Estimated research and development investment needed to bring a new medicine to market, 2009-2018

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KEY POINTS

Question: How much do drug companies spend on research and development to bring a new medicine to market?

Findings: In this study, which included 63 of 355 new therapeutic drugs and biologic agents approved by the Food and Drug Administration between 2009 and 2018, the estimated median capitalized research and development cost per product was $985 million, counting expenditures on failed trials. Data were mainly accessible for smaller firms, products in certain therapeutic areas, orphan drugs, first-in-class drugs, therapeutic agents that received accelerated approval, and products approved between 2014 and 2018.

Meaning: This study provides an estimate of research and development costs for new therapeutic agents based on publicly available data; differences from previous studies may have reflected the spectrum of products analyzed and the restricted availability of data in the public domain.

ABSTRACT

Importance: The mean cost of developing a new drug has been the subject of debate, with recent estimates ranging from $314 million to $2.8 billion.

Objective: To estimate the research and development (R&D) investment required to bring a new therapeutic agent to market, using publicly available data.

Design and Setting: Data on new therapeutic agents approved by the Food and Drug Administration (FDA) between 2009 and 2018 from the US Securities and Exchange Commission, Drugs@FDA database, and ClinicalTrials.gov were analyzed, alongside published data on clinical trial success rates, to estimate the R&D expenditure required to bring a new medicine to market.

Exposures: Conduct of pre-clinical and clinical studies of new therapeutic agents.

Main Outcomes and Measures: Median and mean R&D spending on new therapeutic agents approved by the FDA, capitalized at a real cost of capital rate of 10.5% per year, with bootstrapped confidence intervals. All amounts were reported in 2018 US dollars.

Results: The FDA approved 355 new drugs and biologics over the study period. R&D expenditures were available for 63 (18%), developed by 47 different companies. After accounting for the costs of failed trials, the median capitalized R&D investment to bring a new drug to market was estimated at $985 million (95% confidence interval [CI], $684 million – $1229 million), and the mean investment at $1336 million (95% CI,

$1043 million – $1638 million) in the base-case analysis. Median estimates by therapeutic area (for areas with n ≥ 5) ranged from $766 million (95% CI, $323 million – $1474 million) for nervous system agents to $2772 million (95% CI, $2052 million – $5366 million) for antineoplastic and immunomodulating agents. Data were mainly accessible for smaller firms, orphan drugs, products in certain therapeutic areas, first-in-class drugs, therapeutic agents that received accelerated approval, and products approved between 2014 and 2018. Results varied in sensitivity analyses using different estimates of clinical trial success rates, pre-clinical expenditures, and cost of capital.

Conclusions and Relevance: This study provides an estimate of R&D costs for new therapeutic agents based on publicly available data. Differences from previous studies may have reflected the spectrum of products analyzed, the restricted availability of data in the public domain, and differences in underlying assumptions in the cost calculations.

INTRODUCTION

Rising drug prices have attracted public debate in the United States (US) and abroad on fairness of drug pricing and revenues.[1] Central to this debate is the scale of research and development (R&D) investment by biopharmaceutical companies that is required to bring new medicines to market.[2]

The most widely cited studies of the cost of developing a new drug, by DiMasi et al.,[3,4] reported a sharp increase in the mean cost of developing a single new therapeutic agent, from $1.1 billion in 2003 to $2.8 billion in 2013 (in 2018 US dollars), based on a real cost of capital rate of 11% and 10.5% per year, respectively. Other studies in this period, using confidential or proprietary data, reported figures from $314 million to $2.1 billion (in 2018 US dollars).[5–11]

In 2017, Prasad and Mailankody estimated the R&D costs of new cancer drugs using public data, reported by pharmaceutical firms to the US Securities and Exchange Commission (SEC).[12] They estimated the median R&D cost of bringing a single cancer drug to market to be $780 million (in 2018 US dollars), capitalized at a real cost of capital rate of 7% per year, based on a sample of 10 drugs.[12]

This study estimated the R&D investment required to bring a new therapeutic agent to market, using publicly available data for products approved by the US Food and Drug Administration (FDA) between 2009 and 2018.

