&D expenditure.

CAPITALIZATION
The amounts and types of long-term financing used by a firm to grow and expand its business. It may include common stock, preferred stock, retained earnings and long-term debt. Capitalized costs are out-of-pocket costs that have been discounted at an appropriate discount rate to address the time value of money.

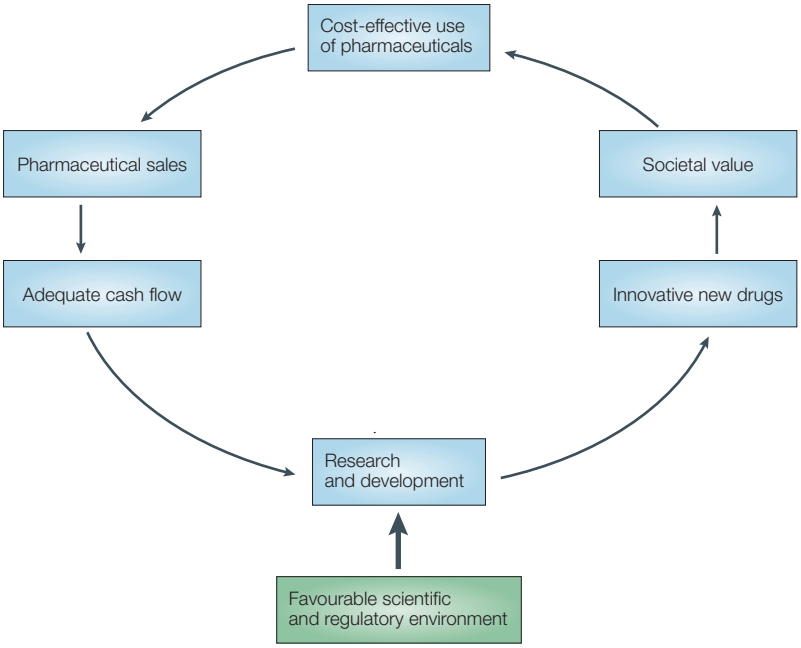


Figure 4 | **Pharmaceutical sales, R&D and expenditure and social value.** Adverse disturbance to the scientific or regulatory environment of drug development, or the use of pharmaceuticals, have detrimental effects on social value, and disruption in the flow of funding from sales to R&D will lead to diminished social returns. For example, inappropriate use of antibiotics diminishes the potential value to society, just as delays in drug development owing to unnecessary regulations increase the cost and time of drug development and thereby reduce societal value. In a similar manner, inadequate resources for conducting pharmaceutical R&D will diminish societal benefits by reducing pharmaceutical innovations.

In its most recent release, CSDD included the cost of studies conducted after receiving marketing approval for an NCE and reported the average to be US $897 million in year 2000 dollars[47]. This estimate is based on their study that covered 68 NCEs developed by 10 pharmaceutical companies in the 1990s[9]. Finally, this review of the evidence would not be complete without also mentioning a recent study by the Boston Consulting Group (BCG), in which the cost of new drug development was estimated to be US $880 million in year 2000 dollars[48]. However, no data were presented in support of this estimated cost.

Summary of cost studies. The previous discussion has outlined the rapidly rising cost of pharmaceutical R&D, due mainly to the increased cost of animal testing and conducting clinical trials. Given the many changes in the research environment described, any estimate of new drug development costs should now give greater weight to more recent studies. It is possible to perform a variety of mathematical manipulations on the data summarized in TABLE 1, but this would be inappropriate, as they were generated at different points in time, using different methods and the environment for research has changed dramatically over the time periods covered. 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[9].

The value of pharmaceutical R&D investment

A theoretical model demonstrating the connections between pharmaceutical R&D and societal value is shown in FIG. 4. Any adverse disturbance to the scientific or regulatory environment of drug development, or the use of pharmaceuticals, will have detrimental effects on social value. Likewise, any disruption in the flow of funding from sales to R&D will lead to diminished social returns. The above discussion has attempted to document the cost of NCE development and to make the point that significant threats to the regulatory environment exist that could adversely affect the potential social benefits of NCE development. We also should note that improvements in the drug development process would yield significant improvements in the current situation. DiMasi has calculated (using the most recent R&D expenditure estimate of US $802 million) that a 25% reduction in clinical phase lengths would reduce total capitalized drug development costs by 16% (an estimated US $129 million)[49]. In the same paper, DiMasi 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. We can conclude that opportunities to improve the benefits to society can come from several pathways, including a more efficient development process, a favourable regulatory environment and improved use of drugs.

There is a large body of literature on the value of pharmaceuticals to society and the cost associated with providing this benefit. The essence of this work can be captured in a single word: balance. Although reasonable people can disagree on where to strike the balance, there is agreement that some cost must be incurred by society if the benefits are to be received. After giving only one or two examples of the benefits from pharmaceutical research, the remainder of this article examines the issue of funding for pharmaceutical R&D.

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 drugs provide value for money. In particular, it is of interest to know whether newer drugs give greater value than their predecessors. 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?

