Research Synthesis: Costs of Pharmaceutical R&D

v1.0 researched and written by Marcela Vieira, edited by Suerie Moon, last updated January 2020

Introduction

The literature on costs for product research and development (R&D) in the pharmaceutical sector is considerable*. The vast majority of the literature focuses on development costs (clinical stage), with less information available on research costs (discovery and pre-clinical stage). Almost all studies are related to new drugs, with scarce data available for other types of medical products and devices. And almost all data are from pharmaceutical companies, with only four papers providing data from other types of organizations conducting drug development.

Search terms

Cost and research and development and pharmaceutical.
Search was conducted using a combination of search mechanisms, mainly in English, with no specific time period of publication.

Synthesis of the literature

The product development process in the health and pharmaceutical sector is characterized as complex, lengthy and costly. R&D costs influence decisions and policy options about how to best incentivize innovation to meet health needs and how to make end products available at affordable prices. This research synthesis focuses on the cost aspect of the process[1]. R&D costs estimations for the development of new drugs range widely, from $43.4 million to $4.2 billion. Estimations are usually from preclinical stage to market approval and most do not include post approval costs, or costs for the discovery stage, although estimates for these are available in the literature. The majority of the studies provide figures for out-of-pocket costs and for capitalized costs (cost of capital/opportunity costs/time costs), which constitutes from 14-51% of total costs depending on the capitalization rate, timeframes and methodology adopted. Table 1 provides a summary of the studies.

There is a variety of methods and data sources (many confidential) used in the studies, which can explain the wide range of cost estimates. The type of expenses that are included as R&D costs can also vary and are not always explicitly mentioned in the calculations (such as costs of failures, expenses related to marketing of the product or tax deductions). A deep analysis of the

[1] There is a separate research synthesis on R&D timeframes and attrition/success rates.

studies is beyond the scope of this research synthesis, which aims to provide an overview of the topic and highlight key findings from the range of studies, including variables that can affect R&D costs and main drivers.

Most of the studies focus on the development of new drugs ("new molecular entities" or "new chemical entities") by large pharmaceutical companies, and exclude cost to develop variations of existing drugs (such as combinations or reformulations). Some provide information on product development by non-commercial actors, but there is a need for further studies on this. There is also a need for more information about costs related to the development of other health technologies beyond drugs.

Summary of the contents

This research synthesis is organized by the following topics:

1) Estimations of R&D costs
    - New drugs – overall
    - New drugs by therapeutic area
    - New drugs by company size
    - Non-commercial product developers
    - Other types of health products
2) Drivers of R&D costs
3) Returns on R&D

Table 1. Summary of recent estimates of new drug development costs (in millions of USD)

Paper	Period	Sample size	Capitalized/ rate	Preclinical	Phase I	Phase II	Phase III	Approval	Post-approval/ Phase IV	Total per drug / (year) dollars	Percentage of capital cost in total
Paul et. al. (2010)	2007	1 pharmaceutical company (Eli Lilly)	No	$ 62	$ 128	$ 185	$ 235	$ 44	-	$ 873 [1] (2008)	51%
			Yes, 11%	$ 150	$ 273	$ 319	$314	$ 48	-	$ 1,778[1] (2008)	
Mestre-Ferrandiz et al. (2012) [2]	In clinical development between 1998-2002	97 projects							-	$ 899 (2011)	40%
			Yes, 11%	$207.4	$468.1	$501.6	$293.8	$34.9	-	$ 1,506 (2011)	
PricewaterhouseCoopers (2012)	2007-2011	308 new drugs approved by the FDA from 2002-2011	Not specified	-	-	-	-	-	-	$ 4,200	-
	2002-2006			-	-	-	-	-	-	$ 2,800	
DiMasi et al. (2016)	Compounds first test in human from 1995-2007 and R&D expenditures from 1990–2013	106 new drugs from 10 multinational biopharmaceutical companies of varying sizes	No	$430	$25.3	$58.6	$255.4	-	$466	$ 1,861 (2013)	35%
					$ 965 [3]						
			Yes, 10.5%	$1,098	$49.6	$95.3	$314	-	$312	$ 2,870 (2013)	
					$ 1,460 [3]						
Prasad et. al. (2017)	Drugs approved between 2006-2015	10 cancer drugs from 10 companies, mostly small	No	-	-	-	-	-	-	$ 648 (2017)	14%
			Yes, 7%	-	-	-	-	-	-	$ 757 (2017)	

ABOUT US

The Knowledge Network on Innovation and Access to Medicines is a project of the Global Health Centre at the Graduate Institute, Geneva. The project seeks to maximize the contributions of research and analysis to producing public health needs-driven innovation and globally-equitable access to medicines.

CONTACT

globalhealthresearch@graduateinstitute.ch

Jayasundara et. al. (2019)	Drugs approved between 2000-2015	100 new orphan drugs and / 602 trials (only NMEs)	No	-	$ 137.12			-	-	(2013)	43%
			Yes, 10.5%	-	$ 242.46			-	-	(2013)	
		100 non-orphan drugs / 561 trials (only NMEs)	No	-	$ 340.30			-	-	(2013)	30%
			Yes, 10.5%	-	$ 488.88			-	-	(2013)	
Deloitte (2019)	R&D expenditures occurred in 2019	183 products from 12 largest pharmaceutical companies (original cohort)	Not specified	-	-	-	-	-	-	$ 1,981 (2019)	-
		30 products from 4 mid-to-large specialized pharmaceutical companies (extension cohort)		-	-	-	-	-	-	$ 2,422 (2019)	-
DNDi (2019)	2003-2019	2 new chemical entities	No	-	-	-	-	-	-	$ 67.2 – 212.8 (4)	-

(1) Total costs in Paul et al. also includes discovery costs not included in the table for space limitation. Costs are breakdown in (out-of-pocket / capitalized): Target-to-hit: $24 / $94; Hit-to-lead: $49 / $166, and Lead optimization: $146 / $414.
(2) Mestre-Ferrandiz et al. does not use the standard division of the R&D into phases, but instead use the following intervals: Interval 1. Pre-first toxicity dose, Interval 2. First toxicity dose to first human dose, Interval 3. First human dose to first patient dose, Interval 4. First patient dose to first pivotal dose, Interval 5. First pivotal dose to first core submission, Interval 6. First core submission to first core launch. For the purpose of this table, we considered interval 1 as preclinical, intervals 2 + 3 as phase I, interval 4 as phase II, interval 5 as phase III and interval 6 as approval.
(3) Estimated total costs across phases of clinical development are not the mere addition of costs incurred in each phase and an explanation is not clearly provided.
(4) The total is adjusted for attrition rates to include cost of failures. The full document presents out-of-pocket expenses per phase of development and type of drug. Original figure in euros (EUR 60-190 million); exchange rate: 1.12.

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1) Estimations of R&D costs

New drugs – overall

- Literature reviews

We identified two studies that reviewed the literature on R&D costs for drug development, one published in 2011 and the other in 2012, and one focusing on the costs of clinical trials published in 2018.

Mestre-Ferrandiz et al. (2012), in a study published by the United Kingdom Office of Health Economics (OHE), identified 10 studies with estimates of R&D costs for new drugs conducted by industry[2], concluding that the available literature shows *"an increase in [average, capitalized] costs from £125 million (USD 199 million) per new medicine in the 1970s to £1.2 billion (USD 1.9 billion) in the 2000s"*. Figures are in 2011 dollars.

Morgan et al. (2011) reviewed 13 articles containing original estimates of the cost of drug development published from 1980 to 2009. They found estimates ranging from USD$92 million cash (USD$161 million capitalized) to USD$883.6 million cash (USD$1.8 billion capitalized), expressed in 2009 dollars. The authors suggested that differences in methods, data sources, and time periods explain some of the variation in estimates. They highlight that lack of transparency limits many studies, especially as *"confidential information provided by unnamed companies about unspecified products forms all or part of the data underlying 10 of the 13 studies"* and concluded that *"despite three decades of research in this area, no published estimate of the cost of developing a drug can be considered a gold standard".*

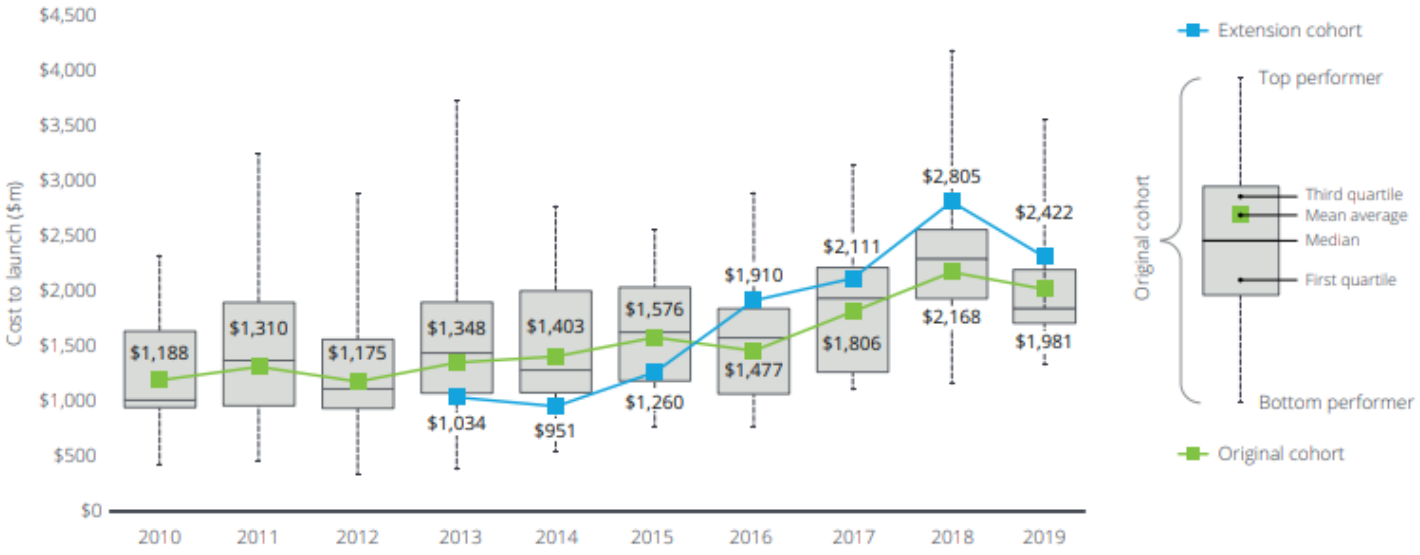
Speich et al. (2018a) conducted a systematic review on costs of randomized clinical trials (RCTs), the most expensive stage of drug development. They found 56 articles, none of which provided empirical cost data for all aspects of a trial, but provided information on several aspects of the trial, such as cost data of different development phases, recruitment costs or site-specific costs, or aggregated overall costs. Results show that *"the median costs per recruited patient were USD 409 (range: USD 41–6,990)"* and overall costs ranged from USD 0.2–611.5 million per RCT. All cost data are in 2017 dollars. The authors highlight that the studies use different methodologies, and that 75% of the articles did not provide detailed information on the methodology and underlying data used in the calculations.

[2] The author notes that *"some papers have estimated the cost of developing new drugs under the auspices of what have become known as "product-development partnerships" (PDPs), especially for neglected diseases. The discussion of these estimates is beyond the scope of this publication"* (p.8).