METHODS

Sample identification and characteristics

We identified all new therapeutic agents, i.e., new drug applications and biologics license applications, approved by the US FDA between 2009 and 2018 in the Drugs@FDA database.[13] For each, we extracted the date of approval, date of submission of investigational new drug application, date of submission of new drug application or biologics license application, indication, type (pharmacologic or biologic), expedited programs (priority review, accelerated approval, fast track, or breakthrough), orphan status, route of administration (oral, injection, intravenous, or other), and manufacturer (**eTable 1**). To capture innovation, we determined whether an agent was first-in-class using publications by FDA officials.[14,15] We checked the data for consistency with published reports.[15,16]

Therapeutic areas were obtained from the anatomical therapeutic chemical classification system database.[17] Where agents were not yet classified, we based our decision on the approved indication.

For each agent, we identified start and end dates of clinical studies (phases 1, 2, and 3 for the FDA-approved indication) from ClinicalTrials.gov (search conducted on 4 April 2019). If there were multiple studies in the same phase the earliest start date was selected. We verified these dates with reports in SEC filings, and used the dates from SEC filings if there were discrepancies. We classified phase 1/2 trials as phase 2, and phase 2/3 trials as phase 3, consistent with other studies.[18–20] Dates of submission of

investigational new drug applications were used to approximate the end of pre-clinical testing; these dates were checked for consistency with filings to ensure clinical testing had not already begun outside the US.

No data were collected from human participants, and all data in this study were publicly available.

R&D data extraction

Publicly traded US companies are legally required by the SEC to file 10-K and 10-Q forms, which are annual and quarterly reports, respectively, of key financial performance indicators. These include audited financial statements and data on R&D expenditures. For every agent in our sample, we searched the SEC website for reports from the firm that received FDA approval for it.[21]

Exclusions. As reports for private US drug firms and foreign companies listed on non-US stock exchanges were unavailable, their products were excluded. For firms with available reports, we screened 10-K and 10-Q filings for data on R&D expenditures on individual drug candidates. We excluded products developed by companies that only reported total R&D expenditures across all drug candidates or across therapeutic areas.

For excluded products, we searched the 10-K and 10-Q forms and online press releases of manufacturers at the time that agents were approved to see if any were developed

in collaboration with other firms via licensing deals. If so, we searched for 10-K and 10-Q forms from those firms in case there were R&D data for the product in question.

Inclusions. For each therapeutic agent with available data, we extracted direct and indirect R&D expenditures in each year of development. Drugs were tracked across years in SEC filings using the brand, generic, or compound names of agents, as appropriate.

Direct R&D expenses included all resources directly allocated to a particular agent. Indirect R&D expenses, which included personnel and overhead costs, were sometimes reported as a lump sum across all drug development programs. If so, we applied the same percentage of direct R&D costs attributable to a particular agent to estimate indirect costs for the same agent. The proportional allocation of personnel and overhead expenses is common practice in costing studies.[22]

Costs were tracked from the year a company started reporting costs for a particular drug candidate in their financial statements until the quarter of approval, which often included 1 or more years of pre-clinical costs. In some cases, at the first mention of the candidate in SEC filings, companies reported the costs incurred since inception of the drug development program. Certain companies only started tracking costs at late stages of pre-clinical development or at phase 1 of development, resulting in an underreporting of pre-clinical costs.

Some drugs were initially developed by companies that subsequently licensed out their drug candidates to other firms which then brought these products to market. In

these cases, it was assumed that any pre-clinical and clinical costs incurred during initial development was included in licensing fees and milestone payments. Hence, where these fees and payments were recorded as R&D expenses for the agent in question, these costs were extracted. Data on costs incurred by the originator firms were not collected.

If SEC filings were missing for 3 or fewer years since the inception of the drug development program (e.g., if a company was privately held during early years of development) and the product did not move between development phases (i.e., either from 1 to 2 or 2 to 3), we extrapolated costs from the closest available year. Products were excluded if >3 years of SEC filings were missing.

Three investigators independently extracted all R&D data used in this study. Discrepancies were resolved through discussions. Where disagreements existed, we assumed the higher estimate of R&D expenditures.

