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.

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?

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
parameters. This was done in 1993 by the Office of Technol-
ogy Assessment (a former US public body): by increasing the
capital opportunity cost (see below) from 9% to a rate vary-
ing from 10% to 14%, and by adjusting for the US inflation rate
during the period in ques-
tion, the "official" cost of research and
development (universally quoted, especially by drug com-
panies) became 359 million dol-
ars (in 1990 dollars) (7).
Simple adjustment for the
inflation rate increased this fig-
ure to 473 million dollars in 2000,
which drug companies conve-
niently rounded up to 500 mil-
ion (8).
Between 1991 and 2002, the
"official" costs of research and
development were simply infla-
tion-corrected updates of the
1991 Tufts Center estimate, itself
based on a sample of drugs whose
clinical development started
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 insti-
tute. Before examining this lat-
estimate in detail, the reader
should know that the Tufts Cen-
ter for the Study of Drug Devel-
opment is an institute specialis-
ing in the pharmaceutical indus-
try. It is affiliated to Tufts University
(Boston), but is financially inde-
pendent from it. It has a unique
database, furnished by data from
drug companies. The Tufts Cen-
ter itself is funded by donations
 especialy 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 cal-
culations.
Methodological problems.
This figure of "802 million dol-
ars" 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 pharma-
cutical firms must cover all their
research and development costs
with sales of the few drugs that
are effectively marketed. Esti-
mates of research and develop-
ment costs therefore usually
include drugs that are abandoned
in the development stage. This
is the case for the "802 million dol-
ars" estimate.
Another important source of
imprecision is the fact that
research and development lasts
several years, making it even
difficult to itemise spend-
ing. There is a dual risk of over-
looking certain costs and of
including spending on other can-
didate 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 twenti-
theth 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 infor-
mation used by the Tufts Cen-
ter team, have never been pub-
lished, and were only provided
by the companies on the under-
standing that they would remain
confidential.
Weightings derived from
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 preclini-
cal research were calculated as
a fraction of the total develop-
ment costs, using data from the
Tufts Center database (contain-
ing information on several hun-
dred 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 devel-
opment calculated from the
database (4).
The figure of "802 million dol-
ars" was arrived at with the fol-
lowing parameters: 21.5% of
drugs that entered phase I trials
eventually received marketing
authorisation; preclinical develop-
ment (including research costs)
accounted for 30% of all
development costs; the interval
from the beginning of clinical tri-
als to marketing authorisation
was 90.3 months (7 years 6
months); preclinical develop-
ment 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 invest-
ment before receipts start to
accru.
2nt. 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 develop-
ment (including 214 million or
63.9% in capital costs); and 467
million dollars for clinical devel-
opment (including 185 million
dollars or 39.6% in capital costs).
Thus, capital costs represent near-
ly half (399 million, 49.8%) of
the "802 million dollars" (4).
An estimate with
many question marks
The "802 million dollar" research and development esti-
mate is highly questionable, for
many reasons.
A single, unverifiable sour-
ce. The single-source origin of
the estimate undermines its
validity. The study itself is unver-
ifiable, as drug companies them-
selves provided the data, on con-
dition 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 unavoid-
able. The Office of Assessment
pointed out in (5).
.................................
(5)
- Pharmaceutical companies prefer to use
the accent on the noble word “research”. Yet,
inpractice, pharmaceutical research and
development is usually based on discover-
ies (receptors, mechanisms of action, etc.)
made in public laboratories.
Pharmaceutical research and development
include synthesis or extraction of a compound
with a potential pharmacological action;
studies of pharmacological action (on cells,
tissues, animals, or computer models); for-
mailation of a product administrable to
humans; toxicity studies (on tissues and ani-
mals); clinical trials (phases I-III before mar-
keing 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).
- The Tufts Center website cites several
enthusiastic endorsements by industry rep-
resentatives. 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 not available
elsewhere” (ref 5).
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 marketed 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 (acipollo, 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 verifiable 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 $34 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 capital 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, underlining 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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e These drugs, which are not new chemical entities, are 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.

f 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.

g Purely in-house research and development is no longer the rule, as the product portfolio 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).

h 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).
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 antibiotic 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 3 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-tos (3) and other drugs that differ little from the reference drug, or that are poorly effective. In contrast, me-tos 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 regard the only way for health professionals and patients to make sense of the issue of research and development costs.

**The death of a model?** From the public health standpoint, the sums spent on research and development of yet another me-too 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 antiinflammatory 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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5- *FDA releases data on phase IV commitments* Scrup 2003; (2853/54): 19.

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**Why the rising costs of pharmaceutical research ?**

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**References**

5- *FDA releases data on phase IV commitments* Scrup 2003; (2853/54): 19.
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, whatever the true figure, must be viewed in the light of other spending, and revenues.

What about profits?

The cost of research and development, whatever the true figure, must be viewed in the light of other spending, and revenues. AstraZeneca and Johnson & Johnson (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 a year for only three hours’ work (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 lobbying, offering international extention 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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