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SPENDING ON NEW DRUG DEVELOPMENT[1]

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SUMMARY

This paper replicates DiMasi *et al*. (*J. Health Econ*. 2003; **22**: 151–185; *Drug Inf. J*. 2004; **38**: 211–223) estimates of expenditure on new drug development using publicly available data. The paper estimates that average expenditure on drugs in human clinical trials is around $27m per year, with $17m per year on drugs in Phase I, $34m on drugs in Phase II and $27m per year on drugs in Phase III of the human clinical trials. The paper's estimated expenditure on new drug development is somewhat greater than suggested by the survey results presented in DiMasi *et al*. (*J. Health Econ*. 2003; **22**: 151–185; *Drug Inf. J*. 2004; **38**: 211–223). The paper combines a 12-year panel of research and development expenditure for 183 publicly traded firms in the pharmaceutical industry with panel of drugs in human clinical trials for each firm over the same period. The paper estimates drug expenditure by estimating the relationship between research and development expenditure and the number of drugs in development for 1682 company/years (183 firms multiplied by the number of years for which we have financial and drug development information). The paper also estimates expenditure on drugs in various therapeutic categories. Copyright © 2009 John Wiley & Sons, Ltd.

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KEY WORDS: pharmaceuticals; drug development

1. INTRODUCTION

DiMasi *et al*. (2003, 2004) estimate the cost of new drug development for all drugs and for drugs in certain therapeutic categories, respectively. The authors estimate the average cost of new drug development to be $802m per new drug. This number has become a central part of the policy debates on numerous issues regarding the pharmaceutical industry including the Medicare Prescription Drug Act, drug importation, generic entry and vaccine development. Drug companies argue the high cost of drug development justifies the high prices paid by governments, insurers and customers. Given the importance of the $802m number to the debate it is important to know whether it is correct and what it means.

DiMasi *et al*. (2003) calculate the cost of new drug development with data from two sources. The authors survey 10 large pharmaceutical firms and ask those firms to report the expenditure in human clinical trials for 68 drugs chosen at random from the Tuft's drug development database called the CSDD. The authors then use information on average success rates and successful durations from the CSDD data to calculate the cost of bringing a new drug to market. Recently, Light and Warburton (2005) point out numerous problems with DiMasi *et al*. (2003). In particular, because 'cost data used

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[1]The authors are not aware of any potential conflicts that may bias their work. As far as the authors are aware, the study raises no ethical issues.

was proprietary and confidential, readers cannot know how each company collected its data, or what was counted as research costs, and no independent verification of the accuracy of the information is possible' (p. 1031). This paper provides an independent verification of the survey cost data by using an alternative publicly available data source on research and development expenditure. Adams and Brantner (2006) verify the second part of DiMasi *et al.* (2003) paper by using publicly available data to estimate success rates and average successful durations.

By comparing aggregate annual expenditure on research and development across firms and over time to the number of drugs in human clinical trials for each firm and each year, we can determine the 'marginal expenditure' on an additional drug in development. If Drug Firm A spends an additional $50m in 1992 relative to 1991 but in 1992 Drug Firm A has two additional drugs in development we argue this provides an estimate of average annual expenditure by Drug Firm A, i.e. $25m per drug per year. Similarly, if Drug Firm B spends $100m more than Drug Firm A in 1992 but Drug Firm B has an additional four drugs in development in 1992, then we estimate drug expenditure to be $25m per drug per year. Note that this is an estimate of the correlation between expenditure and the number of drugs in development. We are not attempting to estimate the impact of an additional dollar of expenditure on the number of drugs in development or the impact of additional drug on the amount of expenditure.