Quality assessments. Consistency and completeness of company reporting in SEC filings varied over time. Many reported detailed R&D costs, which allowed us to track outlays over time for individual candidates. Others reported costs inconsistently or with missing data for some years, requiring various assumptions, for example on timings of transitions between phases and extrapolations when SEC filings were missing.

To aid interpretation, we categorized each estimate as high-, medium-, or low-quality, depending on the availability and consistency of reported data. The categorization was developed through discussion between all authors.

High-quality estimates comprised drugs discovered internally, allowing tracking of costs back to inception of the development program, as well as products licensed at pre-clinical or phase 1 stages with minimal up-front fees or milestone payments captured in SEC filings. Late commercialization deals related to marketing of products in foreign markets were also deemed high-quality estimates, as they would have had little or no effect on R&D expenses incurred on trials required for FDA approval.

Low-quality estimates comprised all acquisitions, licensing deals, or other collaboration agreements in phases 2 or 3, earlier deals where it was unclear whether all costs were captured in data extraction, and estimates requiring extrapolation of 2-to-3 years of data. We classified estimates as medium quality when other judgment calls regarding financial reporting, as agreed upon by the authors, had to be made.

Two investigators independently categorized the quality of estimates and resolved discrepancies through discussions.

Costs of failed trials

Accurate information on costs of failures, i.e., R&D outlays on candidates being developed by companies but not ultimately approved, is essential to estimating the costs of drug development. We accounted for failures using data on aggregate clinical trial success rates from a recent study by Wong et al. (**Table 1**).[18]

Wong et al. reported that 13.8% of therapeutic agents entering phase 1 were ultimately approved by the FDA;[18] the corresponding figures for drugs entering phase 2 and 3 were 35.1% and 59.0%, respectively.[18]

Wong et al.[18] provided success rates through phase 3. We supplemented these rates with a recent estimate of the proportion of biologics license applications and new drug applications that are approved by the FDA (83.2%).[20]

Costing method

For each agent, we estimated expected R&D investment to bring a drug to market in 3 steps.

First, we summed direct and indirect R&D spending on a therapeutic agent in each year. All sums were inflation-adjusted to 2018 dollars using the US consumer price index.

Second, we accounted for failed projects by dividing total R&D expenditures on a drug in a particular year by the corresponding aggregate phase-specific probability of success, as in previous studies of costs of drug development.[3–7] For example, for each drug, we divided phase 1 costs in each year by 0.138, which accounted for spending on the other 6.2 phase 1 trials that would fail, on average, for each successful development program. We used phase 1 rates to adjust pre-clinical expenditures; we used the proportion of biologics license applications and new drug applications that are approved by the FDA to adjust costs once these applications had been submitted to

the agency for regulatory approval. Licensing fees and milestone payments, where captured, were adjusted using the success rate for the trial phase that was ongoing when the payments were made. When a phase shift took place within the financial year, we allocated the cost proportionally to the time spent in each phase. For example, if development moved from phase 1 to phase 2 on July 1st of a given year, we divided the costs equally between each phase. Similarly, in the year of approval, we multiplied the total cost by the fraction of the year elapsed by the time of approval. Hence, if a drug was approved on July 1st we only counted 50% of the costs in the year of approval, since firms often incurred post-approval costs related to pharmacovigilance or testing in other indications.

Third, we applied a real cost of capital rate of 10.5% per year (i.e., weighted average cost of capital in the pharmaceutical industry), as in the DiMasi et al. study.[4] Cost of capital is the required rate of return for an investor and encapsulates a risk-free rate (i.e., opportunity cost) and premium based on the likelihood of business failure.[23]

Sensitivity and subgroup analysis

We ran 4 univariate sensitivity analyses. First, as the results were sensitive to the choice of aggregate clinical trial success rates (by phase), we re-calculated the results using aggregate rates reported in 2 other studies (**Table 1**).[19,20] Second, we re-estimated R&D costs using therapeutic-area-specific rates reported by Wong et al. (**Table 1**), instead of aggregate rates. For example, oncology drugs in phase 1 have a 3.4% chance of ultimately receiving FDA approval, so we divided each year of phase 1 costs for these products by 0.034. Third, we re-ran the analyses using a real cost of

capital rate of 7% (as done by Prasad and Mailankody[12]) and 0% (to show non-capitalized outlays). Fourth, to account for potentially missing pre-clinical expenditures, we adopted the same assumption around pre-clinical costs as DiMasi et al., who reported that pre-clinical costs represented 42.9% of their total R&D estimate.[4] Thus, for each product in our sample, we isolated clinical expenditures and imputed a pre-clinical cost that amounted to this percentage. No imputations were performed for products licensed after clinical development had begun, since it was assumed that licensing fees and milestone payments reflected pre-clinical costs incurred by the company that sold the rights to the product. Additionally, we re-ran the sensitivity analysis but with imputations done for all products, including licensed agents.