- Original calculations

Deloitte Center for Health Solutions have published over the past 10 years annual reports on pharmaceutical R&D. The last report (Deloitte, 2019), estimates the average R&D costs to develop a new drug at USD 1,981 million for the original cohort and USD 2,422 million for the extension cohort, inclusive of costs of failures. The original cohort is composed of 12 largest biopharmaceutical companies (ranked by R&D expenditures in 2009) and the extension cohort is comprised of 4 *"mid-to-large, more specialized companies"* (not specified). The 2019 report also provides an overview of the estimations from the previous reports summarized in the figure below. The estimation is calculated based on total R&D spending by the cohort companies, which in 2019 amounted to USD 79 billion, and the total of assets in late-stage pipeline (defined as *"assets that are filed, in Phase III or Phase II with breakthrough therapy designation as of 30th April each year"*), which included, in 2019, 183 products for the original cohort and 30 for the extension cohort. In 2019, that included 43% of small molecule drugs (down from 67% in 2010), 37% of antibody therapies (up from 15% in 2010) and 20% of other modalities, including cell and gene therapies, protein-based therapies, vaccines and synthetic peptides (proportion stable over the years). The costs are collected from *"publicly available information from audited annual reports or readily available from third-party data providers"* and includes costs from discovery to launch. The methodology used to calculate average R&D cost per product is not specified in detail, and it is unclear whether total costs are out-of-pocket or capitalized, or if they have been adjusted for inflation.

Figure 6. Average R&D cost to develop a compound from discovery to launch, 2010-19 – original and extension cohorts



Source: Deloitte Center for Health Solutions, 2019, p. 13.

DiMasi and co-authors at the Tufts Center conducted a series of studies to estimate private sector R&D costs of drugs. The latest study published in 2016 (DiMasi et al., 2016) estimated the average (mean) pre-tax out-of-pocket cost to be USD$1,395 million (2013 dollars) and USD$2,558 million (2013 dollars) after capitalization at 10.5%. Time costs (or opportunity costs) accounts for 45% of total costs. Breaking down the total costs between preclinical and clinical stages, the estimated preclinical out-of-pocket costs are $430 million and $1,098 million capitalized and for clinical stage out-of-pocket costs are $965 million and $1,460 million capitalized. Therefore, preclinical costs were estimated to represent 32% of total out-of-pocket costs and 42% of total capitalized costs. The study also provides an estimate of post-approval R&D costs at USD$312 million after capitalization, which would increase the cost estimate to USD$2,870 million (2013 dollars) if included. The calculation includes costs related to compounds abandoned during the development process (cost of failures). The calculation does not consider public subsidies or tax deductions/credits tied to R&D expenditures, which would reduce net R&D costs for a company. The estimations were based on a confidential survey through which 10 multinational pharmaceutical companies (not named) of varying sizes self-reported information on R&D costs of 106 new drugs, out of which 19 were biologics (the drugs are not specified). Full R&D costs were not provided for all of the 106 drugs, and the sample size per phase included 78 drugs for preclinical, 97 for phase I, 78 for phase II and 42 for phase III. The sample included self-originated compounds with first test in human anywhere in the world from 1995-2007 and development costs occurred through 2013, including preclinical stage from the point of compound syntheses/isolation until market approval (therefore not including pre-synthesis discovery costs). It is noted that the clinical costs estimations include not only clinical trial costs per se, but also *"R&D costs not directly related to the trials that were incurred during the phase, such as those for long-term animal testing, chemistry, manufacturing and controls (CMC), and company R&D overhead".* It is also noted that total cost estimations are inclusive of "*non-molecule related costs required to run an R&D organization".*

Using similar methodology, in the 2003 study, DiMasi et al. (2003) investigated the costs related to 68 new drugs using self-reported data from 10 multinational pharmaceutical firms. The sample drugs entered clinical development stage anywhere in the world between 1983 and 1994 and development costs were included until 2000. The authors estimated the mean pre-tax pre-approval out-of-pocket cost per new drug in USD$ 403 million (2000 dollars) or USD$ 802 million (2000 dollars), after capitalization at 11%, including the costs of failures. In the 1991 study, the same group of authors (DiMasi etal., 1991) estimated the R&D costs of 93 new chemical entities (including costs of failures) using self-reported data from a survey of 12 US-owned pharmaceutical companies. The selected drugs initiated clinical trials between 1970 and 1982. The estimated pre-tax out-of-pocket cost was USD$114 million (1987 dollars) and US$231 million (1987 dollars) when capitalized at 9%.

Light and Warburton (2011) analyzed the R&D costs estimated by DiMasi et al. (2003) and argued that the costs were inflated to support industry-claims of high risks and costs involved in the development process used to justify high prices of medicines. They formulate several critiques

to the methodology used in the DiMasi study, such as inflated trial costs, exaggerated time for each development phase and capitalization of costs at a high rate. The authors adjust the data to account for those factors and suggest that actual R&D costs might be much lower. There are several estimations adjusted for different factors, with the lowest being median net out-of-pocket costs of USD$43.4 million per new drug (including 50% tax reductions), 18 times lower than the figure in the analyzed study (USD$802 million).

Mestre-Ferrandiz et al. (2012), beyond reviewing the available literature on R&D costs, also presented a new estimative at USD 1,506 million (in 2011 dollars, capitalization at 11%). Out-of-pocket costs were calculated at USD 899 million (2011 dollars). The calculation was *"based on previously unpublished information collected by CMRI in confidential surveys"*[3]. Costs were estimated based on reported R&D expenditures of the companies included in the surveys and the 97 projects in development from 1997-2002.

PricewaterhouseCoopers (2012), calculated the average R&D costs of new drugs to be USD 4.2 billion per molecule in the period 2007-2011 and USD 2.8 billion from 2002-2006. The calculation was based on the total number of new drugs (including biologics) approved by the FDA from 2002-2011, which amounts to 308, and how much the pharmaceutical industry invested in R&D in the same period, totaling USD 1.1 trillion. Estimates seems to be out-of-pocket costs, not capitalized and not adjusted to inflation, but the methodology is not clear in the study. They also reported average industry R&D expenditures to be distributed as following: 7.1% for target selection/validation; 21.5% for screening/lead optimization; 9.2% for proof of mechanism/phase I; 17.4% for proof of concept/phase II; 39.8% for phase III and 5% for approval.

Adams and Brantner (2010) calculated expenditures related to the clinical stage of development of new drugs using publicly available data from 183 publicly traded companies in the pharmaceutical industry in the US in a 12-year period (1989–2001). They estimated that average costs for the clinical stage was USD$27 million per year, being USD$17 million for Phase I trials, USD$34 million for Phase II and USD$27 million for Phase III, which multiplied by average phase durations results in estimates of $24 million, $86 million, and $61 million for Phases I, II, and III, respectively. The authors concluded that their estimated costs were higher than suggested in previous studies. The same authors also conducted a similar study in 2006 (Adams and Brantner, 2006), estimating total clinical stage costs at a range of USD$500 million to USD$ 2 billion per drug, depending on the therapeutic class and on the company. Figures from both studies are in 2000 dollars and capitalized at 11%.

Paul et al. (2010) estimated R&D costs of new drug development, from preclinical (target-to-hit) to launch, based on assumptions of success rates, timeframes and costs per phase based on industry benchmarks and cost data from Eli Lilly and Company. The total out-of-pocket cost to

[3] Definition provided at the glossary of the study (p. 79), "CMRI: CMRI, acquired by Thomson Reuters in 2006, began researching issues in R&D in the early 1980s as the Centre for Medicines Research (CMR). It maintains various databases of drugs/biologics and biopharmaceutical industry activities."

launch one NME is estimated at USD 873 million, and capitalized cost at USD 1,778 million (at 11%). See Table 1 for costs per phase. The authors note that the estimate does not include discovery research, post-launch expenses or overheads.

Public Citizen (2001) conducted an analysis drawing on publicly available US Securities and Exchange Commission (SEC) R&D filings for all major pharmaceutical firms and calculated R&D costs, after-tax deductions, to be from USD 57 million to USD 71 million for the average new drug brought to market in the 1990s, including failures. Pre-tax estimations were calculated to be an average of USD 163 million per new drug approved. The calculations are based on PhRMA data for R&D spending (USD 139.8 billon in the 1990s) and the number of NMEs approved by the US FDA in the period (857). Figures are in 2000 dollars.

The US Congress Office of Technology Assessment – OTA (1993) calculated that *"the average aftertax R&D cash outlay for each new drug that reached the market in the 1980s was about $65 million (in 1990 dollars)"*. And *"the full aftertax cost of these outlays, compounded to their value on the day of market approval, was roughly $194 million (1990 dollars)"*. The study estimated that tax savings and credits reduced out-of-pocket costs by nearly 50 per cent.

The literature review conducted by Mestre-Ferrandiz et al. (2012) also included information on two studies that investigated R&D cost in the period from 1960s to 1980s and updated their estimations to 2011 prices. According to the review, Wiggins[4], in a study published in 1987, investigated the period from 1970-1985 and calculated the development costs of a new drug to be of USD 226m (fully capitalized) (in 2011 prices). The calculation was based on the total number of new molecular entities (NMEs) approved by FDA in the period and an estimation of R&D spending on new drug development in previous years at industry level. Hansen[5], in a study published in 1979, analyzed project-specific data on 67 products that entered clinical testing between 1963 and 1975 and were approved for marketing starting around 1970. Hansen estimated the cost to be US$199m (in 2011 dollars).

Focusing on the preclinical stage, Horvath (2010) estimated the costs of development for small molecule drugs and biologics. The estimations were based on a simulation of preclinical studies costs conducted by the author in 2004. Preclinical studies necessary to obtain the IND – Investigational New Drug Application for small molecule drugs were estimated to last 10 months and cost USD 1.2 million, including manufacturing costs estimated at USD 40,000. For biologics, they were estimated to last 17 months and cost USD 2.6 million, including USD 1.6 million cost to manufacture the material. The author also provides calculations for preclinical studies necessary to support each phase of clinical development up to registration. Total supporting preclinical

[4] Wiggins SN. The cost of developing a new drug. Washington, DC: Pharmaceutical Manufacturers Association; 1987. Apud Mestre-Ferrandiz et al. 2012.
[5] Hansen, R.W. (1979) The pharmaceutical development process: Estimates of current development costs and times and the effects of regulatory changes. In: R.I. Chien (ed.) Issues in Pharmaceutical Economics. Lexington, MA: Lexington Books, pp. 151–187. Apud Mestre-Ferrandiz et al. 2012.

studies were estimated to require 73 months and cost USD 7 million for drugs and 47 months and USD 6.3 million for biologics.

New drugs by therapeutic area

The literature shows that the costs to develop a new medicine can vary significantly according to the therapeutic area. The above-mentioned literature review conducted by Mestre-Ferrandiz et al. (2012) looked into costs by therapeutic area and concluded that the most expensive are neurology, respiratory and oncology, and the less expensive are anti-parasitics and drugs to treat HIV/AIDS due to differences in success rates and development times.