There are a number of advantages to this approach. First, we are using publicly available data so our results can be verified by other researchers. Second, we are using data from 183 publicly traded firms rather than 10 firms selected by the study's authors. Our selection criteria is that the firms have research and development expenditure information in the CompuStat data base, be in the pharmaceutical industry (see Danzon *et al.*, 2004) and have drugs in the Pharmaprojects data set (see Adams and Brantner, 2006). These firms range in size from 100 employees to almost 180 000 employees with sales ranging from $2m annually to almost $45b annually. Third, we are using contemporaneous reports of research and development expenditure where the reports are scrutinized by both the market and the SEC. In their comment on DiMasi *et al.* (2003), Light and Warburton (2005) argue that

> considering the clear interest of pharmaceutical companies in higher (rather than lower) estimates of drug development costs, and sampled firms' likely awareness of the intended use of the survey data, it is not unlikely that companies would deliberately and systematically overstate costs in their survey responses (p. 1031).

We argue that such biases are less likely here given the large number of firms and the checks on the reports including audits.

Of course there are also serious concerns about the approach we use here. First, the data are aggregate research and development expenditure. Those not only include expenditure on drugs in human clinical trials but also include development expenditure on drugs yet to reach trials. To identify the amount spent in human clinical trials we must infer the information from cross sectional and time-series variation in expenditure that is associated with variation in the number of drugs in development. Such variation may lead to spurious estimates. For example, if one firm specializes in anti-infective drugs and we compare the specialty firm's expenditure on anti-infective drugs to that of a firm that has just one or two anti-infective drugs, we may estimate that expenditure on the extra drug as being small. This low estimate may be due savings from specialization rather than an accurate measure of the cost of adding another anti-infective drug.

Second, we are estimating changes for the 'marginal drug', which may be more expensive than the average drug.[2] The relationship between expenditure on the marginal drug and expenditure on the average drug depends on what assumption the reader is willing to make regarding how expenditure per

[2]Thanks to Eric Durbin for pointing this out.

drug changes with the number of drugs. If expenditure per drug is constant then the marginal and the average are the same. On the other hand, if expenditure per drug is increasing with the number of drugs in development then marginal expenditure will be higher than average expenditure. A number of papers suggest that there may be economies of scale or scope in drug development (Cockburn and Henderson, 1996, 2001; Danzon *et al*., 2004). If there are economies of scale then we would expect marginal expenditure to be less than average expenditure.[3] Note that marginal expenditure may be a more useful measure for determining the incentive effects of policy changes.

Third, we use Pharmaprojects' definition of a 'drug development project' and assign the drug to the 'originator'. In general, this definition corresponds to a new patented molecular entity. In the main part of the analysis we drop drugs that are new formulations of existing drugs (i.e. an extended release version of an existing drug). The analysis does not account for the fact that the drug development project is part of a joint venture (and thus expenditure is spread across multiple firms) or is being developed by an altogether different firm (and our method is assigning the drug project to the wrong firm).[4] Such mis-measurement may bias our estimates downward. It should be noted that our counts of drugs in the different phases are measuring the development associated with the originating firm.

In order to have a number that is comparable to DiMasi *et al*.'s (2003) average expenditure over the sample period, we control for differences between firms and differences over time. We attempt to control for some cross-sectional variation by conditioning on net sales. If for example, larger firms spend more on drug development projects than smaller firms then net sales should control for this variation. Similarly, if firms are spending more on drug development projects at the end of the period than at the beginning then our controls for time will provide a better sense of the average expenditure per project during the period. Note that identification of spending per drugs is coming to some extent from the fact that larger firms have more drugs and that there are more drugs over time in the database. The controls attempt to separately identify the effect of having another drug in human clinical trials from the effect of being large or later in time.

DiMasi *et al*. (2003) uses a similar approach to verify their own estimates. The authors use firm level R&D expenditure reported by PhRMA and estimate lagged expenditure on firm level counts of approved drugs. The authors estimate average expenditure per approved drug to be between $354m and $558m. These numbers are similar to their estimate of $403m using the survey data. Other researchers have simply divided aggregate R&D expenditure by the total number of approvals per year. The concern with these approaches is that less than one in four drugs in human clinical trials actually make it to the market and the process can take between 6 and 12 years with substantial variation across drugs (Adams and Brantner, 2003).