As a subgroup analysis, we reported mean and median amounts by therapeutic area, using area-specific rates to adjust for costs of failure.

Statistical analysis

We estimated the mean and median R&D investments across our sample in the base-case and sensitivity analyses. We then restricted the sample to high-quality estimates and re-calculated the mean and median amounts.

We conducted a nonparametric bootstrapped resampling with replacement (1000 iterations) to calculate 95% confidence intervals (CIs) around the estimated mean and median investments in R&D in our sample. We used chi-square tests to identify statistically significant differences in characteristics of the study sample versus

therapeutic agents approved by the FDA between 2009 and 2018 that were excluded from our analysis. We used Kruskal-Wallis and Mann-Whitney U tests, as appropriate, to identify statistically significant differences in median estimated R&D investments across therapeutic areas and other drug characteristics.

All statistical tests were 2-tailed and used a type I error rate of 0.05. The data were analyzed in Stata version 15 (StataCorp).

RESULTS

Between 2009 and 2018, the FDA approved 355 new drugs and biologics. R&D expenditures from SEC government filings were available for 63 of these products, developed by 47 different companies (**Figure 1**). The sample covered 17.7% (63/355) of all new therapeutic agents approved by the FDA over this 10-year period. Twenty-three of the estimates were judged of high quality, 18 medium quality, and 22 low quality. **eTable 2** provides the rationale for the quality categorization of each agent.

Sample characteristics

Table 2 presents statistics for the 63 included therapeutic agents. The sample contained a larger proportion of orphan drugs, therapeutic agents that benefited from expedited development or approval pathways, and first-in-class drugs compared to all FDA-approved products between 2009 and 2018, although these differences were not statistically significant. Differences in the breakdown of products by therapeutic area, accelerated versus regular approval, and approval dates were statistically significant.

R&D investments

Without adjustments for costs of failed trials, no statistically significant differences in the median R&D investment required to bring a new drug to market were observed across any of the drug characteristics shown in **Table 2**, except median costs for biologic drugs that were higher than those for pharmacologic drugs (**eTable 3**). For the 63 agents included in the analysis, the median and mean R&D outlays (i.e., total

non-capitalized direct and indirect expenses incurred during pre-clinical and clinical testing) were estimated to be $319.3 million (95% CI, $236.4 million – $351.4 million) and $374.1 million (95 CI, $301.9 million – $464.2 million), respectively (**eTable 4**). The mean number of years of data per drug was 8.3 (standard deviation, 2.8 years). **eTable 5** shows the dates of phase changes for clinical trials of each included agent.

After accounting for costs of failed trials, the estimated median R&D investment required to bring a new drug to market, capitalized at a rate of 10.5% per year, was $985.3 million (95% CI, $683.6 million – $1228.9 million), and the estimated mean $1335.9 million (95% CI, $1042.5 million – $1637.5 million) (**Table 3**). **Figure 2** shows point estimates for each of the 63 agents, which ranged from $143.2 million (crofelemer) to $6419.0 million (dupilumab).

Restricting the analysis to high-quality estimates (n=23), the estimated median R&D investment increased from $985.3 million to $1048.1 million (95% CI, $796.6 million – $1180.6 million), while the estimated mean declined from $1335.9 million to $1143.3 million (95% CI, $880.4 million – $1442.1 million).

