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Review

The cost of drug development: A systematic review

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ABSTRACT

Objectives: We aimed to systematically review and assess published estimates of the cost of developing new drugs.
Methods: We sought English language research articles containing original estimates of the cost of drug development that were published from 1980 to 2009, inclusive. We searched seven databases and used citation tracing and expert referral to identify studies. We abstracted qualifying studies for information about methods, data sources, study samples, and key results.
Results: Thirteen articles were found to meet our inclusion criteria. Estimates of the cost of drug development ranged more than 9-fold, from USD$92 million cash (USD$161 million capitalized) to USD$883.6 million cash (USD$1.8 billion capitalized). Differences in methods, data sources, and time periods explain some of the variation in estimates. Lack of transparency limits many studies. Confidential information provided by unnamed companies about unspecified products forms all or part of the data underlying 10 of the 13 studies.
Conclusions: Despite three decades of research in this area, no published estimate of the cost of developing a drug can be considered a gold standard. Studies on this topic should be subjected to reasonable audit and disclosure of – at the very least – the drugs which authors purport to provide development cost estimates for.

Contents

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1. Introduction

The pharmaceutical industry is heavily reliant on private and public investment in research to bring new products to market. The development of a new marketable drug product requires the establishment of basic knowledge related to a disease, the discovery of possible treatments, the engineering of methods for drug production, and the performance of tests to establish safety and efficacy. Each stage may be costly because of the complexities of human health, compound manufacturing, and treatment response.

A variety of studies have attempted to measure the cost of developing new drugs, and several commentaries have been written on the topic. Yet, despite the importance of knowledge about drug development costs, we could not find any prior systematic review of evidence concerning the cost of drug development. To address this gap, we sought to answer the following questions: What are the methods used to generate available estimates of the cost of developing a new drug? What is the range of available estimates? What are the components of estimated development costs? Have development cost estimates increased over time? Do cost estimates vary by therapeutic category? In the sections that follow, we describe our literature search and screening process; summarize the studies included and the methods and data sources they employed; review the estimates of the cost of drug development by cost component and across studies, drug classes, and time periods; and discuss the overall quality of available evidence.

2. Methods

2.1. Search strategy

We sought English language research articles on the cost of drug development that were published from 1980 to 2009, inclusive. We used database searching, citation snowballing and expert referral to identify the relevant literature. From January 19 to 21, 2010, we searched seven literature databases: EconLit (Ebsco), International Pharmaceutical Abstracts (OvidSP), MEDLINE (1950 to Present with Daily Update; OvidSP), Public Affairs Information Service and PAIS Archive (CSA), ProQuest Dissertations and Theses, Web of Knowledge databases (Thompson), and Worldwide Political Science Abstracts (CSA). We used search strategies combining the concepts of 'drug development' or 'pharmaceutical research' with the concepts of 'costs' or 'expenditures' — details of the search strategies are available on request. In addition to database searching, we used Internet searches for grey literature, searched our personal libraries (containing over 10,000 reports and publications), and called upon research networks to suggest key articles through April 1, 2010. Citation snowballing was based on the reference lists of the articles that met inclusion criteria after full-text review.

2.2. Inclusion criteria

Our inclusion criteria were that studies generate original estimates of the total cost of drug development and that they describe the sources of data and the methods used to generate their estimates. We included studies that had data at a product, firm, or industry level.

2.3. Screening

We screened potential citations in two stages. First, two of us (SM and CC) each screened half of the citations for relevance against our inclusion criteria, using titles and abstracts. If an abstract was unavailable electronically, articles that could not be excluded based on title alone were passed along to the full-text review stage. After title and abstract screening, each of three authors (SM, PG, and JL)

received a randomly selected third of the remaining citations for full text assessment.

2.4. Abstraction

We used a standardized template to abstract publications satisfying inclusion criteria. This template collected data on the following: type of drug discovery studied (therapeutic class-specific or overall, conventional or biological); time period, country and currency of estimates; data sources and study methods; and results in terms of development success rates and costs.

2.5. Meta-analysis

Because of the variety of methods that are used in this body of the literature, we did not did not aim to carry out a formal statistical meta-analysis of the findings. Instead, we conducted a descriptive analysis of the range of estimates across studies, methods, time periods, and drug classes. This required that we adjust each study's findings for inflation so that cost estimates from different points in time could be compared. We therefore converted all cost data (all were reported in U.S. dollars) to the equivalent of year 2009 US dollars using the US Gross Domestic Product (GDP) deflator (Bureau of Economic Analysis). Exchange rate comparisons were not required because only US currency estimates were found in the final set of studies that met our inclusion criteria.

3. Results

3.1. Included studies

Our initial searches of literature databases resulted in a list of 1806 potentially relevant citations (1718 unique citations after de-duplication). Title and abstract screening eliminated all but 24 of these citations. Most other citations were excluded at this stage because they were not on topic (1651 citations), they were commentaries (19), or they did not provide original estimates of the cost of drug development (22). Two additional, potentially relevant published articles were found through screening of references. Despite our initial constraints on publication dates, we also included one pre-1980 publication for full text review; this article was added because it was the first in a series of potentially relevant studies conducted by a group of collaborators [1]. We also conducted full text review on two articles identified via expert referral that were published after 2009 but before the completion of our study [2,3], for a total of 29 articles undergoing full-text review.

Upon full text review, 13 articles were found to meet our inclusion criteria [1–13]. Six excluded articles were commentaries that did not provide original estimates of the cost of drug development and five were analyses that used published estimates for secondary purposes (e.g., studying returns to R&D investment in the pharmaceutical sector [14]). Four studies evaluated aspects of development costs (e.g., public spending on research or success rates of clinical trials) but were not designed to estimate the total cost of drug development. The 13 articles meeting our inclusion criteria are summarized in Table 1—a table with complete abstraction details is available on request.

