

SURVEY

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Drug costs

Research and development costs: the great illusion

In the first three articles on prescription drug pricing published in our French edition, we examined how the French authorities have attempted, with little success, to control the prices of new drugs (1-3). French inadequacies in this area are partly due to the growing power of pharmaceutical companies, against a background of globalisation, economic liberalisation, and an industry-oriented regulatory framework in Europe. Now we examine the cost of research and development, a major argument used by drug companies to justify high prices.



- The commonly stated average cost of researching and developing a new drug is 802 million dollars.

- This figure comes from an institute largely funded by the pharmaceutical industry, and is based on confidential information also provided by industry sources.

- It includes the cost of failures and financial charges, and is the pre-tax figure. Out-of-pocket spending actually represents only half this sum, and the true costs are halved again when tax is deducted. A detailed analysis of this estimate reveals many other methodological flaws.

- This estimate only concerns new chemical entities entirely developed by the company in question.

- It is based on clinical development costs which are far higher than those quoted by other sources.

- Drug companies claim this estimate is the "official" figure.

- Data on the many drugs that are not fully developed by the company in question are even less consistent.

- The true costs of research and development must be determined transparently if national authorities are to make rational decisions on patents, data protection, and drug pricing.

- Research and development costs must be viewed in the light of drug company profits, which remain the highest of any economic sector.

Only one information source since 1979

The alleged cost of researching and developing a new drug, universally quoted by drug companies and accepted at face value by governments, journalists and other experts, derives from a single source, which estimated in 2002 that, on average, a new drug cost 802 million dollars to develop (4). Before examining the validity of this estimate, here is a brief summary of how it emerged.

An estimate updated every 10 years or so, occasionally adjusted for inflation. The first estimation of research and development costs dates back to 1979 (4), when the Tufts Center for the Study of Drug Development arrived at a figure of 54 million dollars per new drug (5). The first widely quoted estimate of research and development costs was published in 1991 (6), by a team working for the Tufts Center. The method of calculation, derived from that used in 1979, was based on a sample of drugs and on parameters derived from the Tufts Center database, which is fed with information from drug companies (4). In 1991, research and development were estimated to cost 231 million dollars per new drug (in 1987 dollars) (6).

This figure was arrived at after various calculations (see below), that can be repeated with new

All industrialised countries are now confronted by escalating health expenditure, largely fuelled by rising drug-related costs. The latter are growing with population ageing, increasing drug consumption across all age groups (partly due to advertising pressure), and the very high prices of new drugs (1,2).

Drug companies are virtually free to set their own prices in industrialised countries (2,3).

Why do the authorities accept these very high prices when they threaten the very existence of national welfare systems? One frequently cited reason is the "astronomical" cost of research and development (a).

This article asks: is the widely quoted estimate of research and development costs reliable? Are there any rival estimates? and How and why have stated research and development costs escalated over the years?

parameters. This was done in 1993 by the Office of Technology Assessment (a former US public body): by increasing the capital opportunity cost (see below) from 9% to a rate varying from 10% to 14%, and by adjusting for the US inflation rate during the period in question, the "official" cost of research and development (universally quoted, especially by drug companies) became 359 million dollars (in 1990 dollars) (7).

Simple adjustment for the inflation rate increased this figure to 473 million dollars in 2000, which drug companies conveniently rounded up to 500 million (8).

Between 1991 and 2002, the "official" costs of research and development were simply inflation-corrected updates of the 1991 Tufts Center estimate, itself based on a sample of drugs whose clinical development started between 1970 and 1982 (4).

The Tufts team made a new estimate in 2001, with new data collected from a sample of drug companies. They arrived at an average figure of 802 million dollars (in 2000 dollars) for researching and developing a new drug (4).

An industry-funded institute. Before examining this latest estimate in detail, the reader should know that the Tufts Center for the Study of Drug Development is an institute specialising in the pharmaceutical industry. It is affiliated to Tufts University (Boston), but is financially independent from it. It has a unique database, furnished by data from drug companies. The Tufts Center itself is funded by donations (especially from drug companies), to the tune of 65%, and also by sales of products and services (studies, seminars) (b)(5).

