The cost of opportunity

A study on pharmaceutical R&D costs

Gupta Strategists

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About the study

The cost of opportunity is an independent study conducted by Gupta Strategists. Gupta Strategists is a strategy consulting firm focused entirely on healthcare. We provide independent, expert advice in all subsectors of the healthcare industry – from hospitals and insurance companies to pharmaceutical companies and governments. We transform complex issues into innovative ideas and practical solutions, using our expertise to drive impact. Next to our project work, we regularly publish independent research to provide socially relevant insights and highlight important trends. For more information on our work, visit our website: **www.gupta-strategists.nl**

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We would like to thank all participants in the round table discussions on this topic: pharmaceutical companies, insurers, investors, policymakers, doctors and patients. The content and conclusions of this study have substantially matured because of their input.

Furthermore, we would like to thank Fair Medicine for starting our thinking about this study subject, for facilitating access to global data on clinical trials, and for providing critical notes on draft versions of this study. In particular, we thank Simon van der Schans, PhD-candidate at Fair Medicine, for his contribution to the gathering of data and his help during the writing of this study.

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Executive summary

It is commonly known that research and development (R&D) of new medicines is very expensive, but there is much controversy with regard to how expensive it actually is. In this study, we provide detailed and up-to-date insight into R&D costs of medicines using a novel, top-down model built on a single definition of pharmaceutical R&D costs and its principal drivers.

Key insights

Our model shows that the average R&D costs per new molecular entity (NME[1]) are 2.5 bln USD in 2017[2] *(Figure 1)*. These costs are composed of out-of-pocket success costs (7%), out-of-pocket failure costs (40%) and costs of capital (53%). We also conclude that R&D costs differ substantially between different therapeutic areas: the average development costs of a medicine for an orphan disease could be as low as 0.5 bln USD, while the costs of a medicine for an oncological disorder could be as high as 6.5 bln USD.

Implications

The insights of this study can help substantiate discussions on R&D costs with facts. Furthermore, they may help pharmaceutical companies, academic researchers and policymakers in their quest to increase the efficacy of R&D expenditure. While there is no low-hanging fruit, conceptually, this might be achieved in the following ways:

- **Reducing the costs of capital.** Given that it is the largest contributor to R&D costs, it makes sense to explore options for reducing these costs. We see three avenues to do so:
  - *Reducing the time from preclinical phase to market:* by allowing earlier access to market
  - *Reducing the amount of funds that are capitalized:* by regulating the sale of intellectual property through publicly funded institutions
  - *Reducing the rates of return on capital:* by using public finances
- **Reducing development costs of medicines that do not reach the market.** Out-of-pocket failure costs form a substantial part of total R&D costs. Therefore, reducing these costs has a considerable impact on R&D costs. We see different opportunities to do so:
  - *Increasing efficiency of investment decisions:* by reconsidering criteria for investment
  - *Loosening approval criteria:* by letting the market determine efficacy and value
- **Reducing development costs of medicines that reach the market.** Out-of-pocket success costs are small and, as a result, the potential impact of actions to reduce these costs is small as well

Composition of R&D costs of an average NME in 2017
[% of total (bln USD)]