3.2. Research designs

3.2.1. Study methods

The studies that met our inclusion criteria fell into one of four general methods: retrospective cost accounting with project-level data; retrospective econometric analysis with industry- or firm-level data; retrospective cost accounting with industry-level data; and prospective estimates of the cost of developing a hypothetical drug product.

Methods for estimating the cost of drug development using retrospective cost accounting with project-level data were first developed in 1979 by Hansen and have been applied in six subsequent studies involving Hansen, DiMasi, or both [1,5–10]. The Hansen/DiMasi approach involves estimating the average total cost per drug licensed for sale using data on the costs, success rates and durations of each stage of clinical investigation. Stage-specific cost data provide information about the average amount spent per stage of development: e.g., average cost per phase 2 clinical trial. Stage-specific success rates provide information about the average number of projects that must reach a stage in order for one to successfully clear it. Stage-specific durations of investigation provide information about the average timing of different investments made. Combined, these data are used to produce an estimate of the average costs per success among the projects for which relevant data were obtained. Two other studies used all or part of the Hansen/DiMasi approach [3,8].

Other researchers have estimated the cost of drug development using econometric analysis of industry- or firm-level data [2,4]. Wiggins modeled the number of new chemical entities approved for sale each year in the USA as a function of current and lagged research and development spending by the pharmaceutical industry [4]. By inverting the coefficient in the econometric model that describes the effect of total research spending on the number of drugs developed each year, Wiggins arrives at an estimate of the amount of additional spending required to develop one additional drug. Adams and Brantner [2] also used econometric methods; however, rather than modeling product launches as a function of research expenditure, they modeled firm-level research expenditure as a function of the number of drugs a firm had under development at various stages of clinical investigation. This provided an estimate of the additional annual research expenditure required for a firm to have an additional drug at a given stage of development. Both studies using econometric analysis also required data (drawn from published studies by Hansen or DiMasi) on the timing and/or success rates of stages of drug development in order to generate final estimates of the cost of drug development, including opportunity costs of capital (described below) [2,4].

Young combined national-level data on spending and drug development to produce retrospective estimates of the average research costs per drug approval and per new chemical entity approved in the USA [11]. This retrospective accounting with industry-level data provides results similar to the first stages of econometric analysis.

Table 1
Summary of included studies and total estimates of cost of drug development.

Study	Period	Design	Primary data source	Sample	Cash estimate (2009 $-millions)	Capitalized estimate (2009 $-millions)
Hansen and Chien [1]	1963–1975	Retrospective accounting of project-level costs and success rates	Confidential surveys	Sample of unspecified firm-originated compounds	$92	$161
Wiggins [4]	1970–1985	Retrospective econometric analysis of industry-level aggregated data	Published data	All types of new pharmaceutical compounds	$113	$218
DiMasi [5]	1970–1982	Retrospective accounting of project-level costs and success rates	Confidential surveys	Sample of unspecified firm-originated compounds	$193	$391
DiMasi [6]	1970–1982	Retrospective accounting of project-level costs and success rates	Confidential surveys	DiMasi [5] sample, stratified by therapeutic category	$69–140*	$98–229*
DiMasi et al. [7]	1970–1982	Retrospective accounting of project-level costs and success rates	Confidential surveys	DiMasi [5] sample, stratified by unspecified firms	$202–238	$388–581
Young and Surrusco [11]	1990–2000	Retrospective accounting of industry-level aggregated data	Published data	All drug approvals by the US FDA	$207	$422
Global Alliance [12]	~2000	Prospective estimate of project costs	Confidential surveys	Unspecified TB treatment		$139–291
DiMasi et al. [8]	1983–1994	Retrospective accounting of project-level costs and success rates	Confidential surveys	Sample of unspecified firm-originated compounds	$499	$993
DiMasi et al. [9]	1983–1994	Retrospective accounting of project-level costs and success rates	Confidential surveys	DiMasi et al. [8] sample, stratified by category	$312–448*	$464–609*
Adams and Brantner [13]	1989–2002	Retrospective accounting of project-level success rates	Proprietary databases	Sample of unspecified drugs in research databases	548	$562–2623
DiMasi and Grabowski [10]	1990–2003	Retrospective accounting of project-level costs and success rates	Confidential surveys	Sample of unspecified firm-originated biotech compounds	$614	$1362
Adams and Brantner [2]	1989–2001	Retrospective econometric analysis of firm-level aggregated data	Proprietary databases	Sample of unspecified drugs in research databases	$507*	$1535
Paul et al. [3]	~1995–2010	Retrospective accounting of project-level costs and success rates	Confidential surveys	Sample of unspecified compounds	$884	$1800

* Estimates available for clinical costs only.

Prospective estimation of the cost of developing a drug product is the method applied by the Global Alliance for TB Drug Development [12]. This method involves obtaining project-level estimates of the cost of conducting each stage of drug development, from the production of drugs for testing through all various stages of clinical trials.

3.2.2. Study outcomes

A primary outcome of interest in the studies included in this review is the average amount of cash spent directly on research and development per successful drug (referred to as the 'cash' or 'out-of-pocket' estimates). While some studies did not report these cash estimates, all studies included in this review included estimates of the "capitalized" cost of drug development. This includes not only the actual cost of the research and development activities but also the opportunity cost of investing in such activities. The opportunity cost of investing in research and development is the amount of income that could have been generated by investing the same amount of money elsewhere during the life of the project. As we discuss below, studies included in this review used different estimates of the opportunity cost of capital.