A simple estimate

For all its apparent precision (802 million dollars) this estimate of research and development costs is based, on the one hand, on data provided by the drugs industry, and, on the other hand,

on questionable or opaque calculations.

Methodological problems. This figure of "802 million dollars" is not a precisely itemised, average real cost, but a complex estimation. Indeed, it is extremely difficult to attribute specific research and development costs to a particular drug: early research and development activities are not always linked to a specific drug, but to several more or less closely related substances, only some of which will eventually be marketed.

Development failures must be taken into account, as pharmaceutical firms must cover all their research and development costs with sales of the few drugs that are effectively marketed. Estimates of research and development costs therefore usually include drugs that are abandoned in the development stage. This is the case for the "802 million dollars" estimate.

Another important source of imprecision is the fact that research and development lasts several years, making it even more difficult to itemise spending. There is a dual risk of overlooking certain costs and of including spending on other candidate drugs.

To make up for missing data, the Tufts Center team made "mean" estimates from its dataset (see below).

A secret sample of 68 drugs from ten firms. The figure of "802 million dollars" comes from a study of data supplied by 10 drug companies (four of the 10 world leaders, four situated between the tenth and twentieth place, and two lower down on the scale) (4). The study focused on 68 drugs randomly selected from the portfolios of the 10 firms. All were developed by the companies concerned (none were purchased or sold under licence). Their clinical development started between 1983 and 1994, and costs were counted up to the end of 2001 (27 of the 68 drugs had been authorised by the end of

2001) (4). The names of the firms and drugs, and all the other information used by the Tufts Center team, have never been published, and were only provided by the companies on the understanding that they would remain confidential.

Weightings derived from a larger database. Data on the 68 drugs only concerned the costs of clinical development, i.e. human and animal studies (4). The costs of basic and preclinical research were calculated as a fraction of the total development costs, using data from the Tufts Center database (containing information on several hundred drugs) (4).

Research and development costs for the drug sample panel were then calculated from the costs of clinical development, weighted by a mean failure rate and a mean duration of development calculated from the database (4).

The figure of "802 million dollars" was arrived at with the following parameters: 21.5% of drugs that entered phase I trials eventually received marketing authorisation; preclinical development (including research costs) accounted for 30% of all development costs; the interval from the beginning of clinical trials to marketing authorisation was 90.3 months (7 years 6 months); preclinical development lasted 5 years; and the annual capital opportunity cost was 11% (4).

Financial calculations. The notion of capital opportunity costs was used by the Tufts Center team to take into account the fact that research and development requires several years of investment before receipts start to accrue. In principle, it corresponds to what the companies concerned could have earned by investing elsewhere rather than in research and development, on the stock market for example.

The "802 million dollars" break down as follows: 335 million dollars for preclinical development (including 214 million or

63.9% in capital costs); and 467 million dollars for clinical development (including 185 million dollars or 39.6% in capital costs). Thus, capital costs represent nearly half (399 million, 49.8%) of the "802 million dollars" (4).

An estimate with many question marks

The "802 million dollar" research and development estimate is highly questionable, for many reasons.

A single, unverifiable source. The single-source origin of the estimate undermines its validity. The study itself is unverifiable, as drug companies themselves provided the data, on condition of secrecy, and solely to the Tufts Center. In other words, the Tufts estimate cannot be independently reproduced. It all depends on whether or not one trusts the Tufts Center and the companies that provided the data.

Blatant conflicts of interest. It is obviously in drug companies' best interests to overstate their research and development costs. The Tufts Center's main clients are drug companies, and conflicts of interest are therefore unavoidable. The Office of Technology Assessment pointed out in ►►

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a- Pharmaceutical companies prefer to place the accent on the nobler word "research". Yet, in practice, pharmaceutical research and development is usually based on discoveries (receptors, mechanisms of action, etc.) made in public laboratories.