Sensitivity analyses

Table 3 shows the results of univariate sensitivity analyses. When the aggregate success rates reported by Hay et al. were used instead of those reported by Wong et al., the estimated median R&D investment, capitalized at a rate of 10.5% per year, increased from $985.3 million to $1404.9 million (95% CI, $1102.2 million – $1773.4 million), while the estimated mean rose from $1335.9 million to $1976.6 million (95%

CI, $1595.5 million – $2454.8 million). When the rates from Thomas et al. were used, the estimated median R&D investment, capitalized at an annual rate of 10.5%, was $1465.8 million (95% CI, $1121.5 million – $1887.1 million), and the estimated mean $2059.5 million (95% CI, $1639.9 million – $2511.7 million).

When therapeutic-area-specific rates from Wong et al., rather than aggregate rates, were used to account for costs of failed trials for each agent, the estimated median R&D investment, capitalized at a rate of 10.5% per year, increased from $985.3 million to $1385.2 million (95% CI, $1053.9 million – $1971.8 million), and the estimated mean rose from $1335.9 million to $2307.2 million (95% CI, $1726.9 million – $3013.0 million).

When the costs were capitalized at an annual rate of 7%, instead of 10.5%, the median and mean expected investment decreased from $985.3 million to $848.9 million (95% CI, $671.1 million – $1076.6 million) and from $1335.9 million to $1158.6 million (95% CI, $929.3 million – $1407.2 million), respectively. When costs were not capitalized, rather than capitalized at an annual rate of 10.5%, the median and mean expected investment decreased from $985.3 million to $688.2 million (95% CI, $450.8 million – $850.6 million) and from $1335.9 million to $884.8 million (95% CI, $717.1 million – $1084.7 million), respectively.

With the adjustments for potentially missing pre-clinical costs done for 33 of 63 products (i.e., excluding licensed agents), based on the DiMasi et al. approach, the estimated median R&D investment increased from $985.3 million to $1228.9 million (95% CI, $943.8 million – $1900.9 million), while the estimated mean increased from

$1335.9 million to $1800.7 million (95% CI, $1396.4 million – $2268.5 million). With the adjustments for potentially missing pre-clinical costs done for all 63 products, the estimated median R&D investment increased to $1628.4 million (95% CI, $1196.5 million – $2072.2 million), while the estimated mean increased to $2214.7 million (95% CI, $1734.1 million – $2719.9 million).

Restricting the sensitivity analyses to high-quality estimates (n=23), the estimated median and mean R&D investments required to bring a new drug to market increased in most cases (**Table 3**). **eTable 6** shows the estimates for each agent in the base-case and sensitivity analyses.

Subgroup analyses by therapeutic area

Median estimates by therapeutic area (for areas with n ≥ 5), adjusted using area-specific rates and capitalized at 10.5% per year, ranged from $765.9 million (95% CI, $323.0 million – $1473.5 million) for nervous system agents to $2771.6 million (95% CI, $2051.8 million – $5366.2 million) for antineoplastic and immunomodulating agents. The corresponding mean estimates ranged from $1076.9 million (95% CI, $508.7 million – $1847.1 million) for nervous system agents to $4461.2 million (95% CI, $3114.0 million – $6001.3 million) for antineoplastic and immunomodulating agents (**Table 4**).

DISCUSSION

Based on data for 63 therapeutic agents developed by 47 companies between 2009 and 2018, the median and mean R&D investments required to bring a new drug to market were estimated to be $985 million and $1336 million, respectively. Estimates differed across therapeutic areas, with costs of developing cancer drugs the highest. The results included costs of failed clinical trials and varied in sensitivity analyses using different estimates of trial success, pre-clinical expenditures, and cost of capital.

These figures were higher than the median capitalized R&D cost of $780 million (in 2018 US dollars) reported by Prasad and Mailankody for oncology drugs.[12] This may be because adjustments based on clinical trial success rates were applied in the present study to account for costs of failures, whereas Prasad and Mailankody restricted their analysis to companies bringing their first drug to market and then summed the total R&D expenditures of each company during the development periods of the drugs in their sample. Most of the companies included in their study appeared to be more successful than the average company.[24,25] Moreover, their analysis was based on data for 10 oncology drugs, which limits the comparability of their results with the present study.