The opportunity cost of capital depends on who is making the investments. Public investors into drug R&D – governments, universities, charitable bodies, and other not-for-profit organizations – have different objectives and sources of capital than do private for-profit investors. Firms that receive grants and subsidies (including tax exemptions) for research as it is conducted do not incur forgone income on that portion of the investment over the remainder of the research project—the amount provided by grant or subsidy can be reinvested elsewhere upon receipt of the grant or subsidy. Although research and development is supported through various forms of public and non-profit investments and subsidies, none of the studies included in our review provided a detailed accounting of such and, therefore, no study accounted for public support in calculating respective opportunity costs of capital invested in drug development.

3.2.3. Study data

The seven articles by Hansen or DiMasi use data from confidential surveys of pharmaceutical companies to populate their accounting models of the cost of drug development [1,5–10]. The survey instruments for project-specific research costs – obtained from the study authors – contain questions about overall spending on research and development by firms, as well as requests for information about the timing and amount spent on the development of specific compounds that the study authors included in their samples. To estimate industry-average drug development timelines and success rates, Hansen and DiMasi also use information from secondary, proprietary databases about drugs in clinical development that are maintained by the Centre for the Study of Drug Development [1,5–10]. All data are confidential: the names of neither the companies nor the compounds under investigation are divulged.

Three other articles included in this study produced secondary estimates of development costs that drew, in part, on the results from Hansen and/or DiMasi. In 1987, Wiggins [4] drew on research and development spending reported in annual reports of the Pharmaceutical Manufacturers Association and on Hansen's [1] estimates of the pattern of investments over time in order to arrive at capitalized estimates of the cost of drug development [4]. In 2006, Adams and Brantner used proprietary data from the Pharmaprojects database maintained by PJB Publications to compute their own estimates of the duration and success rates for stages of clinical investigation and then applied DiMasi's 2003 estimates of costs per stage of development to complete their model [8,13]. In 2010, Paul et al. [3] used confidential in-house data from Eli Lilly and Company, confidential survey information from the Pharmaceutical Benchmarking Project, and external sources – including DiMasi's 2003 cost estimates [8] – to populate a model of the cost of drug development based on DiMasi's 1991 article [5].

Adams and Brantner's study [2] used firm-level total research expenditure data collected by Danzon et al. [15] from two proprietary databases maintained by Standard & Poor's Financial Services LLC: the CompuStat Industrial file (for US-based firms) and the Global Vantage Industrial/Commercial file (for multinational firms). They merged those firm-level data with the Pharmaprojects database information compiled for their 2006 study [13].

Young used published data on total annual research and development spending reported by Pharmaceutical Research and Manufacturers of America (formerly the Pharmaceutical Manufacturers Association) and annual number of drug approvals from the FDA [11]. The Global Alliance for TB Drug Development used a variety of information sources: a survey of contract research organisations specialising in microbiology, toxicology, and drug metabolism; guidance documents provided by the FDA and EMEA; recommendations of experts in chemical development; Parexel's 1999 Pharmaceutical R&D Statistical Sourcebook; public data on costs of select US-based clinical trials; and interviews with trial experts [12].

3.2.4. Study samples

The studies that met inclusion criteria for this review used data pertaining to various samples of drug types. The articles by Hansen and DiMasi report development costs for unspecified new molecular entities that were never before approved for other uses and that originated throughout the development process within the firms that the authors surveyed for information about research costs [1,5–10]. This excludes approvals for new dosage forms of existing compounds, drugs involving combinations of active ingredients, or approvals for new salts or esters [16]; and it does not include new uses for existing compounds or account for multiple approved uses of a new molecular entity at market launch. Following his 1991 and 2003 studies [5,8], DiMasi published estimates using the same data stratified by firm size or therapeutic category [6,7,9].

Adams and Brantner's 2006 study was based on a sample of 3181 new drugs entering into clinical investigation for which they had sufficient data from the Pharmaprojects database [13]. They excluded drugs being tested for new indications, and reported findings by drug class and company level but did not disclose the names of products or

firms included in their study sample. For their 2010 study, Adams and Brantner's primary research dataset (from Danzon et al. [15]) contained information on 383 firms with at least $20-million in sales during at least one year from 1985 through 2001; they included 183 of such firms for which information could be merged with their secondary dataset (Pharmaprojects) [2]. They do not disclose which firms were in the final sample.

Paul et al. provide estimates for drugs developed by "top 20" biopharmaceutical companies but do not disclose which drugs or companies are included in their sample [3]. The studies by Wiggins and Young draw on industry aggregated data and pertain to all new molecular entities approved for sale in the USA [4,11]. Young also assessed average costs for all drug approvals, including new indications and dosage forms [11]. The estimate provided by the Global Alliance for TB Drug Development was for a hypothetical (as-yet undeveloped) drug for TB [12].

3.3. Study findings

3.3.1. Total cost estimates

Expressed in terms of year 2009 US dollars, the estimates of the average cost of drug development in the 13 published studies included in this review range more than 9-fold — see Table 1. Hansen's 1979 study produced the lowest estimates of the total cost of drug development: USD$92 million in cash outlays and USD$161 million when capitalized [1]. Paul's 2010 study produced the highest overall estimate: USD$883.6 million cash and USD$1.8 billion capitalized [3]. Published estimates vary 4-fold even when restricted to studies published in the past 10 years (pertaining to drugs developed during the 1990s): with cash estimates ranging from Young's 2001 estimate of USD$207 million to Paul's 2010 estimate of USD$883.6 million, and capitalized estimates ranging from the Global Alliance for TB Drug Development's 2001 estimate of $290.6 million to Paul's 2010 estimate of $1.8 billion [3,11,12].