The rate at which older drug therapies are being replaced by newer drugs is given by the estimate that 35% of the amount spent on prescription drugs in 1998 was for drugs introduced since 1991 (REF. 50). 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[51]; this increase was attributed to the use of new medical technologies (including drugs), and Fuchs suggested that there was a positive effect on life expectancy and health status of the elderly. Other investigators have made similar observations and noted that improvements in life expectancy rarely translate into lower cost of care over a person's lifetime. For example, the use of

Box 3 | **Investment by the pharmaceutical industry: the example of the United States**

The US pharmaceutical industry invests heavily in research to develop new chemical entities (NCEs) in comparison with other R&D-orientated businesses such as the electronics, communications and aerospace industries[57]. A comparison of the self-performed pharmaceutical R&D budget of the pharmaceutical industry exceeds that of the US National Institutes of Health (NIH) for all research[58]. For example, in 2001, the pharmaceutical industry research budget was US $30.3 billion, whereas the NIH budget was US $20.3 billion for all areas of research, not just for pharmaceuticals. By any measure, the pharmaceutical industry's effort to develop new NCEs is a research-intensive enterprise.

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[52]. This is the dilemma and the lesson: the value of pharmaceutical innovations often cannot be captured in conventional accounting calculations. Kleinke analysed the question by grouping drugs into six categories on the basis of their return on the payments made[53]. Some drugs are 'fast-pays' (for example, atypical antipsychotics), whereas others are 'no-pays' (for example, sildenafil). There are many others in between these extremes that improve people's quality of life while also increasing cost. Who will pay for these treatments? Regardless of the answer, Kleinke offers an interesting taxonomy that, above all else, demonstrates that pharmaceuticals provide value for users.

A more empirical approach was used by Lichtenberg to support the hypothesis that new drugs within a given diagnosis are of higher quality than older drugs and that this difference can reduce mortality and morbidity, as well as medical spending. Lichtenberg used the 1996 Medical Expenditure Panel Survey (MEPS) data to test this hypothesis and subsequently expanded this analysis using 1997 and 1998 MEPS data[54,55]. In the first study, Lichtenberg found that newer drugs reduced non-drug health expenditure about 7.2 times more than they increased drug expenditure. In the updated study, the use of newer drugs reduced non-drug expenditure for all payers 8.3 times more than the cost of the drugs, and 6.0 times when Medicare was the payer. The findings also indicated that Medicare enrollees with private prescription insurance coverage tended to receive newer drugs which, he argues, demonstrates the effect of drug coverage on quality of care.

Value and cost summary. The studies cited on value are indicative of the approaches used to assess the contributions of pharmaceuticals and, by inference, their value. 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?

Literature on the cost of drug development presented above provides evidence for an intuitive and informal 'cost–benefit' analysis. In addressing this issue further, 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 is therefore 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 (BOX 3), although many would 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. Because health care is viewed differently to consumer products, drug development activities of the pharmaceutical industry are examined closely and subjected to a higher standard of performance than other private sector businesses. There is an expectation that pharmaceuticals will be generally affordable, and that industry resources will be used to develop needed therapies.

Since the mid-1960s, the process of drug approval has been modified to significantly improve the safety and efficacy of drugs for use by the general public. A consequence of these scientific and regulatory changes has been an increase in the time taken and cost of bringing a new drug to market. Because the time from beginning work on a promising compound to its approval for marketing is lengthy, there are many events that can intervene to reduce its economic value. In other words, drug development is risky, time consuming and expensive.

The most recently available data on the cost of developing self-originated NCEs by US pharmaceutical firms estimates the average to be US $802 million, a significant increase over the previous estimate by the same authors using the same methodology. The results suggest that costs are increasing much faster than the general rate of inflation owing to the increasing difficulty of drug discovery, an increase in regulatory requirements regarding clinical trials and pursuit of more difficult therapeutic goals. Although there are lower estimates of NCE development costs (for example, US $110–445 million in 2000 US $), these analyses exclude the cost of capital and sometimes include licensed agents in the analysis. Other methodological differences include different perspectives on taxation (for example, pre- versus post-tax), different discount rates for invested capital, and the use of product-level versus industry-aggregate data. These differences make direct comparisons of the results difficult at best.

The time between drug discovery and marketing approval has been reduced modestly because of the reductions in NDA approval times due to PDUFA,

but there are now signs that approval times could be lengthening. Unfortunately, the overall time from discovery to NDA approval is lengthening because of longer clinical trials and a regulatory environment that demands more evidence of drug safety and efficacy. Given this, it is not surprising that the cost of drug development is increasing.

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, which is 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, the government has been taking on a larger role in paying for innovative new drugs and therefore has a stake in the efficiency of the development process.

Because drugs are viewed differently to other products, the question of efficiency must be addressed. Traditionally, this has principally been 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[56]. He notes that as the 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 toward innovation, especially where the drug benefit is subsidized. Given this trend, alliances between the pharmaceutical industry and patient advocacy groups for the support of innovative new products are likely to expand. 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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Competing interests statement
The authors declare competing financial interests: see Web version for details.

Online links

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