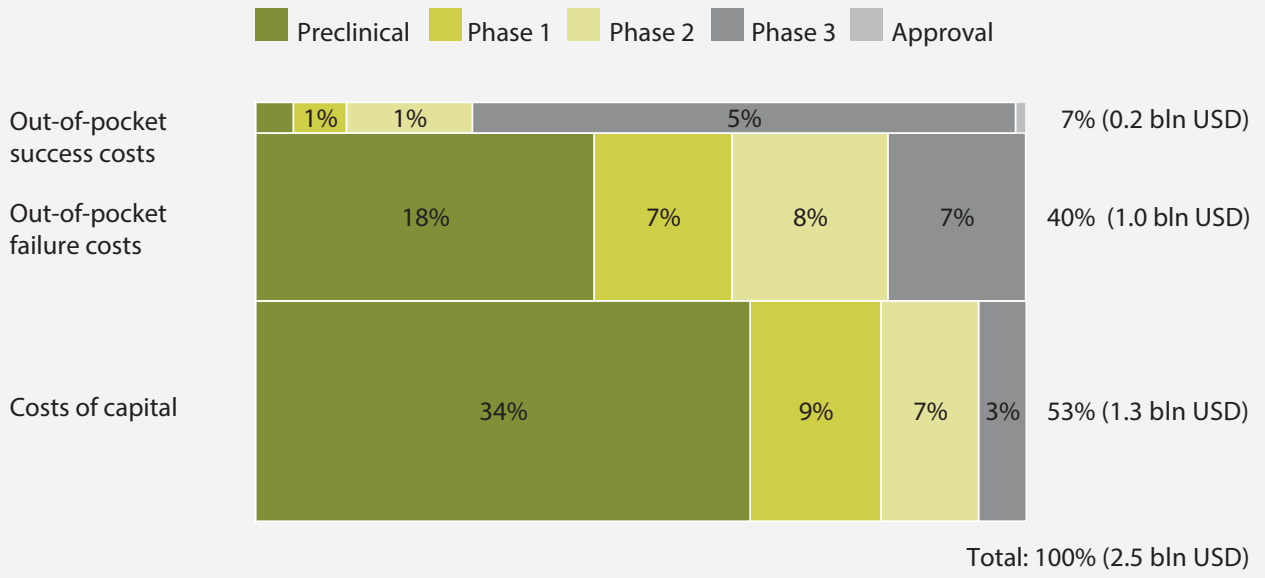


Figure 1. In 2017, total R&D costs of an NME are 2.5 bln USD, consisting of out-of-pocket success costs, out-of-pocket failure costs and costs of capital.

1 In this study, we refer to NMEs as both new small molecular entities (SMEs) and new biologics.

2 R&D of an NME takes place over a long period of time (i.e. 10-15 years). In the study, we use the average year of research as a proxy for the period of R&D (e.g. when R&D took place between 2000-2014, the average year of research is 2007).

Background

The pharmaceutical industry spends a substantial proportion of its annual revenues, 22-25%, on research and development (R&D). In 2017, total spending on pharmaceutical R&D was 160 bln USD *(Figure 2)*[3]. In the public debate on the reasonableness of pharmaceutical pricing (which is not the scope of this study), R&D costs of new medicines are often drawn into the debate. As a side note, when referring to pharmaceutical pricing, it is important to understand that there is no clear relationship between R&D costs and prices of new medicine[3].

Worldwide medicine revenues of pharmaceutical companies and out-of-pocket R&D costs
[bln USD2017, 2000-2017]