Sertkaya et al. (2014), in a report prepared by Eastern Research Group, Inc. for the US Department of Health and Human Services, used *"aggregate data from three proprietary databases on clinical trial costs provided by Medidata Solutions",* to estimate the costs of each phase of the clinical stage of drug development for 13 different therapeutic area. Costs include only information from industry-sponsored trials conducted in the US. A summary of the estimations is available in the figure below. The authors conclude that *"the therapeutic area with the highest average per-study costs across Phases I, II and III is pain and anesthesia ($71.3 million) followed by ophthalmology ($49.9 million) and anti-infective ($41.3 million) trials. Conversely, trials in dermatology, endocrinology, and gastroenterology have the lowest overall costs across the same three phases".* They also looked at costs for Phase IV studies, usually not included in R&D costs estimations, and concluded that *"average Phase IV study costs are equivalent to those of Phase III costs but are much more variable across different therapeutic areas than Phase III costs".* Costs are capitalized at 15%. Beyond per-study costs, Sertkaya et al. (2014) also provide estimations of costs for several components grouped into per-study costs, per-patient costs, and per-site costs, adding additional costs for site overhead (estimated at 25% of per-study costs) and all other additional costs not captured by those categories (estimated at additional 30% of all the costs combined).

Table 1: Total Per-Study Costs (in $ Millions), by Phase and Therapeutic Area [a] [b]

Therapeutic Area	Phase 1	Phase 2	Phase 3	*Phase 1, 2, & 3 Subtotal [d]*	FDA NDA/BLA Review Phase [c]	Phase 4	Total [d]
Anti-Infective	$4.2 (5)	$14.2 (6)	$22.8 (5)	*$41.2 (3)*	$2.0	$11.0 (12)	**$54.2 (10)**
Cardiovascular	$2.2 (9)	$7.0 (13)	$25.2 (3)	*$34.4 (10)*	$2.0	$27.8 (4)	**$64.1 (6)**
Central Nervous System	$3.9 (6)	$13.9 (7)	$19.2 (7)	*$37.0 (6)*	$2.0	$14.1 (11)	**$53.1 (11)**
Dermatology	$1.8 (10)	$8.9 (12)	$11.5 (13)	*$22.2 (13)*	$2.0	$25.2 (7)	**$49.3 (12)**
Endocrine	$1.4 (12)	$12.1 (10)	$17.0 (9)	*$30.5 (12)*	$2.0	$26.7 (6)	**$59.1 (7)**
Gastrointestinal	$2.4 (8)	$15.8 (4)	$14.5 (11)	*$32.7 (11)*	$2.0	$21.8 (8)	**$56.4 (8)**
Genitourinary System	$3.1 (7)	$14.6 (5)	$17.5 (8)	*$35.2 (8)*	$2.0	$6.8 (13)	**$44.0 (13)**
Hematology	$1.7 (11)	$19.6 (1)	$15.0 (10)	*$36.3 (7)*	$2.0	$27.0 (5)	**$65.2 (5)**
Immunomodulation	$6.6 (1)	$16.0 (3)	$11.9 (12)	*$34.5 (9)*	$2.0	$19.8 (9)	**$56.2 (9)**
Oncology	$4.5 (4)	$11.2 (11)	$22.1 (6)	*$37.8 (5)*	$2.0	$38.9 (2)	**$78.6 (3)**
Ophthalmology	$5.3 (2)	$13.8 (8)	$30.7 (2)	*$49.8 (2)*	$2.0	$17.6 (10)	**$69.4 (4)**
Pain and Anesthesia	$1.4 (13)	$17.0 (2)	$52.9 (1)	*$71.3 (1)*	$2.0	$32.1 (3)	**$105.4 (2)**
Respiratory System	$5.2 (3)	$12.2 (9)	$23.1 (4)	*$40.5 (4)*	$2.0	$72.9 (1)	**$115.3 (1)**

[a] The numbers in parentheses represent the rank in descending order.
[b] The cost for each phase assumes that a single trial (i.e., study) is conducted.
[c] The category represents the New Drug Application (NDA)/Biologic License Application (BLA) filing fee for an application requiring clinical data and does not include any establishment or product fees that the filing entity might need to pay in addition.
[d] Totals may not add up due to rounding.

Source: Sertkaya et al., 2014, p. 3-3.

The study by Adams and Brantner (2010) presents estimates of expenditures on drug development according to their therapeutic categories. Their findings show that cardiovascular, dermatological, genitourinary, anticancer and neurological drugs are all above average and that biotech drugs are below average. They also highlighted that new formulations of existing drugs have substantially smaller expenditure than the average. In their 2006 study (Adams and Brantner, 2006), the same authors suggested that variation in R&D costs by therapeutic class might be due to differences in success rates and length of trials, and not on actual spending.

Prasad and Mailankody (2017) examined the R&D costs to bring 10 cancer drugs to market and revenues after approval, using data from 10 companies' filings to the US Securities and Exchange Commission. The selection criteria were drugs developed by companies that had no other product in the market, therefore, mostly small companies. The estimation included all R&D costs reported by the companies, therefore inclusive of costs of other compounds that did not reach regulatory approval (cost of failures). The authors found that the median time to develop a drug was 7.3 years (range, 5.8-15.2 years) and estimated the median out-of-pocket cost of development at USD$648.0 million (range, USD$157.3 million to USD$1,950.8 million). If capitalized for a 7% opportunity costs, median cost was USD$757.4 million (range, USD$203.6 million to USD$2,601.7 million). The authors concluded that the estimated cost to develop a

cancer drug of USD$648.0 million is significantly lower than prior estimates (from USD$320.0 million to USD$2.7 billion). Figures are in 2017 dollars.

Jayasundara et al. (2019) investigated the differences in clinical trial costs to develop orphan drugs and non-orphan drugs. They randomly selected 100 new orphan drugs and 100 non-orphan drugs approved by the US FDA between 2000 and 2015 (new indications, new formulations, new manufactures and new dosage forms of already marketed drugs were excluded). They used the clinicaltrials.org database to identify all clinical trials, numbers of patient enrolled and trial duration for each development phase (phase I to III), amounting to a total of 1,163 trials (602 for orphan drugs and 561 for non-orphan drugs). The costs were calculated based on per-trial cost averages reported at PhRMA 2015 for non-orphan drugs and at EvaluatePharma 2015 for orphan drugs, and adjusted to probability of success based on DiMasi 2016, to include the cost of failures. They found that *"the out-of-pocket clinical costs per approved orphan drug to be $166 million and $291 million (2013 USD) per non-orphan drug. The capitalized clinical costs per approved orphan drug and non-orphan drug were estimated to be $291 million and $412 million respectively".* They also conducted a separate analysis only for new molecular entities (NMEs), which represents 54 out of the 100 non-orphan drugs and 74 of the 100 orphan drugs. This resulted in an *"estimated capitalized cost per approved non-orphan NME was $489 million and the capitalized cost per approved orphan NME was $242 million"*, meaning that the costs to develop orphan drugs are about 50% lower than non-orphan drugs, despite high prices of orphan drugs being attributed to the high cost of drug development. Figures are in 2013 dollars and capitalization was at 10.5% rate.

The above-mentioned paper by Dimasi et al. (2016) provided cost information per clinical phase of development broken-down between small molecules and large molecules (biologics). Out of the 106 drugs included in the study, 19 were large molecules and 87 small molecules. Mean costs for phase I, were USD 23.93 million for large molecules and USD 25.53 million for small molecules; for phase II, USD 91.86 million for large molecules and USD 50.40 million for small molecules; for phase III, USD 281.13 million for large molecules and USD 245.80 for small molecules. After adjusting for approval success rates, which were much higher for large molecules (28.9% compared to 9.3%), clinical costs for the development of small molecules were 44.5% higher than for large molecules.

DiMasi et al. (2016) also found that average development costs are lower for priority drugs, as rated by the US FDA, than for standard drugs. Out-of-pocket costs for clinical stage per approved compound were USD 554 million for standard-rated and USD 385 for priority-rated compounds, while capitalized costs were USD 782 million and USD 489 million respectively. The authors suggests that while priority-rated compounds would tend to be costlier for breaking more new scientific ground, standard-rate compounds usually requires large trials to demonstrate superiority or non-inferiority to similar compounds already in the market. The authors conclude that *"our results can be viewed as supportive, but not conclusive, evidence of higher costs for drug with lower therapeutic significance ratings"*.

DiMasi and Grabowski (2007) estimated the costs of developing biologic drugs by biotech companies, focusing specifically on recombinant proteins and monoclonal antibodies [mAbs], and compared to the costs of developing small-molecule drugs by traditional pharmaceutical companies. They found average out-of-pocket cost estimates per approved biopharmaceutical to be of USD 559 million, separated in USD 198 million for the preclinical stage and USD 361 million for the clinical stage. After capitalization, the average costs amount to a total of USD 1,241 million, being USD 615 million for preclinical and USD 626 for clinical development. They concluded that total out-of-pocket cost per approved biopharmaceutical was lower than for the traditional pharmaceutical companies (USD 559 million vs USD 672 million) and that capitalized cost was nearly the same (USD$1,241 million versus USD$1,318 million). After adjusting for approval success rates (higher for large molecules), the authors concluded that clinical costs per approved compound were 44.6% higher for small molecules than for large molecules, while total development costs were similar for the two types of drugs. Figures are in 2007 dollars.

DiMasi et al. (2004) conducted a study breaking down R&D costs data for the clinical stage of development from 68 drugs (inclusive of failures) into four therapeutic classes. Data was provided by 10 large pharmaceutical companies. All figures are expressed in 2000 US dollars. Overall average of out-of-pocket cost was estimated to be $282 million. The costs related to anti-infective drugs were considerably above average ($362 million) and analgesic/anesthetic drugs were modestly below average ($252 million), while for cardiovascular ($277 million) and CNS - central nervous system ($273 million) the costs were close to the overall average. Considering capitalized costs, the overall average was $466 million, costs were slightly lower for CNS ($464 million) and for cardiovascular ($460 million) drugs, significantly lower for analgesic/anesthetic drugs ($375 million) and higher for anti-infective drugs ($492 million). The same study also estimated worldwide sales for all new drugs approved in the United States from 1990 to 1994 over a 20-year period, using data from IMS Health. The mean net values of sales were $2,434 million for all drugs, $1,080 million for analgesic/anesthetic drugs, $2,199 million for anti-infective drugs, $3,668 million for cardiovascular drugs, and $4,177 million for CNS drugs. The authors concluded that the sales did not correlate well with average development costs, but *"the results are still consistent with a model of firm behavior that posits that R&D efforts will generally shift toward high net return, and away from low net return, therapeutic areas".*

In a similar study published in 1995, the same group of authors (DiMasi et al., 1995a) found that the overall mean capitalized costs per approved NCE including the cost of failures were USD$93 million, being USD$70 million for anti-infective drugs, USD$98 million for cardiovascular, USD$103 million for neuropharmacological and USD$163 million for anti-inflammatory drugs. If costs of unsuccessful projects were excluded, then the mean costs ranged from USD$7.1 million (for topical steroids) to USD$66.7 million (for cardiovascular) (all in 1993 US dollars). The authors highlighted that "phase attrition and approval rates are the most important sources of variability in total clinical period costs between therapeutic categories". In relation to sales, the authors concluded that "development cost estimates by therapeutic category did not correlate strongly with US sales in the fifth year of marketing", mentioning that cardiovascular drugs had revenues

much higher than average, while having on-average development costs, while nonsteroidal anti-inflammatory drugs had average revenues, but much higher than average development costs.