3.3.2. Components of cost estimates

The five studies listed in Table 2 provided separate estimates of preclinical and clinical costs, along with information about estimated clinical success rates and assumed costs of capital [1,3,5,8,13]. Estimates of the preclinical costs per successfully developed drug range 6-fold across these studies. Hansen's 1979 study produced the lowest estimates of the pre-clinical costs of drug development (USD$46 million cash, USD$89 million capitalized) [1]; and Paul's 2010 study produced the highest estimate of pre-clinical costs (USD$284 million cash, USD$834 million capitalized) [3]. Estimated clinical costs are generally larger and more varied across these five studies. Again, the studies by Hansen and Paul provided low and high clinical cost estimates: Hansen's estimate was USD$46 million cash, USD$73 million capitalized [1]; and Paul's estimate was USD$599 million cash, USD$966 million capitalized [3].

Estimates of the success rate for drugs entering into clinical investigation range from 11.7% to 24.0% across five studies in Table 2. (Across all 13 studies in this review, estimated success rates range from 11.7% to 30.2%, as DiMasi used 30.2% in his 2007 study of biotech drugs [10].) Paul's 2010 article contains the lowest estimated success rate, which translates into an estimate of roughly nine failed development projects for every one successfully developed drug [3]. Adams and Brantner's estimated success rate of 24.0% translates into roughly three failed project per successful one [13].

The real (inflation-adjusted) rates of return used to calculate the opportunity costs of investing in research range from 8.0% to 11.0% across five studies in Table 2. (Rates ranged from 8.0% to 11.5% across all studies in this review because DiMasi used 11.5% in his 2007 study of biotech drugs [10].) Rates of return used by authors increased across time periods of the published studies. Earlier studies used a rate of 8.0%, studies published in the 1990s used 9.0%, and more recent studies used rates of 11% or higher.

4. Variation in costs by treatment category

Following publication of his 1991[5] and 2003[8] studies, DiMasi produced follow-on papers that reported the clinical research costs by therapeutic categories using subsamples from his research data [6,9]. The most recent results are reported in Table 3. These estimates vary by 43%, from USD$311.9 million for a sample of analgesic and anaesthetic drugs to USD$448.0 million for a sample of anti-infective drugs. When DiMasi includes an estimate of the opportunity cost of capital invested, his development cost estimates by therapeutic category range by 31%,

Table 2
Estimates of the components of drug development costs from studies providing all components and assumptions.

	Hansen and Chien [1]	DiMasi [5]	DiMasi et al. [8]	Adams and Brantner [13]	Paul et al. [3]
Cash					
Pre-clinical	$46.0	$111.0	$149.8	$164.6	$284.4
Clinical	$46.0	$81.5	$349.0	$383.7	$599.2
Total	$92.0	$192.5	$498.8	$548.3	$883.6
Capitalized					
Pre-clinical	$89.0	$263.7	$414.6	$471.5	$834.0
Clinical	$73.0	$127.5	$578.0	$602.7	$965.6
Total	$161.0	$391.2	$992.6	$1074.3	$1799.6
Assumptions					
Success rate	12.0%	23.0%	21.5%	24.0%	11.7%
Cost of capital	8.0%	9.0%	11.0%	11.0%	11.0%

Notes: Figures converted to year 2009 US dollars using the US Gross Domestic Product (GDP) deflator (Bureau of Economic Analysis).

Table 3
Recent estimates by DiMasi et al. of the clinical costs of drug development by treatment category.

	DiMasi et al. [8]	DiMasi et al. [9]			
Type of drug studied	Overall sample of 68 firm-originated compounds first tested on humans from 1983 to 1994 by an undisclosed sample of firms	CNS-subsample of DiMasi, 2003	Anti-infective-subsample of DiMasi, 2003	Cardiovascular-subsample of DiMasi, 2003	Analgesic/Anaesthetic-subsample of DiMasi, 2003
Cash estimate	$349.0	$337.9	$448.0	$342.8	$311.9
Capitalized	$578.0	$574.3	$608.9	$569.3	$464.1

Notes: Figures converted to year 2009 US dollars using the US Gross Domestic Product (GDP) deflator (Bureau of Economic Analysis).

from USD$464.1 million for a sample of anaesthetics to USD$608.90 million for a sample of anti-infective drugs.

Adams and Brantner also estimated category-specific drug development costs by applying DiMasi's overall (not category-specific) estimates of research costs per stage of development to their own estimates of the category-specific duration per stage of development [13]. This indirect method of estimation produced even wider ranges in cost estimates across therapeutic areas: their capitalized estimates varied by nearly 3-fold across therapeutic categories, from USD$561.9-million for a sample of central nervous system drugs to $1403.5-million for a sample of respiratory treatments [13].

4.1. Changes in findings over time

Estimates of the cost of drug development in published studies have increased over time. This is illustrated in the studies by Hansen, DiMasi and colleagues, for which the research design and data collection processes are generally comparable. As shown in Table 4, Hansen and DiMasi's various estimates of cash spent per successfully developed new compound have increased 8-fold over 30 years: from USD$92 million for drugs developed in the 1960s and 1970s to USD$737.7 million for drugs developed in the 1990s and 2000s (all figures in year 2009 dollars). Over this period, their estimates of capitalized costs have increased nearly 9-fold: from USD$161 million to USD$1446.8 million. These researchers have estimated that the underlying success rates for drugs in development have increased over the period of their studies—from about one in eight drugs being successful to one in five. While part of the increase in their total estimated cost of drug development results from failure of drugs at later stages in the development process, much of the increase in their cost estimates over time stems from higher costs at each stage of the development process [17].

