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Research and development costs: the great illusion

Response to Prescrire

Your Journal "Prescrire" has published in its November 2003 issue, a long article titled "Drug Research and Development Cost: The Great Illusion", whose main purpose was to criticize our estimation of the average research and development cost of a new drug (\$802-million) that we have published in the *Journal of Health Economics* in March 2003. Actually, your article is aimed more at discrediting our work than at really critiquing it. No alternative estimates, no alternative methods, no alternative hypotheses are put forward or suggested. When reading your article, we feel that our estimate would have been wrong in any case (i.e., no matter what were the results of our computations, whether they be 800, 600, 400 or 200 million dollars). In any event, you would have found that our sole purpose was to justify the "exorbitant" prices of the pharmaceutical industry, using questionable methods and unverifiable assumptions. This a priori, final and radical judgment makes it difficult to formulate an answer. We shall try nevertheless, emphasizing the facts that our estimate, even if it is not technically perfect - we recognize its limits in our article - complies with the state of the art in cost estimation methodology, that the underlying hypotheses are credible and that the approach that I, Henry Grabowski and Ronald Hansen, have chosen is intellectually honest.

a) Our methods comply with the state of the art

Our work applied classical investment evaluation methods to the case

of the internal development of a new chemical entity (NCE) by a pharmaceutical company. This kind of investment has two fundamental characteristics: it is risky (it is highly probable that a molecule development will fail before the marketing approval is granted) and it is time consuming (discovery, preclinical development, and clinical development spans several years). Assessing the cost of such an investment requires both data and a model. We are reproached by Prescrire that the famous "\$802 million" results 'from an assessment rather than from an observation of data'. How could it be different? Only prices are directly observable, not costs. Costs - whatever they may be - can be determined according to methods and conventions agreed to by the scientific community.

For instance, the "opportunity cost" notion is not the least bit controversial in economics and finance. But Prescrire presents it as if it was not a "real" cost. Only "half (of the cost) is really spent". Yet, it should be easy for anybody to understand that a loss of income is equivalent to a cost, as well as that an avoided expense is equivalent to an income. This is the very essence of the opportunity cost notion. In investing in pharmaceutical research and development, companies "are losing" the profit from alternative investments that could have been carried out during the same period. Through this notion, we captured the time cost of the R&D process: a \$400 million project spread over 12 years may be, actually, more expensive than a \$500 million project spread over 6 years only, since after 6 years

resources are available again for a new, productive investment.

In connection with this point, let us recall that our work only dealt with NCEs internally developed by companies and approved by the FDA. It did not deal with all new pharmaceutical products reaching the market, including new formulations, new dosage regimens, etc. This is very clearly mentioned in our article and Prescrire's implicit criticism according to which we should extend the costs of NCEs to all new products, is simply groundless. Of course, an initial formulation has to be developed before a new dosage form or a new presentation is registered! It does not make any sense to dilute the cost of a NCE with that of the costs of all new products that can be derived from the original molecule.

Similarly, Prescrire is challenging the way in which we dealt with taxation in our work. Its oddest argument is that research expenses benefit from an "important tax break" as they are deductible from the corporate income tax. But who can reasonably assert that salaried workers are state-subsidized because their remunerations are deductible? The income taxation base is profit (revenues minus costs), not revenues alone. Corporate costs decrease taxes only because they reduce profit! Profit taxation is not a public subsidy to the private sector. It would rather be the opposite, a private sector contribution to the public sector! In our article, page 173-5, we explain at length the way we treat taxation issues. The readers may refer to it.

b) Our hypotheses are credible and justified

The Prescrire article judges "questionable" most of our working hypotheses. Although they are lengthily discussed and justified in our article, Prescrire does not refer to these discussions. Because space is limited, we can only deal with some of the main points.

For instance, your Journal challenges our estimated success rate for new molecules as well as our estimated clinical development time, but without providing any alternate estimates. It merely contrasts devel-

opment time assessments coming from the same database, - our database! - without mentioning that these assessments actually refer to different periods of time!

A more important point: Prescrire asserts that, in our methodology, the cost of capital - and thus the full research and development cost - would depend on drug companies' stock prices. This is simply untrue! As widely explained in our article, page 163, we are using the CAPM ("Capital Asset Pricing Model") to assess the cost of capital, a very classical method in finance (developed by William Sharpe, a 1990 Nobel Prize winner in economics). According to this method, the cost of capital of a given company does not depend on the absolute value of its own stock price, but on the relationship (covariance) between changes in its own stock price return and changes in stock price returns in general. The cost of capital actually depends on the so-called "specific" risk, i.e. the risk that cannot be eliminated by diversifying with a portfolio of stock holdings. Thus, a firm's absolute stock price can change without affecting its cost of capital, if it varies similarly to the stock exchange index.