The rest of the paper proceeds as follows. Section 2 discusses the data used in this study and provides some background information on new drug development. Section 3 presents the results. Section 4 concludes.

2. DATA AND BACKGROUND

This paper combines data from two data sources. Information on each firm's research and development expenditure comes from the Standard Poor's CompuStat Industrial file and Global Vantage Industrial Commercial file used by Danzon *et al*. (2004).[5] This data set provides financial information on publicly traded drug companies including net sales, employment and expenditure on research and development.

[3]To the extent one is concerned that large firms may have lower (or higher) expenditure per drug than smaller firms, some of this variation is accounted for in the analysis through conditioning on sales revenue.
[4]Danzon *et al*. (2005) analyze joint ventures.
[5]All monetary values are in 1999 dollars using the domestic manufacturing Producer Price Index.

Table I. Firm/year summary statistics

Variable	Obs	Mean	Median	Std. Dev.	Max
Number of drugs	2245	4	2	6	45
R&D expenditure ($m)	1682	264	37	551	4678
Net sales ($m)	1701	2355	110	5438	44 611
Employees ('000)	1537	11	1	25	179

Information on drugs in development comes from a Pharmaprojects data set used by Adams and Brantner (2006) and Abrantes-Metz *et al*. (2005). This data set uses public information to track drugs through the development process, providing information on the length of time in different phase as well as when and if drugs completed a development phase. The two data sets overlap for the years 1989–2001. The data sets are matched using the name of the pharmaceutical firm.[6] Pharmaprojects updates its information on the firms developing each drug after a merger, so we used text searches of the database and searches of a related data set called the Manufacturing Index to determine the ownership of drugs over time.[7]

According to Danzon *et al*. (2004) there are 383 firms in their original data. Once we match these firms to firms in the Pharmaprojects data we are left with 183 firms. It is not clear exactly why there are firms that do not match. The two data sets do not exactly overlap in time and that may explain some of it. Another explanation is that the Pharmaprojects does not capture name changes or mergers among smaller firms (see footnote 7). Table I presents some basic summary statistics for this sample of firm/year combinations. Table I shows there are an average of four drugs in development for each firm for each year 1989–2001. Note this measure is not a very good measure of the stock of drugs in development because we only observe drugs entering one of the stages of human clinical trials after 1989. In the average firm/year $264m is spent on research and development, $2355m is made in sales and there are 11 000 employees. Note that medians are substantially lower than the means suggesting that the distributions are all skewed toward zero.

Figures 1–3 present the distribution of the number of drugs in human clinical trials per firm/year, the amount of R&D expenditure per firm/year, and a scatter plot of the two, respectively. The first two figures show that the distributions of drugs and expenditures are heavily skewed to zero. The third figure seems to show a positive correlation between the amount of R&D expenditure per firm per year and the number of drugs in development per firm per year.

Figure 4 presents a summary of the research and development process for new drugs. The first stage of drug discovery is commonly called 'preclinical development'. In this stage pharmaceutical firms analyze thousands of drugs to determine whether one may have an affect on a disease or condition. As candidates are discovered these drugs are tested on animals to determine whether the drug may be safe and effective in human beings. It is estimated that drugs spend over 4 years in preclinical testing. DiMasi *et al*. (2003) do not have direct survey information on preclinical expenditure because pharmaceutical firms do not track preclinical expenditure by particular drug candidates. Given this and given that the Pharmaprojects data are based on public information and are not very reliable regarding drugs in preclinical development, we do not estimate expenditure on preclinical development.

After preclinical development the sponsoring firm applies for an investigation new drug application (IND) with the FDA in order to test the candidate in humans.[8] There are three steps to human clinical

[6]This matching was done by hand in order for it to be as accurate as possible.
[7]This was done for all mergers involving firms in the Forbes' top 20 of pharmaceutical industry over the period as well as any other major mergers in the pharmaceutical industry.
[8]If the firm wants to eventually market the drug in the US the firm must apply for an IND prior to undertaking human trials. That said, there are exceptions.