Pharmaceutical research and development includes synthesis or extraction of a compound with a potential pharmacological action; studies of pharmacological activity (on cells, tissues, animals, or computer models); formulation of a product administrable to humans; toxicity studies (on tissues and animals); clinical trials (phases I-III before marketing authorisation; and phase IV after marketing authorisation); and development of a large-scale manufacturing process. The first two stages correspond to research, and the remainder to development (ref 7).

b- The Tufts Center website cites several enthusiastic endorsements by industry representatives. For example: "If someone were to ask me whether they should join the Tufts Center, I would absolutely recommend it. We have been a sponsor for a number of years and I think the kind of information that the Tufts center provides is just not available elsewhere" (ref 5).

SURVEY

► 1993 that the potential political importance of the Tufts Center estimate might tempt companies to overstate their costs, with not the slightest risk of being found out (7). This commonsense remark is even more valid in 2003, now that "research and development costs" have become a major war horse for the pharmaceutical industry.

Unrepresentative. The Tufts Center estimate is not representative of all new drugs, for several reasons.

First, it concerns only new chemical entities (4), which represent a relatively small proportion of new candidate drugs. According to a drug company employee, new chemical entities represented only 332 (24.1%) of the 1375 drugs marketed worldwide in the period 1975-2000, while the remainder were new indications, new forms, new dose strengths, or new combinations (9). According to the US Food and Drug Administration, new chemical entities represented 35% (361/1035) of drugs marketed in the United States in the period 1989-2000 (10).

New drugs that are not new chemical entities are far cheaper to develop. For example, new indications are generally granted on the basis of clinical trials alone; range extensions and new combinations are generally approved without further clinical trials (c).

Public-sector contribution underestimated. The sample used by the Tufts Center team comprises drugs that were exclusively developed by the 10 companies concerned (4). Yet few new drugs are now entirely researched and developed "in house", a significant part of the work being done (or funded) by the public sector, most notably in the United States where about half of all new chemical entities are discovered by the public sector.

A study published by the US National Bureau of Economic Affairs showed, for example, that 14 of the 21 major drugs mar-

keted in 1965-1992 had benefited from publicly funded research and development (8). A study done by the US National Institutes of Health (NIH) at the request of the consumers' association Public Citizen also showed that public research played a predominant role in the research and development of the five drugs with the biggest worldwide sales in 1995 (aciclovir, captopril, enalapril, fluoxetine and ranitidine) (d) (8,11).

This involvement of the public sector is not simply limited to basic research, but also includes clinical trial sponsorship and funding (e).

A very small sample. Readers should note that the cost of phase III trials, which represents two-thirds of the costs of clinical development in the Tufts Center estimate, was stated for only 33 of the 68 drugs in the sample (especially considering the withdrawal of some drugs after phase I or II studies) (4). These 33 drugs represent a very small proportion of all drugs marketed during the 12-year period studied by the Tufts Center: between 1990 and 1999, for example, 284 new chemical entities were marketed in the United States (4).

Questionable values. All the parameters used by the Tufts Center team are unverifiable and therefore questionable, including the failure rate, the real duration of research and development, and the percentage of costs represented by preclinical development.

Research and development costs are highly sensitive to changes in these parameters. For example, "802 million dollars" falls to 734 million if the global success rate is 23.5% rather than the 21.5% used in the Tufts study (f) (4).

Capital opportunity costs are also a matter for debate. They were calculated by the Tufts Center from financial achievements by drug companies in 1985-2000 (4). This method appears somewhat paradoxical: the more that drug companies' share prices appreciate, the higher the capi-

tal costs, and therefore the higher the cost of research and development. In other words, claimed research and development costs would be lower if drug companies were less profitable!

Yet capital opportunity costs are a key element in the Tufts Center estimate, accounting for 63.9% of preclinical development costs. Each half-point increase or decrease relative to the 11% used by Tufts would correspond to 25 million dollars (4).