New drugs by company size

The size of the company conducting the development process is also appointed as a factor that can affect the costs of R&D. The above-mentioned report by Deloitte Center for Health Solutions (2014), concluded that *"the larger the company, by revenue or R&D spend, the greater the cost to develop each asset and the lower the returns."* The literature review conducted by Mestre-Ferrandiz et al. (2012) concluded that *"results of research on the impact of firm size on R&D productivity and R&D costs are mixed. The evidence from the 1990s and early- to mid-2000s seems to suggest that size matters: multiple tangible and intangible assets are associated with fully integrated organisations, where core capacities can be important across diseases. It remains unclear, however, whether R&D productivity is greater for smaller companies than for traditional "big pharma"".*

Adams and Brantner (2006) also explored the relationship between company size and R&D costs. The authors note that "it has been argued that larger companies have economies of scale and scope in drug development that might be associated with lower development costs". They explained that this might be related to the method used to classify the company "when an ex post measure of size (Top 10 by 2001 income) is used, the average drug from a large firm has a cost much lower than the overall average. However, when ex ante measures of size are used, the cost of the average drug from a large firm is larger than the cost for the overall average drug". Their findings showed that "drugs from firms that had the largest number of drugs in development had an average capitalized cost of $992 million—some $124 million more than the average drug". Therefore, they conclude that the "results do not support the claim that larger firms tend to produce lower-cost drugs", contrasting with previous work that found that drugs from small firms tend to have higher costs than drugs from larger firms.

DiMasi et al. (1995b) analyzed the relationship between R&D costs and the company size, using self-reported data from 12 US pharmaceutical companies. The companies were grouped into three groups according to their sales level. The authors concluded that *"the R&D cost per new drug approved in the US is shown to decrease with firm size, while sales per new drug approved are shown to increase markedly with firm size".*

Non-commercial product developers

DNDi – Drug for Neglected Diseases Initiative (2019), a Product Development Partnership (PDP), published an updated cost estimate to develop and register new combinations or new formulations of existing treatments for EUR 4-32 million, and a new chemical entity for EUR 60-190 million. Costs are based on their own experience of drug development since their foundation

in 2003, inclusive of costs of failures and *"do not include post-registration studies and access costs, nor in-kind contributions from pharmaceutical partners"* (it is mentioned that in-kind contributions amounted to 12.5% of DNDi total expenditures). Costs are "fully-loaded" (including management and indirect costs) out-of-pocket expenses and have not been capitalized. It is not clear if costs have been adjusted for inflation. The report also provides out-of-pocket costs for each stage of development from discovery to registration for 8 drugs: 3 "existing drugs without new formulation", 3 "existing drugs with new formulation" and 2 "new chemical entities". The costs range from EUR 0.1-22.6 million for discovery and preclinical; EUR 1.5-9.9 million for phase I; EUR 3.3-43.8 million for phase II, III and registration and totals from EUR 4-58 million. In 2014, DNDi had estimated its cost of development at EUR 6-20 million for an improved treatment and EUR 30-40 million for a new chemical. If the costs of failures are included, the cost range of an improved treatment would amount to EUR 10-40 million and EUR 100-150 million for a new chemical entity (DNDi, 2014).

The Global Alliance for Tuberculosis Drug Development (2001), a not-for-profit organization created to accelerate the discovery and development of new TB drugs, estimated the costs of successfully developing a new chemical entity to treat TB to be from USD$ 36.8 million to USD$ 39.9 million (excluding costs of failure). This estimation covers preclinical development ($4.9 million to $5.3 million), pharmaceutical development (at least $5.3 million), and Phases I through III of clinical development ($26.6 million). Including the costs of unsuccessful projects, the estimates of the costs of developing an NCE are from USD$ 76 million to USD$ 115 million. These estimates do not include the costs of discovery, which are estimated to range from USD$ 40 million to USD$ 125 million (including the costs of failure), leading to estimated costs of discovering and developing a new anti-TB drug (including the costs of failure) of between USD$ 115 million and USD$ 240 million.

Speich et al. (2018b) provided a retrospective assessment of costs related to two randomized clinical trials conducted in the academic setting. The "Prednisone Trial" (community-acquired pneumonia) was conducted at seven centers in Switzerland from 2009 to 2015 and involved a total of 802 patients for a total time of 59 months. The "Oxantel Trial" (intestinal worms) was conducted within a collaboration of researchers from Switzerland and Tanzania and took place on Tanzania in 2012 involving 480 children over a period of 2 months. The overall costs for the Prednisone-Trial were calculated to be USD 2.3 million, and in the Oxantel-Trial were USD 100,000. The costs stratified by categories of the Prednisone-Trial were *"USD 231,347 (10.1%) for trial conception, planning, and preparation, USD 1,938,958 (84.2%) for patient enrollment, treatment, and follow-up, and USD 129,518 (5.6%) for the time after last patient out"*. For the Oxantel-Trial *"salary costs accounted for the largest amount of the overall costs (i.e., USD 84,447; 84.1%). Costs for the trial conception, planning, and preparation phase were USD 26,437 (26.3%), USD 45,016 (44.8%) for patient enrollment, treatment, and follow-up, and USD 28,537 (28.4%) for the after last patient out phase"*. Costs seen to be out-of-pocket costs, therefore not capitalized, and not adjusted to inflation.

Other types of health products

Light et al. (2009) estimated R&D costs for two new rotavirus vaccines [RotaTeq (Merck) and Rotarix (GlaxoSmithKline or GSK)] based on publicly available information from 5 sources - the U.S. Patent and Trademark Office, the U.S. SEC EDGAR database, Medline, periodicals, and corporate websites – and complemented by interviews with senior informants. They estimated out-of-pocket cost for Phase I trials at $66,000–$264,000 for Merck and $37,600–$150,400 for GSK; Phase II trials at $0.9 million–$1.2 million for Merck and $1.8 million–$2.4 million for GSK, and Phase III trials at $136.1 to $204.1 million for Merck, and $126.4 to $189.7 million for GSK. Total clinical trial costs were estimated at $137–$206 million for Merck and $128–$192 million for GSK. The authors also estimated "manufacturing capital costs" and which resulted in total costs from $137- $539 million for Merck's RotaTeq, and $128-$392 million for GSK's Rotarix. After adjusting for inflation and capitalization at 3%, total R&D costs were estimated at $205-$644 million for Merck and $172 -$551 for GSK. All figures are expressed in 2008 USD.

Gunn et al. (2019) provided estimations of R&D costs for vaccine development at the European Vaccine Initiative (EVI), a not-for-profit organization that supports the development of vaccines against diseases of poverty and emerging infectious diseases. Preclinical stage costs for 3 vaccine candidates were estimated at EUR 2,483,333 and phase I costs were estimated at EUR 1,500,000. The type of costs included in the estimation and the period in which the costs were incurred are not specified.

Odevall et al. (2018) estimated the R&D costs to develop a cholera vaccine (euvichol) through a global public-private partnership between the International Vaccine Institute (IVI) and Eubiologics. They estimated that it took *"6 years and 10 months, and a total cost of approximately 19.7 million USD (including all costs for IVI and Eubiologics)".* The paper was published in 2018, but it is not clear if costs were adjusted for inflation and seen to include only out-of-pocket costs.

Terry et al. (2018) developed a modeling tool to estimate the costs of launching new health products called the Portfolio-To-Impact (P2I) Model. The model is based on assumptions for costs, timeframes and attrition rates for each phase of development from late preclinical stage to phase III clinical trials. The assumptions were based on Parexel's R&D cost sourcebook and refined by interviews *"with a wide variety of stakeholders from Product Development Partnerships, biopharmaceutical and diagnostic companies, and major funders of global health R&D".* The model has different assumptions for different types of products, called "archetypes", including vaccines, new chemical entities, repurposed drugs, biologics and diagnostics. The P2I Model was further refined by Young et al. (2018). A summary of the cost assumptions per each archetype as per version 2 of the P2I Model is provided in the figure below.

Archetype	Cost per phase ($, millions)			
	Preclinical	Phase 1	Phase 2	Phase 3
Simple vaccine	6.7	2.2	13.2	201.0
Complex vaccine	16.6	2.5	13.9	223.0
Unprecedented vaccine	16.6	2.5	13.9	223.0
Simple NCE	5.0	2.2	5.8	32.8
Simple NCE for TB	5.0	2.2	5.8	32.8
Complex NCE	10.0	7.4	6.4	36.1
Simple repurposed drug	5.0	2.2	5.8	17.6
Complex repurposed drug	5.0	2.2	5.8	17.6
Simple biologic	6.7	2.2	13.2	122.0
Simple biologic for TB	6.7	2.2	13.2	122.0
Complex biologic	16.6	2.5	13.9	126.0
	Concept and Research	Feasibility and Planning	Design and Development	Clinical Validation and Launch Readiness
Diagnostic, assay development	1.5	1.5	2.0	3.5
Diagnostic, simple platform development	1.5	1.5	100.0	3.5
Other products	1.2	1.2	1.1	2.6

Sources of data:
P2I model assumptions | McKinsey RAP | Bill & Melinda Gates Foundation

Source: Young et al., 2018, p. 8.

2) Drivers of R&D costs

Sertkaya et al. (2014) also analyzed the main factors impacting the costs of R&D. They conclude that *"the factors that contribute the most to costs across all trial phases include Clinical Procedure Costs (15 to 22 percent), Administrative Staff Costs (11 to 29 percent), Site Monitoring Costs (nine to 14 percent), Site Retention Costs (nine to 16 percent), and Central Laboratory Costs (four to 12 percent)".*

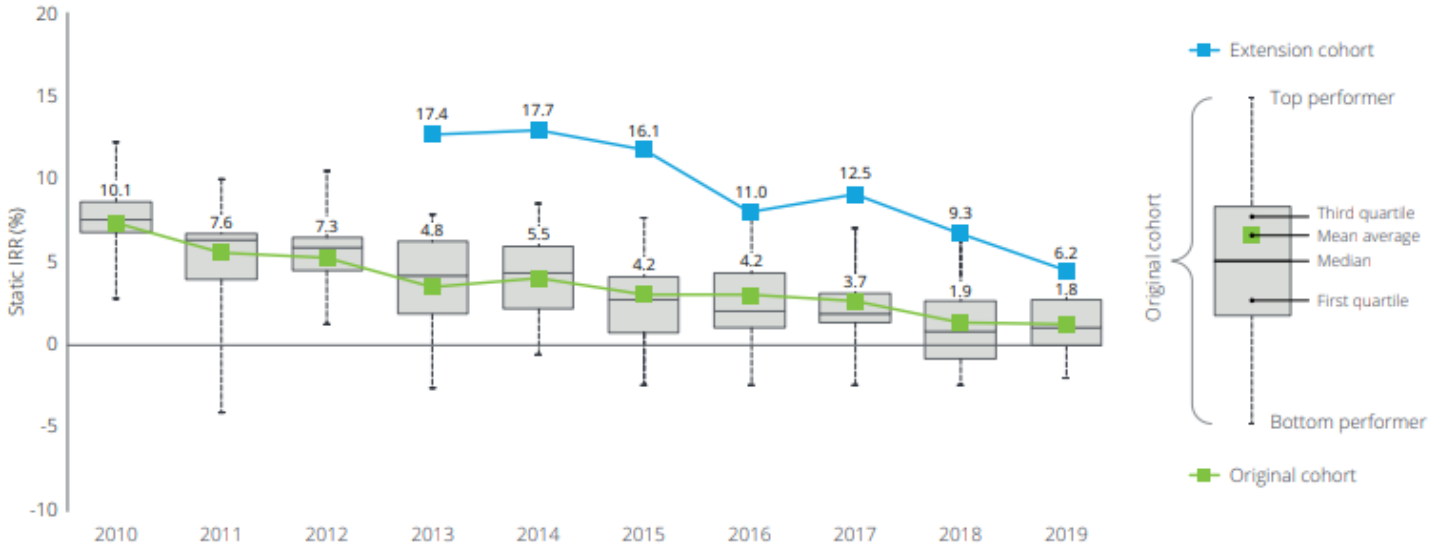
The literature review conducted by Mestre-Ferrandiz et al. (2012) has a section dedicated to main drivers of R&D costs. The study highlights that differences in success rates and development