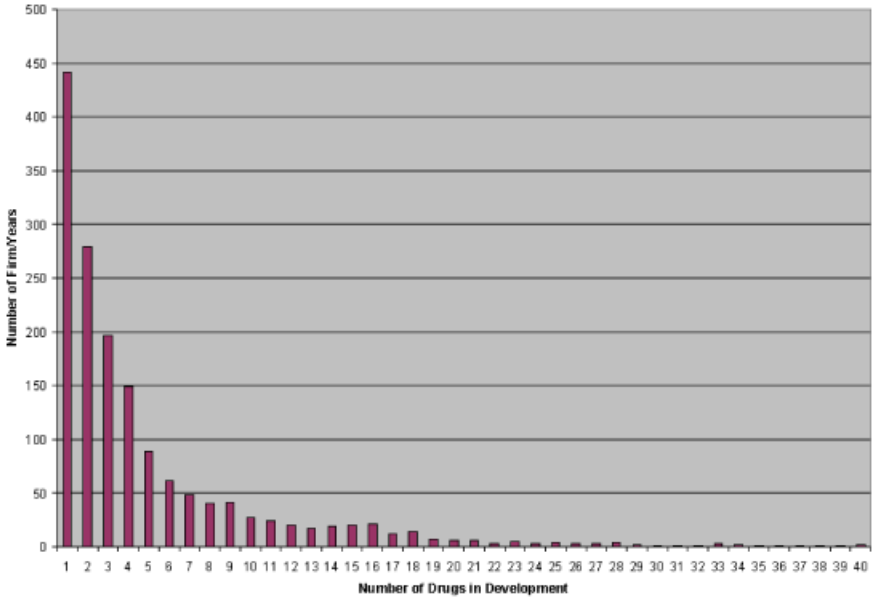

Figure 1. Drugs in development

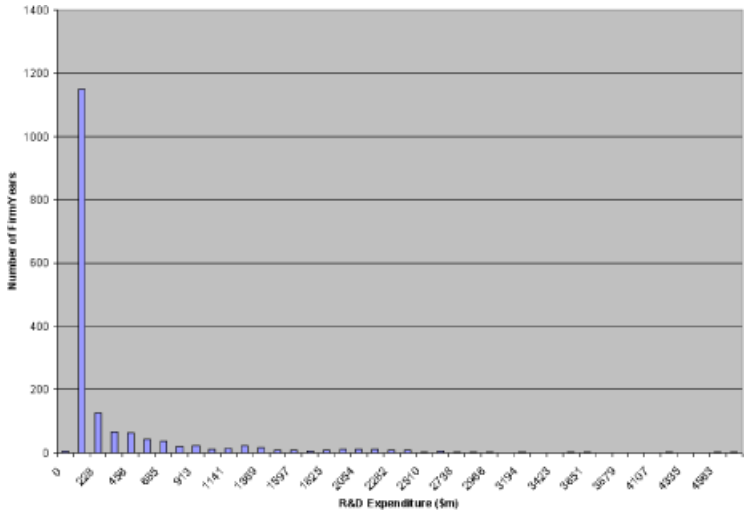

Figure 2. Annual R&D expenditure

trials. In Phase I, the drug is tested for safety on a small group (e.g. 20) of healthy volunteers. Phase II tests concentrate on safety but the test is on a larger group of patients with the condition (e.g. 200). Phase III are the large efficacy trials with upwards of 3,000 patients participating. Once the trials are completed the results of all three stages are presented to the FDA in the form of a new drug application (NDA).

Table II presents some basic summary statistics on the drugs owned by the firms in the sample. The first set of three rows show the mean length in months of successful durations. The second set of three

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