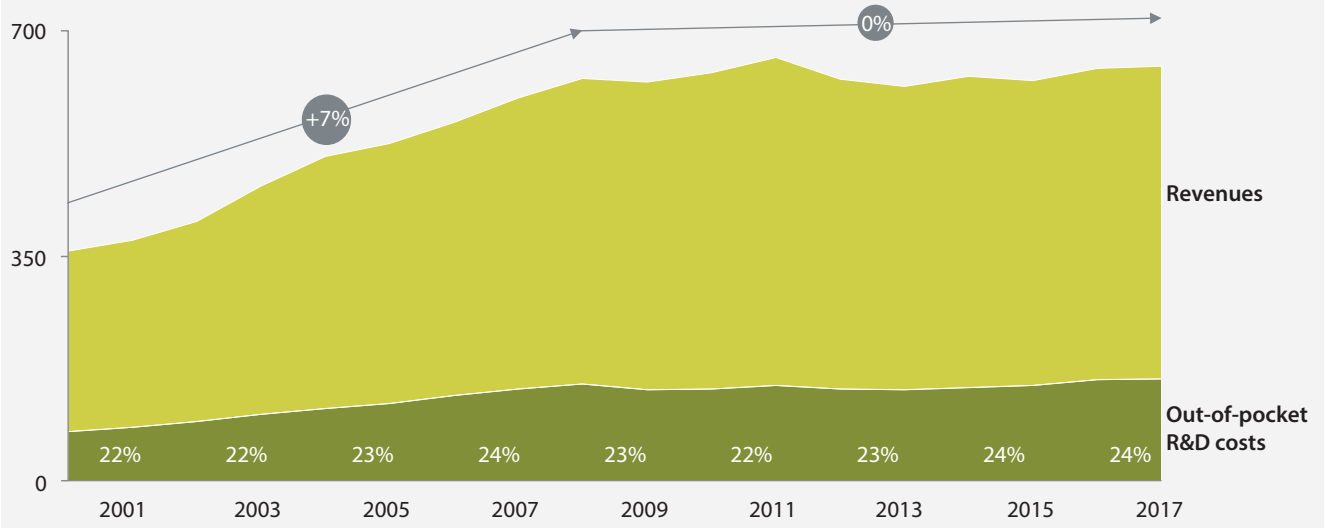


Figure 2. Pharmaceutical companies spent 22%-25% of their total revenue on R&D between 2000-2017[4]. Note: R&D costs shown in this figure cannot be compared with R&D costs per NME as described in this study, since the costs in this figure only consider spend by pharmaceutical companies (and not universities or governments, for example) and include costs incurred in phase 4 trials.

While *Figure 2* gives us information on total R&D spending, it does not provide insight into spending per individual new medicine. R&D costs of new medicines are studied extensively, but the results of these studies vary widely *(Figure 3)*: reported R&D costs differ by a factor thirteen, from 0.2 to 2.6 bln USD per new molecular entity (NME)[5].

Published R&D costs per NME
[bln USD]