Overstated research period. In its 1991 study, the Tufts Center calculated capital opportunity costs by assuming an interval of 98.9 months (8 years 3 months) between the beginning of clinical trials and the granting of marketing authorisation (4). This interval was reduced to 90.3 months (7 years and 6 months) in the 2001 study, because of a marked reduction in the time required to obtain marketing authorisation in the United States (4).

Another Tufts Center team estimated this interval at 87.4 months for drugs marketed between 1996 and 1998, and 80.6 months for drugs considered "important" by the US Food and Drug Administration (35% of drugs during the period in question) (12). According to this Tufts Center team, relative to 1993-1995, the mean intervals observed in 1996-1998 corresponded to a 19% reduction in the duration of clinical trials and a 31% reduction in the time required to obtain marketing authorisation (12).

This latter study also shows that the interval between the beginning of clinical trials and the granting of marketing authorisation is highly variable from one therapeutic category to another, undermining the use of the average value. This interval was only 44.7 months for the nine anti-retroviral drugs marketed between 1996 and 1998, and these were among the most highly priced pharmaceuticals (12).

Only half the stated cost of R&D is actually spent. It is important to note that capital opportunity costs represented

practically half the total figure of 802 million dollars (399 million dollars). In other words, companies actually spent (out-of-pocket) only half the 802 million dollars.

Tax advantages omitted. If the Tufts team had consistently used the same accounting logic, they should also have taken into account specific tax advantages for research and development. Indeed, research and development costs are tax-deductible, contrary to financial investments (7).

US drug companies can also deduct 20% of certain research and development costs from their tax bill (25% in the United Kingdom) (13,14).

Likewise, 50% of clinical development costs for orphan drugs are tax-deductible in the US (13). Overall, drug companies have a far lower taxation rate than other industrial sectors in the United States (26%, compared to 33% on average) (13).

The Office of Technology Assessment assumed that the cost of research and development should be expressed in post-tax figures (7). On this basis, Public Citizen estimated that the real cost of research and development corresponded to total post-tax

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c- These drugs, which are not new chemical entities, and which cost less to research and develop, should not be overlooked (see *Prescrire's* annual awards list, for example). Therapeutic advance is not tied to a novel manufacturing process, or to a new mechanism of action or compound, but is simply measured by the risk-benefit ratio in clinical practice.

d- The websites of Public Citizen (<http://www.citizen.org>) and another US consumers' association, Consumer Project for Technology (<http://www.cptech.org>), offer many useful documents on the pharmaceutical industry, including research and development costs.

e- Purely in-house research and development is no longer the rule, as the product portfolios of the largest drug companies include an increasingly large proportion of drugs sold under licence, and which were largely researched and developed by another company. The world's largest pharmaceutical company, Pfizer, derived 53% of its 2002 turnover from drugs sold under licence (ref 28).

f- Interestingly the proportion of candidate drugs actually brought to market does not only depend on the medical or technical failure rate: it also includes commercially motivated decisions (inadequate market niche).



Why the rising costs of pharmaceutical research ?

The costs of pharmaceutical research and development increased markedly during the last two decades, without reaching the figure of "one billion dollars per new drug" predicted by Eli Lilly in 1991 (1,2). This inflation is often attributed to the rising cost of clinical development (2).

Longer clinical trials? Clinical trials of drugs developed for chronic diseases take longer than trials of occasional treatments such as antibiotics, even if companies usually prefer to choose surrogate endpoints (cholesterol level, etc.) rather than major outcome measures.

But the world market for cephalosporins (the largest-selling anti-infective class), represented only one-third of the market for ulcer treatments in 2002 (21.9 billion dollars) (3).

Slower marketing authorisation? Pharmaceutical companies often complain of slow marketing authorisation procedures (and other official decisions such as pricing), which they say increase the capital opportunity costs of research investment.