The mean estimate of $1.3 billion in the present study was lower than the $2.8 billion (in 2018 US dollars) reported by DiMasi et al., which was based on data for 106 products developed by 10 large firms.[4] The estimate by DiMasi et al. used confidential data on both cost and success rates voluntarily submitted by anonymous companies without independent verification, making them difficult to validate.[12,26–28] The higher

estimate of DiMasi et al. seems to reflect a combination of higher clinical costs incurred by larger drug developers,[29] lower estimates of trial success for each stage of development compared to the more recent data presented by Wong et al., and different assumptions about pre-clinical expenditures as their dataset did not permit allocating these expenditures to specific agents.

The results of the present study varied widely when subject to sensitivity analyses, especially using different success rates and assumptions on pre-clinical costs. The methods employed by Wong et al. to handle missing data were an improvement on earlier studies of trial success rates, and their study was based on a larger sample.[18] Wong et al. also noted that the most cited studies of success rates[19,20,30] originated from researchers with financial ties to the pharmaceutical industry, and elaborated that "previous estimates of drug development success rates [relied] on relatively small samples from databases curated by the pharmaceutical industry and [were] subject to potential selection biases."[18] Also, compared to these earlier studies of success rates,[19,20,30] the timing of the work by Wong et al.[18] more closely aligned with that of the present study, thereby improving its internal validity.

There are challenges in isolating pre-clinical investments by drug companies. It is especially difficult to identify the exact date from which costs should start being allocated to individual agents during the early stages of pre-clinical research. The base-case scenario in this study relied on pre-clinical costs reported by firms in SEC filings, which were likely underestimated since many companies did not attribute costs during the drug discovery stages to individual candidates. DiMasi et al. estimated that pre-clinical costs accounted, on average, for 42.9% of total capitalized costs, based on

aggregated data on pre-clinical spending and assumptions around the duration of pre-clinical testing.[4] Although pre-clinical costs were variously estimated in the present study, including indirectly through license fees, pre-clinical data were directly captured for 19 products. For these products, pre-clinical costs generally accounted for a lower share of the total capitalized costs (ranging from 0.3% to 50.7%, with a median of 12.4%) than what was estimated by DiMasi et al. For comparison, however, the 42.9% estimate was used to impute pre-clinical costs in sensitivity analyses in this study. Further validation work is needed to establish the pre-clinical share of R&D estimates for individual products.

Greater transparency around R&D costs is essential for analysts to check the veracity of claims by companies that the steep prices of new drugs are driven by high development outlays. While these expenditures are undoubtedly high, as shown in this study, it is important for policymakers, regulators, and payers to know the exact scale of these investments. This knowledge can inform the design of pricing policies that give adequate rewards for innovative drugs that bring value to health care systems.

Limitations

This study has several limitations. First, data were unavailable for many products approved by the FDA during the study period. No data were available for products developed by foreign companies not listed on a US stock exchange and large drug firms that did not report R&D figures for individual drug candidates. Thus, there was likely an overrepresentation of smaller firms, which may have run leaner operations than larger ones. This limited the generalizability of the results to all products.

Second, the included agents differed from other drugs approved by the FDA between 2009 and 2018, although not all differences were statistically significant. The sample included a larger proportion of orphan drugs, products in certain therapeutic areas, first-in-class drugs, therapeutic agents that received accelerated approval, and products approved between 2014 and 2018.

Third, there were inconsistencies in R&D reporting between companies, which made it difficult to ensure perfect comparability of R&D figures between firms. These inconsistencies may have been explained by differences in accounting policies. For instance, some firms allocated overhead and administrative costs to direct R&D figures, while others reported these costs separately. Some reported pre-clinical research costs as a separate line item, while others incorporated them in overhead costs. Companies also reported costs associated with licensing deals, drug acquisitions, and collaboration agreements differently, so it is likely that not all costs were fully reflected in some estimates.

Fourth, uncertainties in the analysis may have resulted in under- or overestimations of R&D expenditures for some products. It is difficult to attribute costs to individual drug candidates in the early stages of pre-clinical development, so only the costs reported by firms in SEC filings were considered in the base-case analysis. However, since pre-clinical costs may have been underreported by some companies, sensitivity analyses were conducted to produce an upper-bound estimate of pre-clinical expenditures. Conversely, many drug firms conducted trials for a particular candidate for multiple indications, which may have led to overestimations of costs since trial expenditures

were not broken down by indication but instead reported as annual lump sums for each agent. Also, the estimates did not reflect any public tax credits or subsidies, which may have led to further overestimations of costs incurred by companies.