time drive the costs up or down and also has an effected in the cost of capital. In what related to out-of-pocket costs, the main element *"is the cost of clinical trials, which is affected by the cost per patient and the number of patients required to collect sufficient data."* The review suggested that clinical trial costs had increased over time, due to increased complexity. To reduce costs, a few changes in the development process occurred, such as outsourcing to clinical research organizations (CROs) and location trials emerging economies (Africa, Asia, Eastern Europe, Latin America and the Middle East), which can reduce costs "*both because local costs are lower and because patient recruitment may be faster."* The author highlights, however, that "*although more clinical trials are being conducted in emerging markets, especially Phase III trials, the majority of clinical trials still are conducted in the US and Western Europe, for reasons related to regulatory conditions, relevant expertise and infrastructure."* Technological challenges are also appointed as a factor driving costs up, as targeted diseases are more complex than the ones target before and "personalized/stratified medicine" have more narrow patient population.

3) Returns on R&D

Some studies have compared the revenues obtained by the selling of the drugs to their estimated R&D costs. The above-mentioned series of report on pharmaceutical R&D conducted by Deloitte Center for Health Solutions also calculates the rate of return on R&D. The last 2019 report (Deloitte, 2019) estimates the average internal rate of return (IRR) for the largest pharmaceutical companies (original cohort) to be 1.8% in 2019, down from 10.1% in 2010. For the mid-to-large companies included in the extension cohort, they estimate returns at 6.2% in 2019, down from 17.4% in 2015. They highlight lower return rates are mainly due to *"assets terminations"*. The figure below summarizes the estimated return rates from the reports published in the last decade.

Figure 2. Return on late-stage pipeline, 2010-19 – original and extension cohorts



Source: Deloitte Center for Health Solutions, 2019, p. 09.

Tay-Teo et al. (2019) investigated the return on R&D investments for cancer drugs by comparing incomes from sales to estimated R&D costs. Data from sales was extracted from public financial reports of "originator" pharmaceutical companies (defined as *"companies that held patents or marketing rights"*). The initial dataset included all cancer drugs approved by US FDA from 1989-2017, a total of 156, out of which 99 had enough data to be included in the analysis. The authors found that *"compared with the total risk-adjusted R&D cost of $794 million (range, $2827-$219 million) per medicine estimated in the literature, by the end of 2017, the median cumulative sales income was $14.50 (range, $3.30-$55.10) per dollar invested for R&D. Median time to fully recover the maximum possible risk-adjusted cost of R&D ($2827 million) was 5 years (range, 2-10 years; n = 56)"*. Figures are expressed in 2017 US dollars and were adjusted for inflation. They conclude that *"cancer drugs, through high prices, have generated returns for the originator companies far in excess of possible R&D costs"*.

Prasad and Mailankody (2017), in their above-mentioned paper investigating the R&D costs of cancer drugs, also calculated the total revenue from sales of the 10 drugs since approval to be USD$67.0 billion compared with total R&D spending of USD$9.1 billion (including 7% opportunity costs). The authors concluded that the revenue since approval is substantially higher than the R&D costs.

The report by the US Congress Office of Technology Assessment – OTA (1993) also calculated the average return in investment and concluded that *"each new drug introduced to the U.S. market between 1981 and 1983 returned, net of taxes, at least $36 million more to its investors than was needed to pay off the R&D investment. This surplus return amounts to about 4.3 percent of the price of each drug over its product life"*.

Research gaps

- More transparency on underlying data used to estimate R&D costs
- More information on the impact of tax credits and regulatory incentives that might reduce net costs of R&D borne by product developer
- More studies on R&D costs from not-for-profit product development organizations (e.g. public institutions, academia and product development partnerships)
- Studies targeted for specific informational needs, i.e. studies responding to the analytical needs of company executives or investors may not adequately respond to the needs of policymakers, buyers, or the public.
- Costs estimations for the development of other health products beyond drugs (e.g. vaccines, diagnostics, other medical devices)

Cited papers with abstracts

Adams, Christopher P., and Van V. Brantner. 2006. "Estimating The Cost Of New Drug Development: Is It Really $802 Million?" *Health Affairs* 25 (2): 420–28. https://doi.org/10.1377/hlthaff.25.2.420.
Abstract: This paper replicates the drug development cost estimates of Joseph DiMasi and colleagues ("The Price of Innovation"), using their published cost estimates along with information on success rates and durations from a publicly available data set For drugs entering human clinical trials for the first time between 1989 and 2002, the paper estimated the cost per new drug to be 868 million dollars. However, our estimates vary from around 500 million dollars to more than 2,000 million dollars, depending on the therapy or the developing firm.

Adams, Christopher Paul, and Van Vu Brantner. 2010. "Spending on New Drug Development." *Health Economics* 19 (2): 130–41. https://doi.org/10.1002/hec.1454.
Abstract: 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.

Deloitte Centre for Health Solutions. 2019. "Ten Years on Measuring the Return from Pharmaceutical Innovation 2019." https://www2.deloitte.com/content/dam/Deloitte/uk/Documents/life-sciences-health-care/deloitte-uk-ten-years-on-measuring-return-on-pharma-innovation-report-2019.pdf.
Abstract: Not available.

DiMasi, Joseph A, Ronald W Hansen, Henry G Grabowski, and Louis Lasagna. 1991. "Cost of Innovation in the Pharmaceutical Industry." *Journal of Health Economics* 10 (2): 107–42. https://doi.org/10.1016/0167-6296(91)90001-4.
Abstract: The research and development costs of 93 randomly selected new chemical entities (NCEs) were obtained from a survey of 12 U.S.-owned pharmaceutical firms. These data were used to estimate the pre-tax average cost of new drug development. The costs of abandoned NCEs were linked to the costs of NCEs that obtained marketing approval. For base case

parameter values, the estimated out-of-pocket cost per approved NCE is $114 million (1987 dollars). Capitalizing out-of-pocket costs to the point of marketing approval at a 9% discount rate yielded an average cost estimate of $231 million (1987 dollars).

DiMasi, Joseph A., Ronald W. Hansen, Henry G. Grabowski, and Louis Lasagna. 1995a. "Research and Development Costs for New Drugs by Therapeutic Category: A Study of the US Pharmaceutical Industry." *PharmacoEconomics* 7 (2): 152–69. https://doi.org/10.2165/00019053-199507020-00007.
Abstract: The clinical period (i.e. clinical trial and long term animal testing) development costs of a random sample of new chemical entities (NCEs) were examined for differences in average cost. All of the NCEs studied were first tested in humans between 1970 and 1982, and were classified for the purposes of the study by therapeutic class. The costs of unsuccessful projects were included with those of projects that resulted in US marketing approval. Including income forgone from expending funds before returns are earned ('time costs'), the capitalised (i.e. out-of-pocket plus time) clinical period costs per approved NCE were $US70, $US98, $US103 and $US163 million (1993 dollars) for anti-infective, cardiovascular, neuropharmacological and nonsteroidal anti-inflammatory drugs, respectively. Combining the data for all therapeutic categories, the mean clinical period cost per approved NCE was $US93 million. Omitting costs associated with unsuccessful projects, the mean capitalised clinical period costs for approved NCEs ranged from $US7.1 million (for topical steroids) to $US66.7 million (for cardiovascular agents) [1993 dollars]. The estimates of total clinical period costs per approved NCE depend on average out-of-pocket clinical phase costs, attrition rates across phases (i.e. the rates at which compounds drop out of active testing), the probability of marketing approval, and development and regulatory review times. Phase attrition and approval rates are the most important sources of variability in total clinical period costs between therapeutic categories. Development cost estimates by therapeutic category did not correlate strongly with US sales in the fifth year of marketing. Cardiovascular NCEs had much higher than average sales revenues, but clinical development costs for these drugs were only slightly above average. Conversely, nonsteroidal anti-inflammatory drugs attained average sales revenues, but had much higher than average development costs.

Dimasi, Joseph A., Henry G. Grabowski, and John Vernon. 1995b. "R&D Costs, Innovative Output and Firm Size in the Pharmaceutical Industry." *International Journal of the Economics of Business* 2 (2): 201–19. https://doi.org/10.1080/758519309.
Abstract: This study examines the relationships between firm size, R&D costs and output in the pharmaceutical industry. Project–level data from a survey of 12 US–owned pharmaceutical firms on drug development costs, development phase lengths and failure rates are used to determine estimates of the R&D cost of new drug development by firm size. Firms in the sample are grouped into three size categories, according to their pharmaceutical sales at the beginning of the study period. The R&D cost per new drug approved in the US is shown to decrease with firm size, while sales per new drug approved are shown to increase markedly with firm size. Sales distributions are highly skewed and suggest that firms need to search for blockbuster drugs

with above average returns. The results are consistent with substantial economies of scale in pharmaceutical R&D, particularly at the discovery and preclinical development phases.

DiMasi, Joseph A, Ronald W Hansen, and Henry G Grabowski. 2003. "The Price of Innovation: New Estimates of Drug Development Costs." Journal of Health Economics 22 (2): 151–85. https://doi.org/10.1016/S0167-6296(02)00126-1.
Abstract: The research and development costs of 68 randomly selected new drugs were obtained from a survey of 10 pharmaceutical firms. These data were used to estimate the average pre-tax cost of new drug development. The costs of compounds abandoned during testing were linked to the costs of compounds that obtained marketing approval. The estimated average out-of-pocket cost per new drug is US$ 403 million (2000 dollars). Capitalizing out-of-pocket costs to the point of marketing approval at a real discount rate of 11% yields a total pre-approval cost estimate of US$ 802 million (2000 dollars). When compared to the results of an earlier study with a similar methodology, total capitalized costs were shown to have increased at an annual rate of 7.4% above general price inflation.