5. Discussion

Differences in data, methods, and subjects of investigation likely drive the wide variation in published estimates of the cost of drug development. For example, Young provides estimates based on aggregated research spending reported by the pharmaceutical industry and aggregated new drug approvals reported by the US FDA [11]. In comparison to the firm- and project-level analyses, Young's estimates of the cost of drug development are very low. The Global Alliance for TB Drug Development prospectively estimated the cost of developing an approved TB drug, which resulted in an estimate that is specific to a drug class and lower than other studies in the same time period [12]. In contrast, studies by Hansen and DiMasi are based on self-reported information about unnamed drugs developed in-house by pharmaceutical companies [1,5–10]. They produce estimates of the cost of drug development that are relatively high and that have increased dramatically in inflation-adjusted terms over 30 years.

Table 4
Estimates of the cash and capitalized cost of drug development by Hansen and DiMasi.

	Hansen and Chien [1]	DiMasi [5]	DiMasi et al. [8]	DiMasi* and Grabowski [10]
Drugs first tested from...	1963 to 1975	1970 to 1982	1983 to 1994	1990 to 2003
Cash				
Pre-clinical	$46	$111.0	$149.8	$164.7
Clinical	$46	$81.5	$349.0	$573.0
Total	$92	$192.5	$498.8	$737.7
Capitalized				
Pre-clinical	$89	$263.7	$414.6	$481.9
Clinical	$73	$127.5	$578.0	$964.9
Total	$161	$391.2	$992.6	$1446.8
Assumptions				
Success rate	12.0%	23.0%	21.5%	21.5%
Cost of capital	8.0%	9.0%	11.0%	11.5%

Notes: Figures converted to year 2009 US dollars using the US Gross Domestic Product (GDP) deflator (Bureau of Economic Analysis).

* Projected estimates of the cost of a "traditional" pharmaceutical to this later period for comparison with estimated costs of developing biological drugs in that era [10].

One of the greatest impediments to making sense of (and therefore meaningful use of) published results is the lack of transparency about study samples and data. Including the studies that rely on results from work by Hansen and/or DiMasi, confidential information provided on a self-reported basis by unnamed drug companies about samples of unspecified products forms all or part of the data underlying 10 of the 13 empirical studies of the cost of drug development [1,3–10,13]. Results based on confidential surveys of unnamed companies about unnamed products are impossible to assess for accuracy, representativeness, or sensitivity to outliers [11,18–21]. Of course, we recognize that full disclosure of proprietary information is not essential to the scientific method provided that data are made available to third party researchers for the purposes of replication and validation. Yet, even recent studies by authors who purport to be providing transparent and replicable methods draw on proprietary databases and fail to disclose which firms or products are included in their study samples, which poses major barriers to replication and interpretation [2,13].

6. Conclusions

Despite three decades of research in this area, no published estimate of the cost of developing a new drug can be considered a gold standard. Existing studies vary in their methods, data sources, samples, and therefore estimates. While some methods are methodologically strong and some findings have been widely cited, the fact that the data and even the subjects of investigation are kept secret make it impossible to assess validity and reliability. Studies on this topic should be subject to reasonable audit and disclosure of – at the very least – the drugs which authors purport to provide development cost estimates for. Only then will we be able to meaningfully interpret and apply the evidence generated from studies of the cost of new drug research and development.

Competing interests

Steve Morgan has been retained by the Canadian Department of Justice and the British Columbia Ministry of Health Services to provide expert testimony on matters related to pharmaceutical policy. In 2007, Joel Lexchin was retained by a law firm representing Apotex to provide expert testimony about the effects of promotion on the sales of medications. From 2007 to 2008 he was retained as an expert witness by the Canadian federal government in its defense of a lawsuit challenging the ban on direct-to-consumer advertising of prescription drugs in Canada. Paul Grootendorst has provided expert testimony on behalf of both generic and branded drug companies and has received financial and in-kind research support from pharmaceutical companies.

Authors' contributions

Steve Morgan contributed to the review protocol, screening and abstraction of citations, and analysis of results; he drafted the initial manuscript. Paul Grootendorst and Joel Lexchin contributed to the review protocol, abstraction of citations, analysis of results, and revision of the manuscript. Colleen Cunningham contributed to the review protocol, screening citations, analysis of results, and revision of the manuscript. Devon Greyson conducted the literature searches and contributed to the review protocol, analysis of results, and revision of the manuscript.