CONCLUSIONS

This study provides an estimate of R&D costs for new therapeutic agents based on publicly available data. Differences from previous studies may have reflected the spectrum of products analyzed, the restricted availability of data in the public domain, and differences in underlying assumptions in the cost calculations.

ONLINE APPENDIXES

Appendix 1: Supplementary tables.

AUTHOR CONTRIBUTIONS

Dr. Wouters had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Wouters.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Wouters.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Wouters.

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Table 1. Clinical trial success rates by phase (on aggregate and by therapeutic area). [a]

	Phase 1 to approval, %	Phase 2 to approval, %	Phase 3 to approval, %	FDA submission to approval, % [b]
Aggregate rates (by source)				
Wong et al. [18]	13.8	35.1	59.0	83.2
Thomas et al.[19]	9.6	15.3	49.6	85.3
Hay et al. [20]	10.4	16.2	50.0	83.2
Therapeutic-area-specific rates (from Wong et al.) [18]				
Oncology	3.4	6.7	35.5	81.7
Metabolism and endocrinology	19.6	24.1	51.6	80.4
Cardiovascular	25.5	32.3	62.2	84.5
Central nervous system	15.0	19.5	51.1	82.2
Autoimmune and inflammation	15.1	21.2	63.7	80.3
Ophthalmology [c]	32.6	33.6	74.9	80.4
Infectious disease	25.2	35.1	75.3	84.9
Other [d]	20.9	27.3	63.6	80.4

Abbreviations: FDA, Food and Drug Administration.

[a] Rates across all indications for individual therapeutic agents (as opposed to rates for lead indications, which were higher in all phases). Only the success rates used in this analysis were reported. Phase 1 trials, which usually include up to 100 healthy volunteers and may take several months to conduct, are primarily used to assess the tolerability and safety of a therapeutic agent in different doses; these are sometimes referred to as first-in-human trials. Phase 2 trials, which can involve up to a few hundred patients with a disease or condition and take several months to 2 years to complete, are typically used to gather data on the efficacy and safety of a therapeutic agent in different doses. Phase 3 trials, which can involve several thousand participants with a disease or condition and may take 1 to 4 years to run, are generally used to confirm the efficacy and safety of the dose of the therapeutic agent believed to provide the best risk-benefit ratio.[31]

[b] This was the proportion of new drug applications and biologics license applications approved by the FDA. Wong et al.[18] reported aggregate and therapeutic-area-specific rates through phase 3. These data were supplemented with estimates of FDA submission to approval rates from Hay et al.; if a particular category from the Wong et al. study was not reported by Hay et al., then the category "Other" was used.[20]

[c] This category was applied to therapeutic agents classified as treating "sensory organ" diseases, i.e., anatomical therapeutic chemical classification system code S.

[d] Based on the rates for "all [agents] without oncology" reported by Wong et al.[18] These rates were applied to therapeutic agents which fell outside the other categories.

Table 2. Characteristics of new therapeutic agents approved by the FDA between 2009 and 2018.[a]

Characteristics	No. (%)		P value
	Included agents (n=63)	Full sample (n=355)	
Agent type			
Pharmacologic	47 (75)	271 (76)	.72
Biologic	16 (25)	84 (24)	
Therapeutic area [b]			
Antineoplastic and immuno-modulating agents	20 (32)	116 (33)	.02
Alimentary tract and metabolism	15 (24)	44 (12)	
Nervous system	8 (13)	33 (9)	
Anti-infective agents for systemic use	5 (8)	40 (11)	
Other	15 (24)	122 (34)	
Orphan drug	31 (49)	145 (41)	.14
Drug received accelerated approval	14 (22)	41 (12)	.003
Drug benefited from any expedited development or approval pathway [c]	48 (76)	234 (66)	.06
Innovativeness			
First in class	27 (43)	127 (36)	.20
Next in class	36 (57)	228 (64)	
Route of administration [d]			
Oral	28 (44)	187 (53)	.20
Injection	20 (32)	87 (25)	
Intravenous	10 (16)	41 (12)	
Other	5 (8)	40 (11)	
Approval dates			
2009 to 2013	17 (27)	142 (40)	.02
2014 to 2018	46 (73)	213 (60)	

Abbreviations: FDA, Food and Drug Administration; R&D, research and development.