DiMasi, Joseph A., Henry G. Grabowski, and John Vernon. 2004. "R&D Costs and Returns by Therapeutic Category." *Drug Information Journal* 38 (3): 211–23. https://doi.org/10.1177/009286150403800301.
Abstract: Objectives: This study examines the degree to which therapeutic class accounts for variability in drug development costs. It also scrutinizes how sales levels vary across the associated therapeutic classes for those drugs that have reached the marketplace. Data and Methods: A stratified random sample of 68 investigational drugs that first entered clinical testing anywhere in the world from 1983 to 1994 was selected from the pipelines of 10 pharmaceutical firms. Clinical period cost data were obtained for these compounds by phase. The sample consisted both of drugs that failed in testing and drugs that obtained marketing approval. We grouped the drugs by therapeutic category. Clinical period costs per approved new drug (inclusive of failures) were obtained for the analgesic/anesthetic, antiinfective, cardiovascular, and central nervous system (CNS) therapeutic classes. Worldwide sales profiles for new drugs approved in the United States from 1990 to 1994 over a 20-year product life cycle were computed based on IMS Health sales data. All costs and sales were expressed in year 2000 dollars. Results: Out-of-pocket clinical period cost per approved drug (inclusive of failures) for cardiovascular ($277 million) and CNS ($273 million) drugs was close to the overall average ($282 million). However, antiinfective drug costs were considerably above average ($362 million) and analgesic/anesthetic drug costs were modestly below average ($252 million). The results were qualitatively similar when the development timelines were used to determine capitalized (out-of-pocket plus time) costs. In comparison to the overall average of $466 million, the capitalized cost per approved drug was slightly lower for CNS ($464 million) and for cardiovascular ($460 million) drugs. The capitalized costs were $375 million for analgesic/anesthetic drugs and $492 million for antiinfective drugs. The mean net present values of life cycle sales for new drugs approved in the first half of the 1990s were $2434 million, $ 1080 million, $2199 million, $3668 million, and $4177 million for all drugs, analgesic/anesthetic drugs, antiinfective drugs,

cardiovascular drugs, and CNS drugs, respectively. Conclusions: Development costs vary substantially from drug to drug. A drug's therapeutic class can explain some of that variability. The sales of new drugs by broad therapeutic category did not correlate well with average development costs. However, given the dynamic nature of pharmaceutical markets and changes over time in research and development (R&D) expenditure shares, the results are still consistent with a model of firm behavior that posits that R&D efforts will generally shift toward high net return, and away from low net return, therapeutic areas.

DiMasi, Joseph A., and Henry G. Grabowski. 2007. "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics* 28 (4–5): 469–79. https://doi.org/10.1002/mde.1360.

Abstract: The costs of developing the types of new drugs that have been pursued by traditional pharmaceutical firms have been estimated in a number of studies. However, similar analyses have not been published on the costs of developing the types of molecules on which biotech firms have focused. This study represents a first attempt to get a sense for the magnitude of the R&D costs associated with the discovery and development of new therapeutic biopharmaceuticals (specifically, recombinant proteins and monoclonal antibodies [mAbs]). We utilize drug-specific data on cash outlays, development times, and success in obtaining regulatory marketing approval to estimate the average pre-tax R&D resource cost for biopharmaceuticals up to the point of initial US marketing approval (in year 2005 dollars). We found average out-of-pocket (cash outlay) cost estimates per approved biopharmaceutical of $198 million, $361 million, and $559 million for the preclinical period, the clinical period, and in total, respectively. Including the time costs associated with biopharmaceutical R&D, we found average capitalized cost estimates per approved biopharmaceutical of $615 million, $626 million, and $1241 million for the preclinical period, the clinical period, and in total, respectively. Adjusting previously published estimates of R&D costs for traditional pharmaceutical firms by using past growth rates for pharmaceutical company costs to correspond to the more recent period to which our biopharmaceutical data apply, we found that total out-of-pocket cost per approved biopharmaceutical was somewhat lower than for the pharmaceutical company data ($559 million vs $672 million). However, estimated total capitalized cost per approved new molecule was nearly the same for biopharmaceuticals as for the adjusted pharmaceutical company data ($1241 million versus $1318 million). The results should be viewed with some caution for now given a limited number of biopharmaceutical molecules with data on cash outlays, different therapeutic class distributions for biopharmaceuticals and for pharmaceutical company drugs, and uncertainty about whether recent growth rates in pharmaceutical company costs are different from immediate past growth rates.

DiMasi, Joseph A., Henry G. Grabowski, and Ronald W. Hansen. 2016. "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs." *Journal of Health Economics* 47 (May): 20–33. https://doi.org/10.1016/j.jhealeco.2016.01.012.

Abstract: The research and development costs of 106 randomly selected new drugs were obtained from a survey of 10 pharmaceutical firms. These data were used to estimate the average pre-tax cost of new drug and biologics development. The costs of compounds

abandoned during testing were linked to the costs of compounds that obtained marketing approval. The estimated average out-of-pocket cost per approved new compound is $1395 million (2013 dollars). Capitalizing out-of-pocket costs to the point of marketing approval at a real discount rate of 10.5% yields a total pre-approval cost estimate of $2558 million (2013 dollars). When compared to the results of the previous study in this series, total capitalized costs were shown to have increased at an annual rate of 8.5% above general price inflation. Adding an estimate of post-approval R&D costs increases the cost estimate to $2870 million (2013 dollars).

DNDi. 2014. "An Innovative Approach to R&D for Neglected Patients: Ten Years of Experience and Lessons Learned by DNDi." Drugs for Neglected Diseases Initiative. http://www.dndi.org/wp-content/uploads/2009/03/DNDi_Modelpaper_2013.pdf
Abstract: Not available.

DNDi. 2019. "15 Years of Needs-Driven Innovation for Access: Key Lessons, Challenges, and Opportunities for the Future." Drugs for Neglected Diseases Initiative. https://www.dndi.org/wp-content/uploads/2019/10/DNDi_ModelPaper_2019.pdf
Abstract: Not available.

Global Alliance for TB Drug Development. 2001. "Executive Summary for the Economics of TB Drug Development." http://www.tballiance.org/downloads/publications/TBA_Economics_Report_Exec.pdf.
Abstract: Not available.

Gunn, Alexander, Shashika Bandara, Gavin Yamey, Flavia D´Alessio, Hilde Depraetere, Sophie Houard, Nicola Viebig, and Stefan Jungbluth. 2019. "Pipeline Analysis of a Vaccine Candidate Portfolio for Diseases of Poverty Using the Portfolio-To-Impact Modelling Tool." F1000Research 8 (July): 1066. https://doi.org/10.12688/f1000research.19810.1.
Abstract: Background: The Portfolio-To-Impact (P2I) P2I model is a recently developed product portfolio tool that enables users to estimate the funding needs to move a portfolio of candidate health products, such as vaccines and drugs, along the product development path from late stage preclinical to phase III clinical trials, as well as potential product launches over time. In this study we describe the use of this tool for analysing the vaccine portfolio of the European Vaccine Initiative (EVI). This portfolio includes vaccine candidates for various diseases of poverty and emerging infectious diseases at different stages of development. Methods: Portfolio analyses were conducted using the existing assumptions integrated in the P2I tool, as well as modified assumptions for costs, cycle times, and probabilities of success based on EVI's own internal data related to vaccine development. Results: According to the P2I tool, the total estimated cost to move the 18 candidates currently in the EVI portfolio along the pipeline to launch would be about US $470 million, and there would be 0.69 cumulative expected launches during the period 2019-2031. Running of the model using EVI-internal parameters resulted in a significant increase in the expected product launches. Conclusions: The P2I tool's underlying assumptions could not be tested in our study due to lack of data available. Nevertheless, we expect that the accelerated

clinical testing of vaccines (and drugs) based on the use of controlled human infection models that are increasingly available, as well as the accelerated approval by regulatory authorities that exists for example for serious conditions, will speed up product development and result in significant cost reduction. Project findings as well as potential future modifications of the P2I tool are discussed with the aim to improve the underlying methodology of the P2I model.

Horvath, Christopher. 2010. "Comparison of Preclinical Development Programs for Small Molecules (Drugs/Pharmaceuticals) and Large Molecules (Biologics/Biopharmaceuticals): Studies, Timing, Materials, and Costs." In *Pharmaceutical Sciences Encyclopedia*, by Shayne Cox Gad, pse166. Hoboken, NJ, USA: John Wiley & Sons, Inc. https://doi.org/10.1002/9780470571224.pse166.
Abstract: Successful and efficient development of a new pharmaceutical requires the planning of an integrated development program that coordinates the trilogy of product manufacture—chemistry, manufacturing, and controls (CMC), preclinical studies (distribution, metabolism, and pharmacokinetic [DMPK], pharmacology and toxicology), and clinical trials—within the framework of the regulatory development strategy. Preclinical safety studies must support each successive phase of clinical development, as well as any significant changes to the method(s) of manufacturing, formulating, or administering the pharmaceutical. This article aims to compare the studies, materials, and costs associated with hypothetical preclinical development programs intended to support the clinical development of a small molecule (drug) and a large molecule (biologic).

Jayasundara, Kavisha, Aidan Hollis, Murray Krahn, Muhammad Mamdani, Jeffrey S. Hoch, and Paul Grootendorst. 2019. "Estimating the Clinical Cost of Drug Development for Orphan versus Non-Orphan Drugs." Orphanet Journal of Rare Diseases 14 (1): 12. https://doi.org/10.1186/s13023-018-0990-4.
Abstract: Background: High orphan drug prices have gained the attention of payers and policy makers. These prices may reflect the need to recoup the cost of drug development from a small patient pool. However, estimates of the cost of orphan drug development are sparse. Methods: Using publicly available data, we estimated the differences in trial characteristics and clinical development costs with 100 orphan and 100 non-orphan drugs. Results: We found that the out-of-pocket clinical costs per approved orphan drug to be $166 million and $291 million (2013 USD) per non-orphan drug. The capitalized clinical costs per approved orphan drug and non-orphan drug were estimated to be $291 million and $412 million respectively. When focusing on new molecular entities only, we found that the capitalized clinical cost per approved orphan drug was half that of a non-orphan drug. Conclusions: More discussion is needed to better align on which cost components should be included in research and development costs for pharmaceuticals.

Light, Donald W, and Rebecca Warburton. 2011. "Demythologizing the High Costs of Pharmaceutical Research." *BioSocieties* 6 (1): 34–50. https://doi.org/10.1057/biosoc.2010.40.

Abstract: It is widely claimed that research to discover and develop new pharmaceuticals entails high costs and high risks. High research and development (R&D) costs influence many decisions and policy discussions about how to reduce global health disparities, how much companies can afford to discount prices for lower- and middle-income countries, and how to design innovative incentives to advance research on diseases of the poor. High estimated costs also affect strategies for getting new medicines to the world's poor, such as the advanced market commitment, which built high estimates into its inflated size and prices. This article takes apart the most detailed and authoritative study of R&D costs in order to show how high estimates have been constructed by industry-supported economists, and to show how much lower actual costs may be. Besides serving as an object lesson in the construction of 'facts', this analysis provides reason to believe that R&D costs need not be such an insuperable obstacle to the development of better medicines. The deeper problem is that current incentives reward companies to develop mainly new medicines of little advantage and compete for market share at high prices, rather than to develop clinically superior medicines with public funding so that prices could be much lower and risks to companies lower as well.

Light, Donald W., Jon Kim Andrus, and Rebecca N. Warburton. 2009. "Estimated Research and Development Costs of Rotavirus Vaccines." Vaccine 27 (47): 6627–33. https://doi.org/10.1016/j.vaccine.2009.07.077.
Abstract: Diseases like rotavirus afflict both upper- and lower-income countries, but most serious illnesses and deaths occur among the latter. It is a vital public health issue that vaccines for these types of global diseases can recover research and development (R&D) costs from high-priced markets quickly so that manufacturers can offer affordable prices to lower-income nations. Cost recovery depends on how high R&D costs are, and this study attempts to replace high, unverified estimates with lower, more verifiable estimates for two new vaccines, RotaTeq (Merck) and Rotarix (GlaxoSmithKline or GSK), based on detailed searches of public information and follow-up interviews with senior informants. We also offer a new perspective on "cost of capital" as a claim for recovery from public bodies. Our estimates suggest that companies can recover all fixed costs quickly from affluent markets and thus can offer these vaccines to lower-income countries at prices they can afford. Better vaccines are a shared project between companies and public health agencies; greater transparency and consistency in reporting of R&D costs is needed so that fair prices can be established.