Yet, in the Tufts Center study, the drug registration period fell by 12.1 months between 1991 and 2002 (2). The International Conference on Harmonization (ICH), created at the industry's initiative, rapidly led to harmonisation of regulatory requirements in the United States, Europe and Japan, leading to cost savings and shorter development periods for drug companies. Supplementary protection certificates, which add up to 5 years of monopoly protection after drug patent expiry, prolong sales at premium prices (4).

More difficult marketing authorisation? Companies often complain that regulatory demands are increasingly difficult to satisfy.

Nevertheless, the 1980s and 1990s saw the advent of accelerated (fast-track) marketing authorisation procedures, mainly due to pressure from patients with AIDS. And many marketing authorisations are now granted on

the basis of inadequate evidence, especially in cancer and orphan diseases (see our New Products column). And when marketing authorisation is granted on the condition that further trials are conducted, the data are actually provided in only a minority of cases (5).

The number of patients required to obtain convincing results in comparative clinical trials is also used as an argument by drug companies. Yet the required group sizes increase as the difference between treatments diminishes. In other words, comparative clinical trials are especially expensive for me-too^a and other drugs that differ little from the reference drug, or that are poorly effective. In contrast, me-too^a probably cost less in terms of preclinical research, as they are largely based on the original drug.

Waning research? In the 1980s and 1990s, some predicted the demise of classical pharmaceutical research based on systematic screening of candidate compounds, claiming that developments in biotechnology heralded a "new golden age" (6). Patients are still waiting...

Now, the holy grail is to be found in genomics and proteomics. It has been estimated that genomics could cut research and development costs by 300 million dollars per new product (7). But these hazardous predictions are mainly intended to persuade investors to leave one stock market bubble for another.

High-spending research. Pharmaceutical companies, intoxicated by their multibillion-dollar blockbusters of the 1990s, currently have extremely high overheads, due to their growing use of subcontractors, swelling intellectual property rights (royalties, etc.); and disproportionate salaries.

The death of a model? From the public health standpoint, the sums spent on research and development of yet another me-too^a product are quite simply obscene. But companies will continue to invest such sums if it enables them

to cash in on a market worth ten of billions dollars annually (anti-ulcer drugs, cholesterol-lowering agents, antidepressants, non-steroidal anti-inflammatory drugs, etc.) (4).

In contrast, these sums are ridiculously small when it comes to finding a new short-course antituberculous drug (potentially saving 2 million lives each year worldwide). Nevertheless the last drug specifically developed for tuberculosis was marketed in 1964. As a result a public-private partnership has been set up to make up for the lack of industry investment in tuberculosis treatment (8).

The key question is who really benefits from the enormous investment in research and development of drugs with no therapeutic advantages or no real utility? It is time for governments to stimulate research and development oriented towards real population needs and not simply shareholder profits. This is the only way for health professionals and patients to make sense of the issue of research and development costs.

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a- The term "me-too" is used for drugs with a chemical structure very similar to that of a princeps drug in a new class. Companies develop me-toos in order to take a share of a profitable market (for example, lansoprazole, then pantoprazole, then rabeprazole, were developed in the wake of omeprazole) (ref 9).

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out-of-pocket spending. This simple adjustment lops about three-quarters off the cost estimate published by the Tufts Center (15).

Clinical trials costs overestimated. The Tufts team set a 115 million dollar figure on mean phase III development costs (4).

Yet this implies either an astronomical cost per patient, or inclusion of massive numbers of patients.

Data from the US National Cancer Institute suggest that the mean per-patient cost of a phase III trial was 7 000 dollars in 1995-1996 (16). If we apply this unit

cost to the 115 million dollar estimate from the Tufts Center, more than 16 000 patients would be included in phase III trials, which is plainly ludicrous. The Tufts team itself calculated that an average of only 5303 patients participate in all phases of pre-marketing clinical development (4).

Even this is twice the number (2667 patients) calculated by the Food and Drug Administration for 185 new chemical entities authorised in the United States between 1995 and 1999 (17).