[a] Chi-square tests were carried out on the data for included agents (n=63) vs. excluded ones (n=292).

[b] Other therapeutic areas included blood and blood forming organs, cardiovascular system, dermatologicals, musculo-skeletal system, sensory organs, and various.

[c] Included accelerated approval, breakthrough therapy, fast track, orphan drug, and priority review.

[d] Injection included intramuscular and subcutaneous; other routes included multiple, ophthalmic, and topical.

Table 3. Median expected R&D expenditure on new therapeutic agents approved by FDA (2009-2018) in main and sensitivity analyses.

Parameter varied in sensitivity analysis	R&D costs for all included agents (n=63), $ millions [95% CI]	R&D costs for high-quality sample (n=23), $ millions [95% CI]
Source of clinical trial success rates		
Wong et al. (base case)[18]	985.3 [683.6 – 1228.9]	1048.1 [796.6 – 1180.6]
Hay et al.[20]	1404.9 [1102.2 – 1773.4]	1620.3 [1191.8 – 1773.4]
Thomas et al.[19]	1465.8 [1121.5 – 1887.1]	1678.4 [1259.7 – 1999.3]
Aggregate vs. therapeutic-area-specific success rates		
Aggregate rates (base case) [18]	985.3 [683.6 – 1228.9]	1048.1 [796.6 – 1180.6]
Area-specific rates [18]	1385.2 [1053.9 – 1971.8]	1220.1 [994.3 – 2118.3]
Cost of capital rate		
10.5% (base case)	985.3 [683.6 – 1228.9]	1048.1 [796.6 – 1180.6]
7%	848.9 [671.1 – 1076.6]	930.0 [692.0 – 1018.1]
0%	688.2 [450.8 – 850.6]	697.9 [567.9 – 850.6]
Adjustment for potential underreporting of spending on pre-clinical trials		
No (base case)	985.3 [683.6 – 1228.9]	1048.1 [796.6 – 1180.6]
Yes, excluding licensed	1228.9 [943.8 – 1900.9]	1482.0 [1104.7 – 1860.9]
Yes, including licensed	1628.4 [1196.5 – 2072.2]	1751.1 [1255.3 – 2246.9]

Abbreviations: $, United States dollars; CI, confidence interval; FDA, Food and Drug Administration; R&D, research and development.

Table 4. Mean and median expected R&D expenditure on new therapeutic agents approved by FDA (2009-2018) by therapeutic area.

Therapeutic area [a]	**Sample size**	**Median, $ millions [95% CI]** [b]	**Mean, $ millions [95% CI]** [b]
Antineoplastic and immunomodulating agents	20	2771.6 [2051.8 – 5366.2]	4461.2 [3114.0 – 6001.3]
Alimentary tract and metabolism	15	1217.6 [613.9 – 1792.4]	1430.3 [920.8 – 2078.7]
Nervous system	8	765.9 [323.0 – 1473.5]	1076.9 [508.7 – 1847.1]
Anti-infectives for systemic use	5	1259.9 [265.9 – 2128.3]	1297.2 [672.5 – 1858.5]
Dermatologicals	4	747.4	1998.3
Cardiovascular system	3	339.4	1152.4
Musculo-skeletal system	3	1052.6	937.3
Blood and blood-forming organs	2	793.0	793.0
Sensory organs	2	1302.8	1302.8
Other [c]	1	1121.0	1121.0

Abbreviations: $, United States dollars; CI, confidence interval; FDA, Food and Drug Administration; R&D, research and development.

[a] Therapeutic areas were obtained from the anatomical therapeutic chemical classification system database.[17] Where agents were not yet classified, the categorization was based on the approved indication.

[b] Bootstrapped confidence intervals were not calculated for therapeutic areas with n < 5. Estimates were based on therapeutic-area-specific success rates reported by Wong et al.[18]

[c] The product Valtessa (patiromer) was assigned to the therapeutic area "Various" under the subgroup "Drugs for treatment of hyperkalemia and hyperphosphatemia".