Another point: under the pretext that our sample only focuses on "internally developed" products, we would underestimate the impact of public financing. Once again, this is not true. It should be noted that an innovative medicine could have been supported by the NIH (National Institutes of Health), especially during the early fundamental research phase, and be later developed in phases I - II - III by a private company for registration purposes using its own resources. In fact, the five "blockbusters" mentioned in the Prescrire article as having benefited from an important public research effort in the USA met the criteria for inclusion in our sample!

By connecting our phase III cost estimate (\$115 million) to an estimation of an average cost per patient in phase III clinical trials (\$7,000), your article concludes that this implies that: "more than 16,000 patients are included in phase III clinical trials, which is obviously wrong". ►►

► Firstly, the relevant Phase III cost figure to use from our paper is \$86 million, relating to all investigational drugs entering Phase III, rather than the estimate above that relates only to medicines reaching the market. Secondly, the cost of \$7,000 per patient comes from a particular source, the National Cancer Institute which in fact leads clinical trials for reasons other than drug development for registration purposes (1). Other estimates can be found in the literature. For example, according to a report from the Global Alliance for TB (tuberculosis) Drug Development, an independent international organization (www.tballiance.org), the projected cost for a phase III trial for a new antituberculosis drug in a developed country is around \$22,000 to \$26,000 per patient, according to assumptions. Based upon these figures, which are still likely to be underestimated, our assessment is credible, even following Prescrire's criteria.

Similarly, you contrast with our figure an estimate of an out-of-pocket cost of \$8 million dollars for the development of an orphan drug. It is true that orphan drugs development is undoubtedly cheaper, with fewer and shorter trials including fewer patients. But it should be noted that the quoted figure includes only some development expenses (not all!), provided that they have been carried out on United States territory, and that they focus on an orphan indication, as opposed to a new drug. Obviously, the cost for a particular new indication is not the same as the cost for developing a new drug for multiple indications.

c) Our work is intellectually honest

Your article starts its attack by stating that the Tufts Center for the Study of Drug Development (TCSDD) - to which the first author is affiliated and which maintains the proprietary database we used in our study - is a "company funded University institute." This is widely known and has never been concealed. Let us, however, note that our work is published in the *Journal of Health Economics*, a scientific journal with independent peer review and an international reputation. In submitting our article we, ipso facto, adhere to validation principles for

scientific work. Even though it is true that, for reasons easy to understand, the raw data we used are proprietary and confidential and cannot be published, we however are ready, like any scientist, to submit ourselves to any legitimate appraisal, in particular to the appraisal of the editors and referees of the journal that have accepted our work. Our database is singular and confidential. However, it is not "unverifiable" and the situation is not basically different from that of clinical databases.

Finally, as your article mentions as a reference source the Office of Technology Assessment Report from 1993 that "cross-examined" our former 1991 study (2), we will faithfully quote its conclusions (p.66): "the estimates by DiMasi and colleagues of the cash outlays required to bring a new drug to the market and the time profile of those costs provide a reasonably accurate picture of the mean R&D cash outlays for NCEs first tested in humans between 1970 and 1982. 'Our 2003 article used, basically, the same methodology applied to a more recent set of NCEs (products first tested in humans between 1983 and 1994). Why should it be less accurate' than the 1991 one?"

Joseph DiMasi
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1- This point is stressed by Professor Richard Frank of Harvard Medical School in a *Journal of Health Economics* editorial that he dedicated to our article. NIH clinical research costs cannot be compared with the cost of pharmaceutical company clinical research performed for registration purposes.

2- *Journal of Health Economics*, 1991, Vol. 10, 107-142.



Our article in the November issue of *la revue Prescrire*, entitled "Coût de la recherche et développement du médicament: la grande illusion" (also in *Prescrire International* February 2004), was simply intended to offer our readers a clearer perspective on the "802 million dollars" cost of drug research and development widely quoted by the pharmaceutical companies and mass media in France.

Strong criticism in the United States. The claimed "802 million dollars" R&D cost has also been criticised in the United States, not only by consumer groups (Public Citizen, Consumer Project for Technology, and Families USA) and the media, but also in a report on pharmaceutical companies by the Minnesota Attorney General (1). We decided to give our readers the facts, so that they could draw their own conclusions.

A result publicised more than a year before full publication. Your letter states that we confused criticism of your study itself and the way in which the results were used. You also say that much of the information we "revealed" was clearly stated in your article.

However, some key information was far from evident in your article. For example, the title "The price of innovation: new estimates of drug development costs", fails to state that the study concerned only new chemical entities, and even the abstract fails to mention this crucial fact. The key definition used for the study appears only in a footnote (note 12, page 157) (2). Likewise, the average number of patients enrolled in clinical trials (5303) is given in parentheses, in footnote 41, page 177.