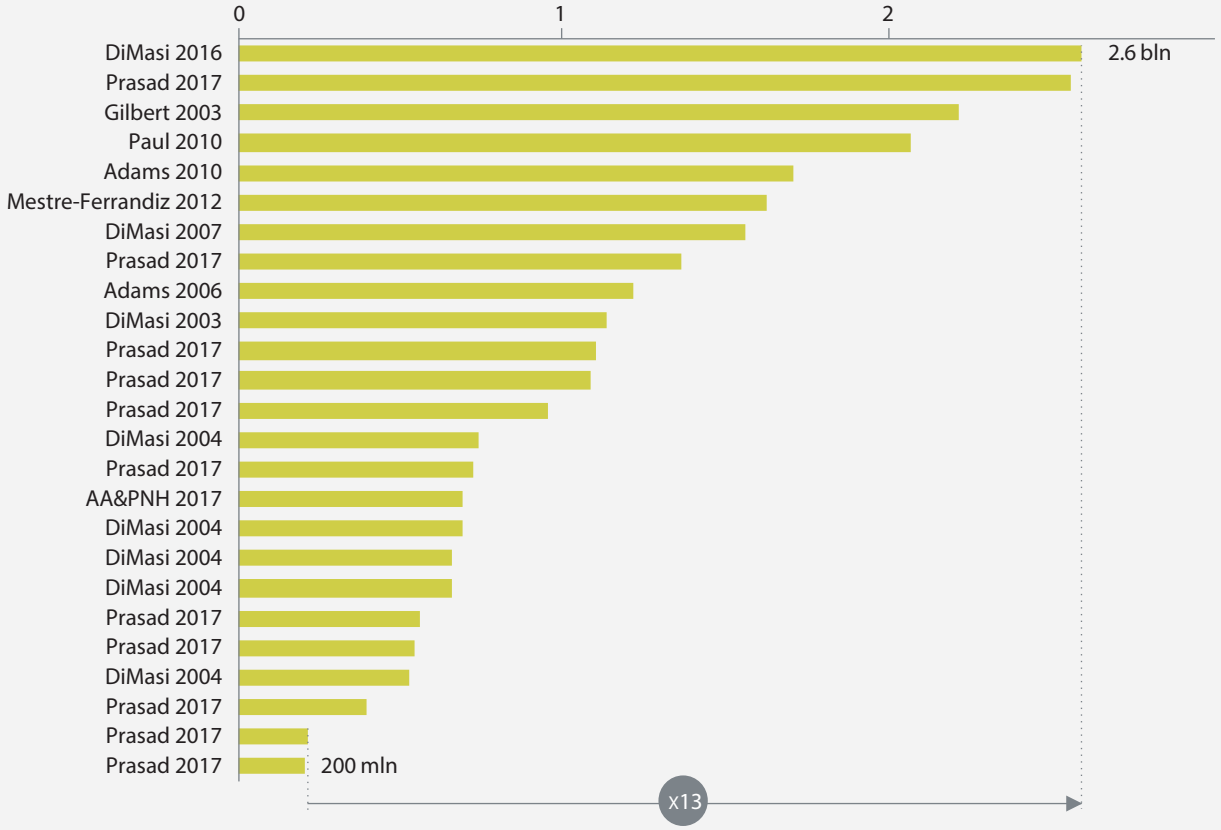


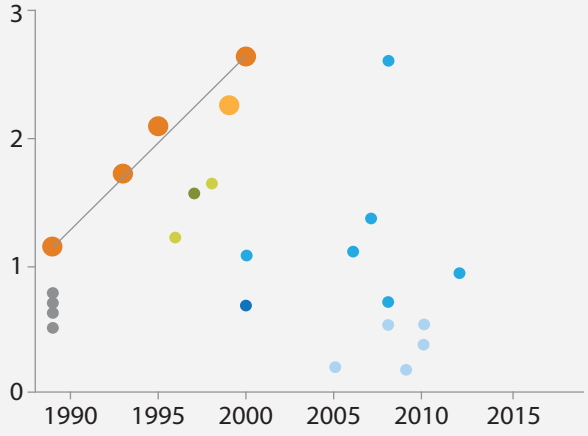
Figure 3. Reported R&D costs per NME vary widely between studies[6].

The difference in results can be explained, at least partly, by the fact that these studies use R&D costs from different time periods. Furthermore, they apply different definitions of R&D costs *(Figure 4)*:

- Firstly, the studies include different subsets of NMEs; they either study a broad sample of self-originated NMEs (orange dots), NMEs in a specific therapeutic area (grey dots), or biologic (dark green dots).
- Secondly, failure costs are either attributed to successfully developed NMEs (orange, green and grey dots) or are not considered at all (blue dots).
- And finally costs of capital, which are costs associated with the capital required over the period it takes to develop a new medicine, are valued differently. Costs of capital are reflected by the WACC and the value of the WACC varies between 0% and 11.5% in the studies.

Figure 4 illustrates that these variations lead to significantly different R&D costs estimates and, as a result, reported R&D costs per NME are difficult to compare and interpret.

R&D costs per NME in average year of R&D costs
[bln USD per NME, 1990-2015]



Legend

Sample	Self originated?	Failures included?	WACC
Average	✓	✓	10.5-11.5%
Average	✓	✓	10.5-11.5%
Biotech	✓	✓	10.5-11.5%
Average	~	✓	10.5-11.5%
Specific area	✓	✓	10.5-11.5%
Single drug	✓	X	0%
Single drug	✓	X	7%
Single drug	X	X	7%

Figure 4. Reported R&D costs per NME vary widely, dependent on year of study and definition of R&D costs. Left graph shows total R&D costs in bln USD (y-axis) per average year of study[7] (x-axis) per individual study (colored dots). The legend on the right describes the definition of R&D costs used in each individual study (color of dots corresponds with left graph)[6]. Note to legend: in sample column, 'average' means that the study draws conclusions on all NMEs, while 'biotech', 'specific area' and 'single drug' indicate that the study draws conclusions on specific NME subsets. A tilde in column self originated indicates that a study is based on both self originated and licensed in NMEs.

In this study, we provide a detailed and up-to-date insight into R&D costs of NMEs using a novel, top-down model built on a single definition of R&D costs and its principal drivers. Using this model, we reconcile the different cost estimates of bringing a new medicine to market and explore the impact of factors that drive these costs. Furthermore, we put forward different ways to potentially moderate R&D costs of NMEs. We believe these insights provide a fact base that will help pharmaceutical companies, academic researchers and policymakers in their quest to increase the value obtained from the billions spent on pharmaceutical R&D each year.