Mestre-Ferrandiz, Jorge, Jon Sussex, A Towse. "The R&D Cost of a New Medicine". Office of Health Economics, London. 2012. https://www.ohe.org/publications/rd-cost-new-medicine.
Summary: The cost of R&D for a successful new medicine has been an important policy issue at least since the 1960s. Cost estimates matter not just because of intellectual curiosity or for industry understanding of its performance, but because they are a key aspect of the international debate about the reasonableness of pharmaceutical prices and the magnitude of the long-term investments involved. This publication reviews research published over the last three decades, which shows an increase in costs from £125 million ($199 million) per new medicine in the 1970s to £1.2 billion ($1.9 billion) in the 2000s (both in 2011 prices). An OHE costs

analysis based on new data for 1998-2002 agrees with comparable analyses for the same time period. The study explores four major factors that are producing higher R&D costs: out-of-pocket expenses, success/failure rates, R&D times and the cost of capital. It also discusses measures companies are taking now to improve efficiency and offers a glimpse into the promise and challenges presented by the new, gene-based sciences.

Morgan, Steve, Paul Grootendorst, Joel Lexchin, Colleen Cunningham, and Devon Greyson. 2011. "The Cost of Drug Development: A Systematic Review." *Health Policy* 100 (1): 4–17. https://doi.org/10.1016/j.healthpol.2010.12.002.
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.

Odevall, Lina, Deborah Hong, Laura Digilio, Sushant Sahastrabuddhe, Vittal Mogasale, Yeongok Baik, Seukkeun Choi, Jerome H. Kim, and Julia Lynch. 2018. "The Euvichol Story – Development and Licensure of a Safe, Effective and Affordable Oral Cholera Vaccine through Global Public Private Partnerships." Vaccine 36 (45): 6606–14. https://doi.org/10.1016/j.vaccine.2018.09.026.
Abstract: Cholera, a diarrheal disease primarily affecting vulnerable populations in developing countries, is estimated to cause disease in more than 2.5 million people and kill almost 100,000 annually. An oral cholera vaccine (OCV) has been available globally since 2001; the demand for this vaccine from affected countries has however been very low, due to various factors including vaccine price and mode of administration. The low demand for the vaccine and limited commercial incentives to invest in research and development of vaccines for developing country markets has kept the global supply of OCVs down. Since 1999, the International Vaccine Institute has been committed to make safe, effective and affordable OCVs accessible. Through a variety of partnerships with collaborators in Sweden, Vietnam, India and South Korea, and with public and private funding, IVI facilitated development and production of two affordable and WHO-prequalified OCVs and together with other stakeholders accelerated the introduction of these vaccines for the global public-sector market

Paul, Steven M., Daniel S. Mytelka, Christopher T. Dunwiddie, Charles C. Persinger, Bernard H. Munos, Stacy R. Lindborg, and Aaron L. Schacht. 2010. "How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge." Nature Reviews Drug Discovery 9 (3): 203–14. https://doi.org/10.1038/nrd3078.
Abstract: The pharmaceutical industry is under growing pressure from a range of environmental issues, including major losses of revenue owing to patent expirations, increasingly cost-constrained healthcare systems and more demanding regulatory requirements. In our view, the key to tackling the challenges such issues pose to both the future viability of the pharmaceutical industry and advances in healthcare is to substantially increase the number and quality of innovative, cost-effective new medicines, without incurring unsustainable R&D costs. However, it is widely acknowledged that trends in industry R&D productivity have been moving in the opposite direction for a number of years. Here, we present a detailed analysis based on comprehensive, recent, industry-wide data to identify the relative contributions of each of the steps in the drug discovery and development process to overall R&D productivity. We then propose specific strategies that could have the most substantial impact in improving R&D productivity.

Prasad, Vinay, and Sham Mailankody. 2017. "Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval." *JAMA Internal Medicine* 177 (11): 1569. https://doi.org/10.1001/jamainternmed.2017.3601.
Abstract: Importance: A common justification for high cancer drug prices is the sizable research and development (R&D) outlay necessary to bring a drug to the US market A recent estimate of R&D spending is $2.7 billion (2017 US dollars). However, this analysis lacks transparency and independent replication. Objective: To provide a contemporary estimate of R&D spending to develop cancer drugs. Design, Setting, and Participants: Analysis of US Securities and Exchange Commission filings for drug companies with no drugs on the US market that received approval by the US Food and Drug Administration for a cancer drug from January 1, 2006, through December 31, 2015. Cumulative R&D spending was estimated from initiation of drug development activity to date of approval. Earnings were also identified from the time of approval to the present. The study was conducted from December 10, 2016, to March 2, 2017. Main Outcomes and Measures: Median R&D spending on cancer drug development. Results: Ten companies and drugs were included in this analysis. The 10 companies had a median time to develop a drug of 7.3 years (range, 5.8-15.2 years). Five drugs (50%) received accelerated approval from the US Food and Drug Administration, and 5 (50%) received regular approval. The median cost of drug development was $648.0 million (range, $157.3 million to $1950.8 million). The median cost was $757.4 million (range, $203.6 million to $2601.7 million) for a 7% per annum cost of capital (or opportunity costs) and $793.6 million (range, $219.1 million to $2827.1 million) for a 9% opportunity costs. With a median of 4.0 years (range, 0.8-8.8 years) since approval, the total revenue from sales of these 10 drugs since approval was $67.0 billion compared with total R&D spending of $7.2 billion ($9.1 billion, including 7% opportunity costs). Conclusions and Relevance: The cost to develop a cancer drug is $648.0 million, a figure significantly lower than prior estimates. The revenue since approval is substantial (median, $1658.4 million; range, $204.1

million to $22 275.0 million). This analysis provides a transparent estimate of R&D spending on cancer drugs and has implications for the current debate on drug pricing.

Public Citizen. 2001. "Rx R&D Myths: The Case Against the Drug Industry's R&D 'Scare Card.'" Washington, DC, Public Citizen's Congress Watch. https://www.citizen.org/wp-content/uploads/rdmyths.pdf.
Executive summary: This new Public Citizen report reveals how major U.S. drug companies and their Washington, D.C. lobby group, the Pharmaceutical Research and Manufacturers of America (PhRMA), have carried out a misleading campaign to scare policy makers and the public. PhRMA's central claim is that the industry needs extraordinary profits to fund expensive, risky and innovative research and development (R&D) for new drugs. If anything is done to moderate prices or profits, R&D will suffer, and, as PhRMA's president recently claimed, "it's going to harm millions of Americans who have life-threatening conditions." But this R&D scare card – or canard – is built on myths, falsehoods and misunderstandings, all of which are made possible by the drug industry's staunch refusal to open its R&D records to congressional investigators or other independent auditors. Using government studies, company filings with the U.S. Securities and Exchange Commission and documents obtained via the Freedom of Information Act, Public Citizen's report exposes the industry's R&D claims.

PwC. 2012. "From Vision to Decision - Pharma 2020." PricewaterhouseCoopers. https://www.pwc.com/gx/en/pharma-life-sciences/pharma2020/assets/pwc-pharma-success-strategies.pdf.
Abstract: Not available.

Sertkaya, A., A. Birkenbach, A. Berlind, and J. Eyraud. 2014. "Examination of Clinical Trial Costs and Barriers for Drug Development." https://aspe.hhs.gov/report/examination-clinical-trial-costs-and-barriers-drug-development.
Abstract: Pharmaceutical companies conduct clinical trials for many reasons. The most obvious goal of clinical trials is to demonstrate safety and efficacy to gain Food and Drug Administration (FDA) approval. FDA provides guidance to developers about what constitutes acceptable clinical trials and appropriate outcomes. Improving the drug development process, especially by conducting better (meaning providing more information on safety or efficacy) and faster clinical trials, can foster innovation in medical product development. The primary purposes of this study: 1) to better understand sponsors' strategies in the design and execution of clinical trials, 2) to identify factors that may delay, hinder, or lead to unsuccessfully completed trials, and 3) to develop an operational model of clinical trial decision-making to enable examination of what-if scenarios by end-users. This study models the decision-making process for a drug sponsor as a stylized decision tree that looks at the process for formulating a clinical trial from the point of view of an expected-revenue-maximizing sponsor in the face of uncertainty (or risk). The simplified clinical decision-making model incorporates the following considerations: Therapeutic area; Potential market size/revenues for the drug; Clinical stage; Success probabilities by clinical stage. In addition to identifying the costs of the clinical trials, the

following barrier mitigation strategies were analyzed: Use of electronic health records (EHR); Looser trial enrollment restrictions; Simplified clinical trial protocols and reduced amendments; Reduced source data verification (SDV); Wider use of mobile technologies, including electronic data capture (EDC); Use of lower-cost facilities or at-home testing; Priority Review/Priority Review vouchers; Improvements in FDA review process efficiency and more frequent and timely interactions with FDA. Overall, the therapeutic area with the highest clinical research burden across all phases is respiratory system ($115.3 million) followed by pain and anesthesia ($105.4 million) and oncology ($78.6 million) trials. Use of lower-cost facilities/in-home testing and wider use of mobile technologies appear to be most effective in reducing costs across therapeutic areas and trial phases. Use of lower-cost facilities and/or in-home testing can reduce per-trial costs by up to $0.8 million (16 percent) in Phase I, $4.3 million (22 percent) in Phase II, and $9.1 million (17 percent) in Phase III, depending on therapeutic area.

Speich, Benjamin, Belinda von Niederhäusern, Nadine Schur, Lars G. Hemkens, Thomas Fürst, Neera Bhatnagar, Reem Alturki, et al. 2018a. "Systematic Review on Costs and Resource Use of Randomized Clinical Trials Shows a Lack of Transparent and Comprehensive Data." Journal of Clinical Epidemiology 96 (April): 1–11. https://doi.org/10.1016/j.jclinepi.2017.12.018.
Abstract: Objectives: Randomized clinical trials (RCTs) are costly. We aimed to provide a systematic overview of the available evidence on resource use and costs for RCTs to support budget planning. Study Design and Setting: We systematically searched MEDLINE, EMBASE, and HealthSTAR from inception until November 30, 2016 without language restrictions. We included any publication reporting empirical data on resource use and costs of RCTs and categorized them depending on whether they reported (i) resource and costs of all aspects at all study stages of an RCT (including conception, planning, preparation, conduct, and all tasks after the last patient has completed the RCT); (ii) on several aspects, (iii) on a single aspect (e.g., recruitment); or (iv) on overall costs for RCTs. Median costs of different recruitment strategies were calculated. Other results (e.g., overall costs) were listed descriptively. All cost data were converted into USD 2017. Results: A total of 56 articles that reported on cost or resource use of RCTs were included. None of the articles provided empirical resource use and cost data for all aspects of an entire RCT. Eight articles presented resource use and cost data on several aspects (e.g., aggregated cost data of different drug development phases, site-specific costs, selected cost components). Thirty-five articles assessed costs of one specific aspect of an RCT (i.e., 30 on recruitment; five others). The median costs per recruited patient were USD 409 (range: USD 41–6,990). Overall costs of an RCT, as provided in 16 articles, ranged from USD 43–103,254 per patient, and USD 0.2–611.5 Mio per RCT but the methodology of gathering these overall estimates remained unclear in 12 out of 16 articles (75%). Conclusion: The usefulness of the available empirical evidence on resource use and costs of RCTs is limited. Transparent and comprehensive resource use and cost data are urgently needed to support budget planning for RCTs and help improve sustainability.