The "802 million dollars" figure was publicised by the Tufts Center long before your study was published, notably in a very brief summary released on 30 November 2001 (3). Your manuscript was submitted to the *Journal of Health Economics* in January 2002, resubmitted with modifications in May 2002, finally accepted in October 2002, and published in 2003: more than a year after the "802 million dollars" controversy began. Yet in late 2001 you refused to discuss your study in detail on the Ip-Health discussion forum, "because it had not yet been published" (4).

We preferred to wait for the full article before examining your study in depth.

Clarification. We underlined the fact that the "802 million dollars" figure was an estimate, or a calculation, and not a measurement. This may be self-evident to economists like you, but our subscribers are health professionals who prefer to base their views on precise clinical data rather than on extrapolations and estimates. We also drew our readers' attention to some of your methodological choices that might have been "overlooked" by those publicising the 802 million dollars figure, such as pharma sales representatives.

We did not really discuss the notion of capital opportunity costs. We simply drew readers' attention to the fact that 49% of the "802 million dollars" had not been "out-of-pocket" spent.

You say we were wrong to state that a given company's opportunity costs depend on the value of their shares. But this is not what we said: on the contrary, we stated that you had based your calculations on the overall stock-market performance of the entire pharmaceutical sector (2).

We also underlined that the "802 million dollars" in R&D costs applied only to new chemical entities, which represent a minority of new medicinal products. And we did not say that you had suggested the contrary, but stressed that fact in order to show the excessive extrapolations that could follow from your results.

Pre- or post-tax? Taxes can indeed be neglected when comparing R&D costs between different industrial sectors, but only when the playing field is level. This is not the case in the United States. And if one takes into account (as you did) capital opportunity costs based on returns on financial investment, it is only logical to take account of specific tax deductions and reductions for drug research and development.

American drug companies are less heavily taxed than other industrial sectors: not only because R&D costs are deductible from their taxable income, but also because of specific tax breaks.

It is noteworthy that the Office of Technology Assessment recommends the use of post-tax costs (5).

A changing estimate, not an immutable fact. In our discussion of the time taken for a new candidate drug to reach the market, we mentioned another study from the Tufts Center (done during a period we clearly specified, i.e. partly overlapping with your own study) showing that this time was far shorter in 1996-1998 than in 1993-1995. You will be aware that the Tufts Center published another new study in November 2003, showing that the fast-track marketing authorisation procedure set up by the FDA in 1997 has cut the time taken for R&D by 2-2.5 years for the drugs approved between 1998 and 2003 (6). This clearly shows that the "802 million dollars" estimate is not set in stone.

We chose not to quote the figures published by the Global Alliance for TB drug development, which you referred to when discussing the cost of clinical trials, as they too are simple estimates. We preferred to compare your figures with the real cost of clinical trials funded by the National Cancer Institute. It is worth pointing out, however, that the Global Alliance for TB drug development estimated the total cost of research and development for a new anti-tuberculous drug (including failures) at between 115 and 240 million dollars, i.e. a figure much lower than "802 million dollars" (7).

We agree, as stated in our article, that orphan drug R&D represents a special case.

In conclusion, current drug research and development costs may well be too high. Not because they undermine drug company profits, which are still more than comfortable, but because they are not commensurate with the added therapeutic value of most new chemical entities. And added therapeutic value is what interests our readers, health professionals who select, prescribe and dispense drugs on a daily basis.

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- 1- Office of the Minnesota Attorney General "Follow the money - The pharmaceutical industry - the other drug cartel". Website <http://www.ag.state.mn.us> consulted on 12 January 2004.
- 2- DiMasi J et al. "The price of innovation: new estimates of drug development costs" *Journal Health Economics* 2003; **22**: 151-185.
- 3- "Tufts Center for the Study of Drug Development Pegs Cost of a New Prescription Medicine at \$ 802 million" News release 30-11-01. Website <http://csdd.tufts.edu> consulted on 12 January 2004.
- 4- DiMasi J "WSJ on \$802: \$282 million for clinical trials?" 4 December 2001. Website <http://www.lists.essential.org> consulted on 12 January 2004.
- 5- "Pharmaceutical R&D: costs, risks and rewards" Office of Technology Assessment 1993: 71 pages.
- 6- "FDA's fast track initiative cut total drug development time by three years, according to Tufts CSDD" 13-11-2003. Website <http://csdd.tufts.edu> consulted on 12 January 2004.
- 7- The global alliance for TB drug development "Estimating drug development costs". In: "The economics of TB drug development". Website <http://www.tballiance.org> consulted on 12 January 2004.

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