3 e.g. www.forbes.com/sites/johnlamattina/2015/05/20/do-rd-costs-matter-when-it-comes-to-drug-pricing/#281a9c107994

4 Annual reports of pharmaceutical companies.

5 All revenues and R&D costs in this report are adjusted to 2017 dollars with worldwide inflation of high-income countries.

6 AA&PNH (2017); Adams (2006, 2010); DiMasi (2003, 2004, 2007, 2016); Gilbert (2003); Mestre-Ferrandiz (2012); Paul (2010); Prasad (2017).

7 R&D of an NME takes place over a long period of time (i.e. 10-15 year). In the model, we use the average year of research as a proxy for the period of R&D (e.g. when R&D took place between 2000-2014, the average year of research is 2007).

Insights

R&D costs per NME are 2.5 bln USD in 2017

The total costs of development of an NME are 2.5 bln USD in 2017 *(Figure 5)*. In absolute terms, the out-of-pocket success costs, representing the costs directly associated with the development trajectory of drugs that successfully reach the market, are 'only' 0.2 bln USD. By contrast, the out-of-pocket failure costs (i.e. the costs incurred for all drug candidates that do not reach the market) and costs of capital (COC, i.e. costs associated with capital required for out-of-pocket success and failure costs) are the largest components of development costs of an NME, 1.0 bln USD and 1.3 bln USD, respectively.

Composition of R&D costs of an average NME in 2017
[% of total (bln USD)]

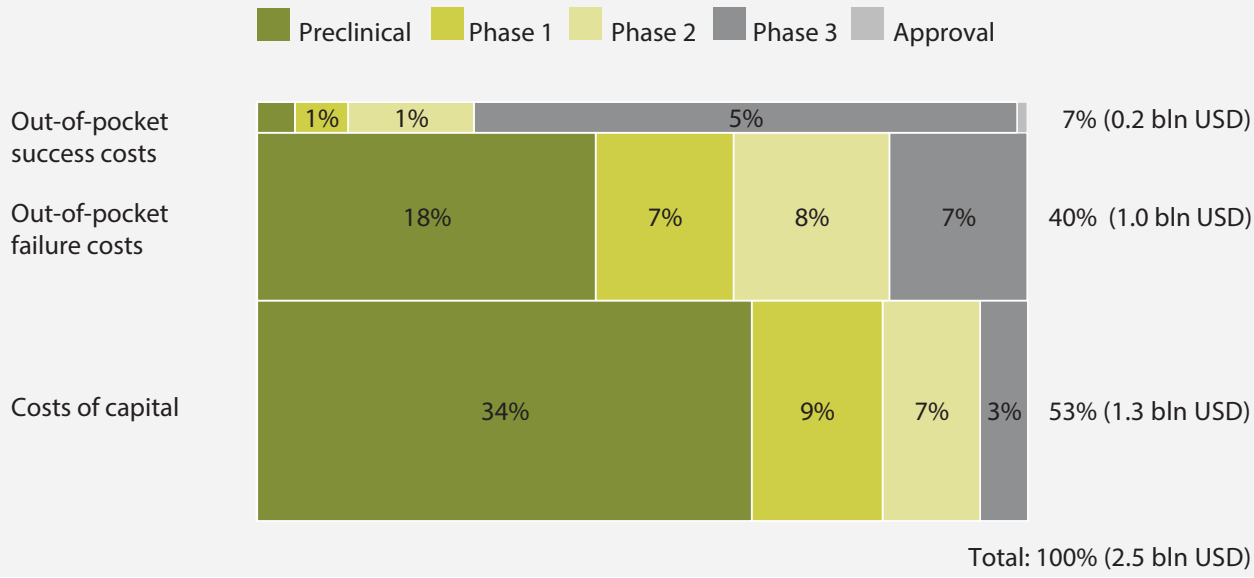


Figure 5. In 2017, total R&D costs of an NME are 2.5 bln USD, consisting of out-of-pocket success costs, out-of-pocket failure costs and costs of capital.