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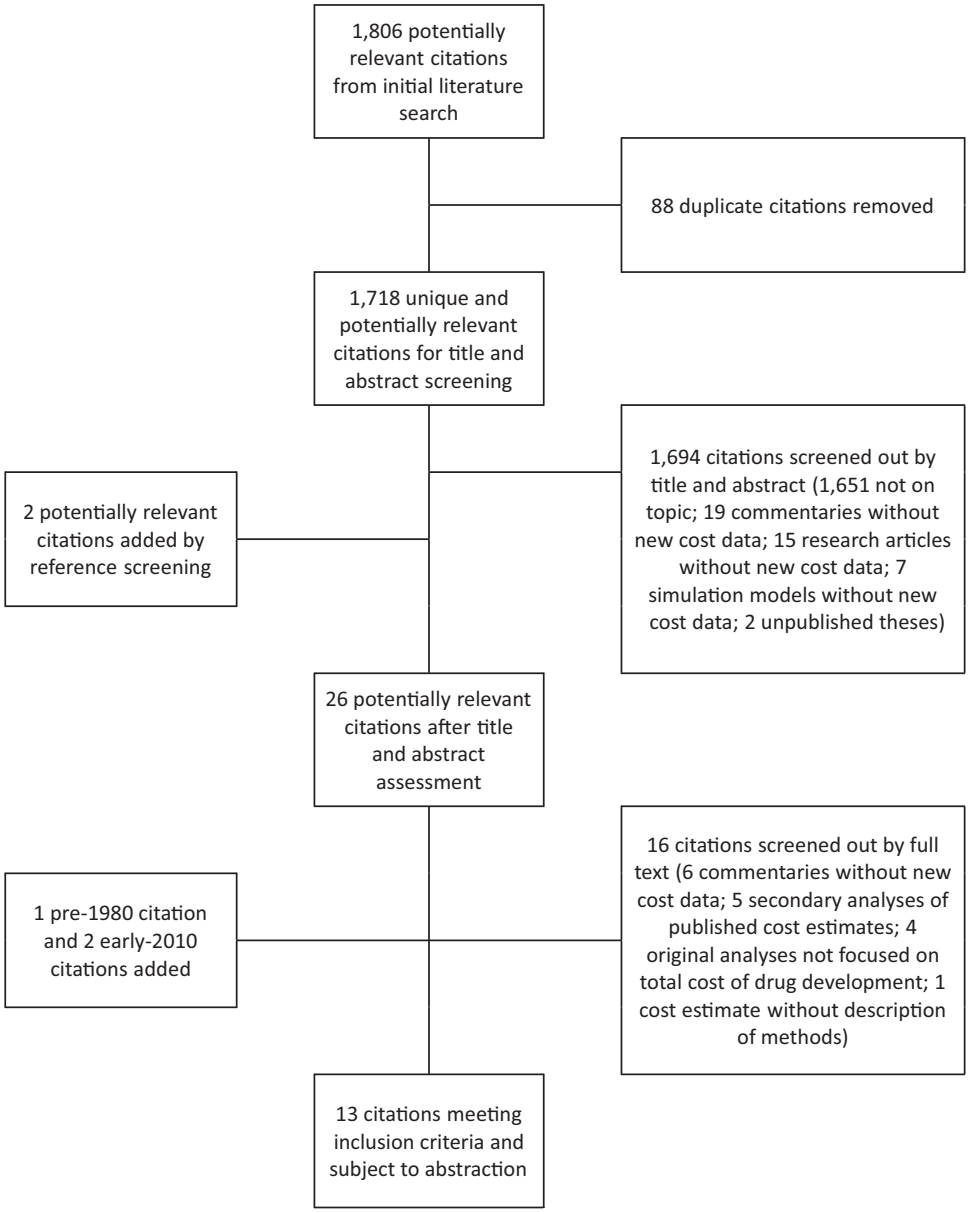
Appendix A.

Database searches.

EconLit (*EBSCO*)
Search date: 19th January 2010
Results: 207
S1 ((((ZW "pharmaceutical")) or ((ZW "pharmaceuticals"))) or ((ZW "pharmaceuticals, r&d, patents, prizes, innovation"))) or ((ZW "drug market") or (ZW "drug patents."))
S2 "drug development"
S3 Costs
S4 (Costs) and (S1 or S2)
S5 ((Costs) and (S1 or S2)) and (S3 and S4)
International Pharmaceutical Abstracts (*IPA*) (*OvidSP*)
Search date: 19th January 2010
Results: 133
1. R&D.mp.
2. Drug development.mp.
3. Costs.mp.
4. 1 or 2
5. 3 and 4
6. limit 5 to (English language and yr = "1980–2009")
MEDLINE (*1950 to Present with Daily Update*) (*OvidSP*)
Search date: 19th January 2010
Results: 764
1. *Drug Industry/ec [Economics]
2. *Drug Evaluation, Preclinical/ec [Economics]
3. Drug Approval/ec [Economics]
4. *Drug Costs/
5. *Costs/ and Cost Analysis/sn [Statistics & Numerical Data]
6. Technology, Pharmaceutical/ec [Economics]
7. Drugs, Investigational/ec [Economics]
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. (Costs and Cost Analysis).mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier]
10. *Capital Expenditures/sn [Statistics & Numerical Data]
11. *Pharmaceutical Preparations/
12. Drug development.mp.
13. 9 or 10
14. 11 or 12
15. 13 and 14
16. 8 and 13
17. 8 and 14
18. 15 or 16 or 17
19. Cost of developing a new drug.m_titl.
20. Drug development cost.m_titl.
21. Drug development costs.m_titl.
22. 19 or 20 or 21
23. 18 or 22
24. Limit 23 to (english language and yr="1980 - 2009")
25. *Limit 24 to* (*case reports or classical article or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or "corrected and republished article" or evaluation studies or journal article or letter or meta analysis or multicenter study or randomized controlled trial or "review" or technical report or validation studies*)
26. 22 not 25
27. From 24 keep 1–764
Public Affairs Information Service (*PAIS*) *International and PAIS Archive* (*CSA*)
Search date: 21st January 2010
Results: 94 published articles
(DE = (("Pharmaceutical industry") or "Drugs" or ("Pharmaceutical research" PR "Drugs – Costs")) and DE = (("Research and development") or ("Research and development – Costs"))) or DE = (("Pharmaceutical research – Economic aspects") or ("Pharmaceutical industry – Costs") or ("Pharmaceutical research – Finance" OR "Pharmaceutical research – Costs"))
ProQuest Dissertations and Theses
Search date: 19th January 2010
Results: 52
("drug development" OR "drug R&D" OR "pharmaceutical R&D") AND (costs OR "capital expenditure")
Web of Science/Knowledge
Search date: 19th January 2010
Results: 547
Topic = ("drug development" OR "Drug R&D" OR "pharmaceutical R&D") AND Topic = (cost*)
Refined by: Document Type = (ARTICLE OR REVIEW) AND Languages = (ENGLISH)
Time span = 1980–2009
Databases = SCI-EXPANDED, SSCI, A&HCI.
Worldwide Political Science Abstracts (*CSA*)
Search date: 21st January 2010
Results: 9
DE = Medications and DE = (Research and Development)

Appendix B.