Speich, Benjamin, Belinda von Niederhäusern, Claudine Angela Blum, Jennifer Keiser, Nadine Schur, Thomas Fürst, Benjamin Kasenda, et al. 2018b. "Retrospective Assessment of Resource

Use and Costs in Two Investigator-Initiated Randomized Trials Exemplified a Comprehensive Cost Item List." Journal of Clinical Epidemiology 96 (April): 73–83. https://doi.org/10.1016/j.jclinepi.2017.12.022.
Abstract: Objectives: Randomized clinical trials (RCTs) are costly and published information on resource requirements for their conduct is limited. To identify key factors for making RCTs more sustainable, empirical data on resource use and associated costs are needed. We aimed to retrospectively assess resource use and detailed costs of two academic, investigator-initiated RCTs using a comprehensive list of cost items. Study Design and Setting: The resource use of two investigator-initiated RCTs (Prednisone-Trial [NCT00973154] and Oxantel-Trial [ISRCTN54577342]) was empirically assessed in a standardized manner through semistructured interviews and a systematically developed cost item list. Using information about yearly salaries, resource use was translated into costs. In addition, we collected all "other costs" including fixed priced items. Overall costs as well as cost of different study phases were calculated. Results: The personnel time used in the Prednisone-Trial trial was approximately 2,897 working days and the overall costs were calculated to be USD 2.3 million, which was USD 700,000 more than planned. In the Oxantel-Trial 798 working days were spent and the overall costs were as originally planned USD 100,000. Cost drivers were similar between the two RCTs with recruitment delays explaining the additional costs in the Prednisone-Trial. Conclusion: This case study provides an example of how to transparently assess resources and costs of RCTs and presents detailed empirical data on type and magnitude of expenses. In the future, this model approach may serve others to plan, assess, or monitor resource use and costs of RCTs.

Tay-Teo, Kiu, André Ilbawi, and Suzanne R. Hill. 2019. "Comparison of Sales Income and Research and Development Costs for FDA-Approved Cancer Drugs Sold by Originator Drug Companies." JAMA Network Open 2 (1): e186875. https://doi.org/10.1001/jamanetworkopen.2018.6875.
Abstract: Importance: High costs and risks of research and development (R&D) have been used to justify the high prices of cancer drugs. However, what the return on R&D investment is, and by extension what a justifiable price might be, is unclear. Objective: To compare incomes from the sales of cancer drugs with the estimated R&D costs. Design, Setting, and Participants: This observational study used global pharmaceutical industry sales data to quantify the cumulative incomes generated from the sales of cancer drugs for companies that have held patents or marketing rights (originator companies). All cancer drugs approved by the US Food and Drug Administration from 1989 to 2017 were identified from the United States Food and Drug Administration's website and literature. Itemized product sales data were extracted from the originator companies' consolidated financial reports. For drugs with data missing in specific years, additional data was sought from other public sources, or where necessary, estimated values from known reported values. Drugs were excluded if there were missing data for half or more of the years since approval. Data analysis was conducted from May 2018 to October 2018. Main Outcomes and Measures: Sales data were expressed in 2017 US dollars with adjustments for inflation. Cumulative incomes from the sales of these drugs were compared against the R&D costs estimated in the literature, which had been adjusted for the costs of capital and trial failure (risk adjusted). Results: Of the 156 US Food and Drug Administration–approved cancer drugs

identified, 99 drugs (63.5%) had data for more than half of the years since approval and were included in the analysis. There was a median of 10 years (range, 1-28 years) of sales data with 1040 data points, 79 (7.6%) of which were estimated. Compared with the total risk-adjusted R&D cost of $794 million (range, $2827-$219 million) per medicine estimated in the literature, by the end of 2017, the median cumulative sales income was $14.50 (range, $3.30-$55.10) per dollar invested for R&D. Median time to fully recover the maximum possible risk-adjusted cost of R&D ($2827 million) was 5 years (range, 2-10 years; n = 56). Cancer drugs continued to generate billion-dollar returns for the originator companies after the end-of-market exclusivity, particularly for biologics. Conclusions and Relevance: Cancer drugs, through high prices, have generated returns for the originator companies far in excess of possible R&D costs. Lowering prices of cancer drugs and facilitating greater competition are essential for improving patient access, health system's financial sustainability, and future innovation.

Terry, Robert F, Gavin Yamey, Ryoko Miyazaki-Krause, Alexander Gunn, and John C. Reeder. 2018. "Funding Global Health Product R&D: The Portfolio-To-Impact Model (P2I), a New Tool for Modelling the Impact of Different Research Portfolios." Gates Open Research 2 (July): 24. https://doi.org/10.12688/gatesopenres.12816.2.
Abstract: Background: The Portfolio-To-Impact (P2I) Model is a novel tool, developed to estimate minimum funding needs to accelerate health product development from late stage preclinical study to phase III clinical trials, and to visualize potential product launches over time. Methods: A mixed methods approach was used. Assumptions on development costs at each phase were based on clinical trial costs from Parexel's R&D cost sourcebook. These were further refined and validated by interviews, with a wide variety of stakeholders from Product Development Partnerships, biopharmaceutical and diagnostic companies, and major funders of global health R&D. Results: the tool was used to create scenarios describing the impact, in terms of products developed, of different product portfolios with funding ranging from $1 million per annum through to $500 million per annum. These scenarios for a new global financing mechanism have been previously presented in a report setting out the potential for a new fund for research and development which would assist in accelerating product development for the diseases of poverty. Conclusion: The P2I tool does enable a user to model different scenarios in terms of cost and number of health products launched when applied to a portfolio of health products. The model is published as open access accompanied with a user guide. The design allows it to be adapted and used for other health R&D portfolio analysis as described in an accompanying publication focussing on the pipeline for neglected diseases in 2017. We aim to continually refine and improve the model and we ask users to provide us with their own inputs that can help us update key parameters and assumptions. We hope to catalyse users to adapt the model in ways that can increase its value, accuracy, and applications.

United States Congress, Office of Technology Assessment. 1993. "Pharmaceutical R&D: Costs, Risks, and Rewards". Washington, D.C: Office of Technology Assessment, Congress of the U.S. https://ota.fas.org/reports/9336.pdf.

Summary (extracts): In this assessment, the Office of Technology Assessment examined the costs of pharmaceutical research and development (R&D), the economic rewards from that investment, and the impact of public policies on both costs and returns. Below is a brief synopsis of the study's major conclusions: SUMMARY OF FINDINGS: Pharmaceutical R&D is a costly and risky business, but in recent years the financial rewards from R&D have more than offset its costs and risks. The average aftertax R&D cash outlay for each new drug that reached the market in the 1980s was about $65 million (in 1990 dollars). The R&D process took 12 years on average. The full aftertax cost of these outlays, compounded to their value on the day of market approval, was roughly $194 million (1990 dollars). Each new drug introduced to the U.S. market between 1981 and 1983 returned, net of taxes, at least $36 million more to its investors than was needed to pay off the R&D investment. This surplus return amounts to about 4.3 percent of the price of each drug over its product life. Over a longer span of time, economic returns to the pharmaceutical industry as whole exceeded returns to corporations in other industries by about 2 to 3 percentage points per year from 1976 to 1987, after adjusting for differences in risk among industries. A risk-adjusted difference of this magnitude is sufficient to induce substantial new investment in the pharmaceutical industry. The National Institutes of Health (NIH) and other Public Health Service laboratories have no mechanism to protect the public's investment in drug discovery, development and evaluation. These agencies lack the expertise and sufficient legal authority to negotiate limits on prices to be charged for drugs discovered or developed with Federal funds.

Young, Ruth, Tewodros Bekele, Alexander Gunn, Nick Chapman, Vipul Chowdhary, Kelsey Corrigan, Lindsay Dahora, et al. 2018. "Developing New Health Technologies for Neglected Diseases: A Pipeline Portfolio Review and Cost Model." Gates Open Research 2 (August): 23. https://doi.org/10.12688/gatesopenres.12817.2.
Abstract: Background: Funding for neglected disease product development fell from 2009-2015, other than a brief injection of Ebola funding. One impediment to mobilizing resources is a lack of information on product candidates, the estimated costs to move them through the pipeline, and the likelihood of specific launches. This study aimed to help fill these information gaps. Methods: We conducted a pipeline portfolio review to identify current candidates for 35 neglected diseases. Using an adapted version of the Portfolio to Impact financial modelling tool, we estimated the costs to move these candidates through the pipeline over the next decade and the likely launches. Since the current pipeline is unlikely to yield several critical products, we estimated the costs to develop a set of priority "missing" products. Results: We found 685 neglected disease product candidates as of August 31, 2017; 538 candidates met inclusion criteria for input into the model. It would cost about $16.3 billion (range $13.4-19.8B) to move these candidates through the pipeline, with three-quarters of the costs incurred in the first 5 years, resulting in about 128 (89-160) expected product launches. Based on the current pipeline, there would be few launches of complex new chemical entities; launches of highly efficacious HIV, tuberculosis, or malaria vaccines would be unlikely. Estimated additional costs to launch one of each of 18 key missing products are $13.6B assuming lowest product complexity or $21.8B assuming highest complexity ($8.1B-36.6B). Over the next 5 years, total estimated costs to move

current candidates through the pipeline and develop these 18 missing products would be around $4.5B (low complexity missing products) or $5.8B/year (high complexity missing products). Conclusions: Since current annual global spending on product development is about $3B, this study suggests the annual funding gap over the next 5 years is at least $1.5-2.8B.

** For the purposes of this review, we have established three categories to describe the state of the literature: thin, considerable, and rich.*

- *Thin: There are relatively few papers and/or there are not many recent papers and/or there are clear gaps*
- *Considerable: There are several papers and/or there are a handful of recent papers and/or there are some clear gaps*
- *Rich: There is a wealth of papers on the topic and/or papers continue to be published that address this issue area and/or there are less obvious gaps*

Scope: While many of these issues can touch a variety of sectors, this review focuses on medicines. The term medicines is used to cover the category of health technologies, including drugs, biologics (including vaccines), and diagnostic devices.

Disclaimer: The research syntheses aim to provide a concise, comprehensive overview of the current state of research on a specific topic. They seek to cover the main studies in the academic and grey literature, but are not systematic reviews capturing all published studies on a topic. As with any research synthesis, they also reflect the judgments of the researchers. The length and detail vary by topic. Each synthesis will undergo open peer review, and be updated periodically based on feedback received on important missing studies and/or new research. Selected topics focus on national and international-level policies, while recognizing that other determinants of access operate at sub-national level. Work is ongoing on additional topics. We welcome suggestions on the current syntheses and/or on new topics to cover.