Finally, regarding the special case of orphan drugs, official US data show that the mean ►►

SURVEY

► cost of research and development was only 8 million dollars (including failures, and before tax) for the 36 orphan drugs it approved in 1998 and 1999 (18). It was 11 million dollars overall for the period 1998-2000, and 34 million dollars for new chemical entities (17 million after tax) (17).

What about profits?

The cost of research and development, whatever the true figure, must be viewed in the light of other spending, and revenues.

Billions of dollars in advertising. The pharmaceutical industry spends about the same amount on advertising as it does on research and development. French companies for example say they devote 12.1% of their budget to research and development and 11% to advertising and information (19).

In 2002, five companies (Pfizer, GlaxoSmithKline, Merck, AstraZeneca and Johnson & Johnson) each spent more than 1.3 billion dollars on publicity (maximum nearly three billion) (20). In 2002, six drugs (Inexium[®], Vioxx[®], Tazor[®], Ogas[®], Zocor[®] and Celebrex[®]) each had a publicity budget of more than 500 million dollars (756 million for Inexium[®]) (20).

Direct-to-consumer advertising of prescription drugs cost more than three billion dollars in 2001, including 459 million for GlaxoSmithKline alone (20).

Multibillion blockbusters. In 2001, 36 drugs each had worldwide sales of more than a billion dollars (21). The first ten had sales figures above 2.7 billion dollars each in 2002, Tazor[®] reaching almost 8 billion (20). The world's biggest drug company, Pfizer, markets 10 drugs with sales of more than a billion dollars each (in 2002) (20).

Record profits and salaries. For more than three decades, pharmaceuticals have been the most profitable industrial sector (22). According to a study by *Fortune* magazine, drug company

profits represented 18.5% of turnover in 2001 (compared to 12.5% for research and development). This is eight times more than the median profitability of the world's 500 top companies (all sectors), including the banking sector (13.5%), the second most profitable (22). In 2002, pharmaceutical companies again outclassed all other sectors in terms of profitability, despite their highly publicised "difficulties" (23).

A study by economists from Montreal university, focusing on nine of the world's largest drug companies, showed that they spent 113 billion dollars on research and development for the period 1991-2000, while their shareholders reaped some 146 billion dollars in dividends (g) (24).

Drug company employees are better-paid than workers in other industrial sectors. A study of the French pharmaceutical industry confirmed these findings (25).

A study of nine drug companies showed that their CEOs each earned 21 million dollars in 2001, excluding the value of unexercised stock options (h)(i) (26).

These high salaries obviously impact on the cost of research and development. For example, doctors who recruit for clinical trials receive several thousand euros per patient. Thus, a British general practice can earn 20 000 euros a year for only three hours' work a week (27).

So, if drug research and development costs are so high, it is also because drug companies have very high overheads. And everyone wants a share of the pie: personnel, shareholders, researchers, subcontractors, and health professionals (see page 35).

The real and legitimate costs of research and development

The Tufts Center estimate of 802 million dollars per new drug is probably far too high.

Ideally, government authorities should themselves estimate the cost of research and development, and especially the cost of clinical trials. Instead, they feebly comply with industry lob-

bies, offering international extension of patent rights, longer patent protection, greater protection of clinical trial data and increasingly high drug prices.

When the authorities yield to pharmaceutical companies' demands, especially for high drug prices, without having access to reliable data on research and development costs, they ignore the basic rules of sound economic management and risk accelerating the demise of publicly funded welfare systems.

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g- Abbott, BMS, Lilly, GlaxoWellcome, Merck, Pfizer, Schering-Plough, Smith-Kline Beecham and Warner Lambert (ref 24).

h- Abbott, Allergan, BMS, Lilly, Merck, Pfizer, Pharmacia, Schering-Plough and Wyeth (ref 26).

i- In 2002, the (British) GlaxoSmithKline CEO demanded an annual salary of 30 million dollars, in order to "catch up with his American counterparts". Shareholders rejected this rise because it was not commensurate with the company's stock performance. The CEO countered that he might "feel less motivated" if he was refused the rise (ref 29).

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