Diagram of article selection.



Appendix C.

Summary of studies containing original estimates of the cost of drug development.

	Hansen and Chien [1]	Wiggins [4]	DiMasi [5]
Discovery type and time period	Sample of unspecified number of firm-originated compounds first tested in humans from 1963 to 1975 by an undisclosed sample of firms	All types of new pharmaceutical compounds developed between 1970 and 1985	Sample of 93 firm-originated compounds first tested in humans from 1970 to 1982 by an undisclosed sample of firms
Data source	Confidential survey	Annual survey of the PMA, US FDA, and Hansen (1971)	Confidential survey and proprietary database at the CSDD
Possible to replicate?	No	Yes	No
Key assumptions			
Total success rate estimated	12.0%		23.0%
Cost of capital used	8.0%	8.0%	9.0%
Cash estimate (*2009 USD$-millions*)			
Pre-clinical	$46		$111.0
Clinical	$46		$81.5
Total	$92	$113.4	$192.5
Capitalized (*2009 USD$-millions*)			
Pre-clinical	$89		$263.7
Clinical	$73		$127.5
Total	$161	$218.2	$391.2
	DiMasi et al. [22]	DiMasi et al. [22]	DiMasi et al. [22]
Discovery type and time period	Anti-infective subsample of the compounds in DiMasi 1991, which contained 93 firm-originated compounds first tested in humans from 1970 to 1982 by an undisclosed sample of firms	Cardiovascular subsample of the compounds in DiMasi 1991, which contained 93 firm-originated compounds first tested in humans from 1970 to 1982 by an undisclosed sample of firms	Neuropharmacological subsample of the compounds in DiMasi 1991, which contained 93 firm-originated compounds first tested in humans from 1970 to 1982 by an undisclosed sample of firms
Data source	Confidential survey and proprietary database at the CSDD	Confidential survey and proprietary database at the CSDD	Confidential survey and proprietary database at the CSDD
Possible to replicate?	No	No	No
Key assumptions			
Total success rate estimated	30.2%	26.2%	20.3%
Cost of capital used	9.0%	9.0%	9.0%
Cash estimate (*2009 USD$-millions*)			
Pre-clinical			
Clinical	$68.7	$87.2	$85.7
Total			
Capitalized (*2009 USD$-millions*)			
Pre-clinical			
Clinical	$98.2	$137.4	$144.5
Total			
	DiMasi et al. [22]	DiMasi et al. [7]	DiMasi et al. [7]
Discovery type and time period	NSAID subsample of the compounds in DiMasi 1991, which contained 93 firm-originated compounds first tested in humans from 1970 to 1982 by an undisclosed sample of firms	Small-firm originating subsample of the compounds in DiMasi 1991, which contained 93 firm-originated compounds first tested in humans from 1970 to 1982 by an undisclosed sample of firms	Medium-firm originating subsample of the compounds in DiMasi 1991, which contained 93 firm-originated compounds first tested in humans from 1970 to 1982 by an undisclosed sample of firms
Data source	Confidential survey and proprietary database at the CSDD	Confidential survey and proprietary database at the CSDD	Confidential survey and proprietary database at the CSDD
Possible to replicate?	No	No	No
Key assumptions			
Total success rate estimated	22.2%	23.8%	17.4%
Cost of capital used	9.0%	9.0%	9.0%
Cash estimate (*2009 USD$-millions*)			
Pre-clinical		$183.6	$118.7
Clinical	$139.6	$67.6	$119.8
Total		$251.2	$238.4
Capitalized (*2009 USD$-millions*)			
Pre-clinical		$466.3	$279.0
Clinical	$228.6	$114.2	$190.5
Total		$580.5	$469.4

Appendix C (*Continued*)

	DiMasi et al. [7]	DiMasi et al. [8]	DiMasi et al. [9]
Discovery type and time period	Large-firm originating subsample of the compounds in DiMasi 1991, which contained 93 firm-originated compounds first tested in humans from 1970 to 1982 by an undisclosed sample of firms	Sample of 68 firm-originated compounds first tested in humans from 1983 to 1994 by an undisclosed sample of firms	CNS-subsample of DiMasi 2003, which contained 68 firm-originated compounds first tested in humans from 1983 to 1994 by an undisclosed sample of firms
Data source	Confidential survey and proprietary database at the CSDD	Confidential survey and proprietary database at the CSDD	Confidential survey and proprietary database at the CSDD
Possible to replicate?	No	No	No
Key assumptions			
Total success rate estimated	27.9%	21.5%	
Cost of capital used	9.0%	11.0%	
Cash estimate (*2009 USD$-millions*)			
Pre-clinical	$118.8	$149.8	
Clinical	$83.6	$349.0	$337.9
Total	$202.4	$498.8	
Capitalized (*2009 USD$-millions*)			
Pre-clinical	$264.7	$414.6	
Clinical	$123.6	$578.0	$574.3
Total	$388.2	$992.6	

	DiMasi et al. [9]	DiMasi et al. [9]	DiMasi et al. [9]
Discovery type and time period	Anti-infective-subsample of DiMasi 2003, which contained 68 firm-originated compounds first tested in humans from 1983 to 1994 by an undisclosed sample of firms	Cardiovascular-subsample of DiMasi 2003, which contained 68 firm-originated compounds first tested in humans from 1983 to 1994 by an undisclosed sample of firms	Analgesic/anaesthetic-subsample of DiMasi 2003, which contained 68 firm-originated compounds first tested in humans from 1983 to 1994 by an undisclosed sample of firms
Data source	Confidential survey and proprietary database at the CSDD	Confidential survey and proprietary database at the CSDD	Confidential survey and proprietary database at the CSDD
Possible to replicate?	No	No	No
Key assumptions			
Total success rate estimated			
Cost of capital used			
Cash estimate (*2009 USD$-millions*)			
Pre-clinical			
Clinical	$448.0	$342.8	$311.9
Total			
Capitalized (*2009 USD$-millions*)			
Pre-clinical			
Clinical	$608.9	$569.3	$464.1
Total			

	DiMasi and Grabowski [10]	DiMasi and Grabowski [10]	Young and Surrusco [11]
Discovery type and time period	13 therapeutic recombinant proteins and monoclonal antibodies (mAbs) first entering clinical trials from 1990 to 2003 and 4 biotech compounds first entering clinical trials from 1983 to 1994	Traditional pharmaceutical drugs developed during period comparable to biological drugs studied (see column to left)	All drug approvals by the US FDA from 1990 to 2000
Data source	Confidential data from biotech firm and CSDD data	"Time-adjusted" costing data from DiMasi et al. [8]	R&D data from PhRMA reports and drug approval data from the US FDA.
Possible to replicate?	No	No	Yes
Key assumptions			
Total success rate estimated	30.2%	21.5%	
Cost of capital used	11.5%	11.5%	9.0%
Cash estimate (*2009 USD$-millions*)			
Pre-clinical	$217.3	$164.7	
Clinical	$396.3	$573.0	
Total	$613.6	$737.7	$206.7
Capitalized (*2009 USD$-millions*)			
Pre-clinical	$675.1	$481.9	
Clinical	$687.2	$964.9	
Total	$1362.2	$1446.8	$422.0

Appendix C (*Continued*)

	Global Alliance for TB Drug Development [12]	Global Alliance for TB Drug Development [12]	Adams and Brantner [13]
Discovery type and time period	"Low cost" scenario based on prospective estimate of the cost of developing a TB treatment, including the cost of failures (circa 2000)	"High cost" scenario based on prospective estimate of the cost of developing a TB treatment, including the cost of failures (circa 2000)	A sample of 3181 drugs that went into development between 1989 and 2002
Data source	A variety of sources, including a survey of contract research organizations	A variety of sources, including a survey of contract research organizations	Pharmaprojects database, and cost-per-phase estimates from DiMasi (2003)
Possible to replicate?	Requires access to survey results	Requires access to survey results	Requires access to proprietary datasets
Key assumptions			
Total success rate estimated			24.0%
Cost of capital used			11.0%
Cash estimate (*2009 USD$-millions*)			
Pre-clinical			$164.6
Clinical			$383.7
Total			$548.3
Capitalized (*2009 USD$-millions*)			
Pre-clinical	$48.4	$151.3	$471.5
Clinical	$92.0	$139.2	$602.7
Total	$139.2	$290.6	$1074.3
	Adams* and Brantner [13]	Adams* and Brantner [13]	Adams* and Brantner [13]
Discovery type and time period	A sample of antiparasitic drugs developed between 1989 and 2002	A sample of respiratory drugs developed between 1989 and 2002	A sample of drugs developed by "Firm E" between 1989 and 2002
Data source	Pharmaprojects database, and cost-per-phase estimates from DiMasi (2003)	Pharmaprojects database, and cost-per-phase estimates from DiMasi (2003)	Pharmaprojects database, and cost-per-phase estimates from DiMasi (2003)
Possible to replicate?	Requires access to proprietary datasets	Requires access to proprietary datasets	Requires access to proprietary datasets
Key assumptions			
Total success rate estimated	53.0%	70.0%	58.0%
Cost of capital used	11.0%	11.0%	11.0%
Cash estimate (*2009 USD$-millions*)			
Pre-clinical			
Clinical			
Total			
Capitalized (*2009 USD$-millions*)			
Pre-clinical			
Clinical			
Total	$561.9	$1403.5	$644.8
	Adams* and Brantner [13]	Adams and Brantner [2]	Paul et al. [3]
Discovery type and time period	A sample of drugs developed by "Firm C" between 1989 and 2002	A sample of 2245 drugs that were under development from 1989 to 2001	An unspecified sample of products developed over past 15 years by Eli Lilly and undisclosed firms participating in the Pharmaceutical Benchmarking Forum
Data source	Pharmaprojects database, and cost-per-phase estimates from DiMasi (2003)	Pharmaprojects database, and data that Danzon [15] compiled from CompuStat and Global Vantage	Eli Lilly and Company, and KMR Group "Pharmaceutical Benchmarking Forum"
Possible to replicate?	Requires access to proprietary datasets	Requires access to proprietary datasets	No
Key assumptions			
Total success rate estimated	70.0%	25.6%	11.7%
Cost of capital used	11.0%	11.0%	11.0%
Cash estimate (*2009 USD$-millions*)			
Pre-clinical			$284.4
Clinical		$507.4	$599.2
Total			$883.6
Capitalized (*2009 USD$-millions*)			
Pre-clinical			$834.0
Clinical			$965.6
Total	$2622.5	$1534.8	$1799.6

* Adams and Brantner published estimates for several drug classes and firms; data provided here are the highest and lowest estimates of these sub-analyses.

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