The total R&D costs of an NME consist of three components:

- *Out-of-pocket success costs:* out-of-pocket success costs account for 7% of total development costs, representing 0.2 bln USD in 2017. Most of these costs are incurred in phase 3 trials. These costs are driven by the trial size, i.e. the number of patients required to demonstrate a clinically meaningful and statistically significant treatment effect, and the trial cost per participant.
- *Out-of-pocket failure costs:* out-of-pocket failure costs account for 40% of total R&D costs, representing 1.0 bln USD in 2017. Most of the failure costs can be attributed to the preclinical phase and phase 1 trials. Failure costs largely depend on failure rates. Interestingly, failure rates differ significantly between therapeutic areas: the failure rate for oncology drugs is ~98%, whereas for hematology drugs it is ~89% (see *Figure 21* in the Appendix for more information). Aside from scientific characteristics of the medicine, failure rates are driven by policy (e.g. higher hurdles for winning approval) and investment decisions by pharmaceutical companies.

- *Costs of capital:* COC account for approximately half of total R&D costs per NME, in absolute terms 1.3 bln USD. The COC are mainly driven by trial duration and the WACC. If it takes longer to develop a portfolio of medicines such that at least one of them successfully reaches the market, higher amounts of funding are needed from capital markets. *Figure 6* shows the buildup of total R&D costs over the course of an R&D trajectory and illustrates that the relative contribution of the COC increases during the trajectory: from 15% at the start of phase 1 to 53% at approval.

Buildup of R&D costs of an average NME in 2017
[bln USD, years from start of R&D trajectory]

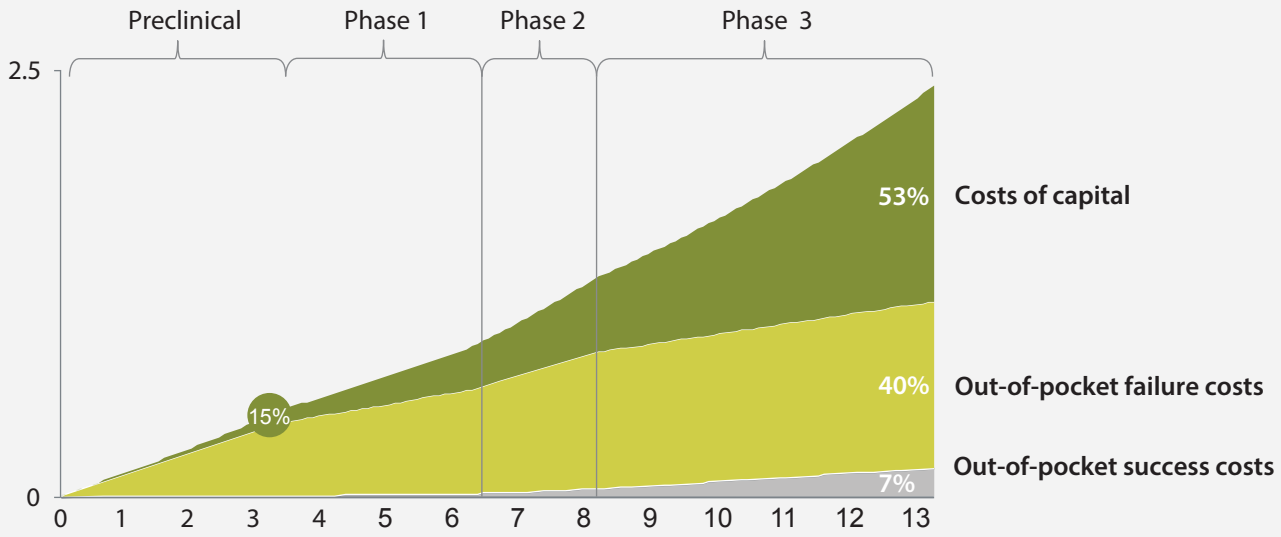


Figure 6. Cumulative R&D costs during an average R&D trajectory of 10-15 years. Assumption: R&D costs within a phase are equally distributed over time.

R&D costs per NME vary between therapeutic areas

Total R&D costs differ substantially between therapeutic areas: the average development costs of a medicine for an orphan disease could be as low as 0.5 bln USD, while the costs of a medicine for an oncological disorder could be as high as 6.5 bln USD *(Figure 7)*.

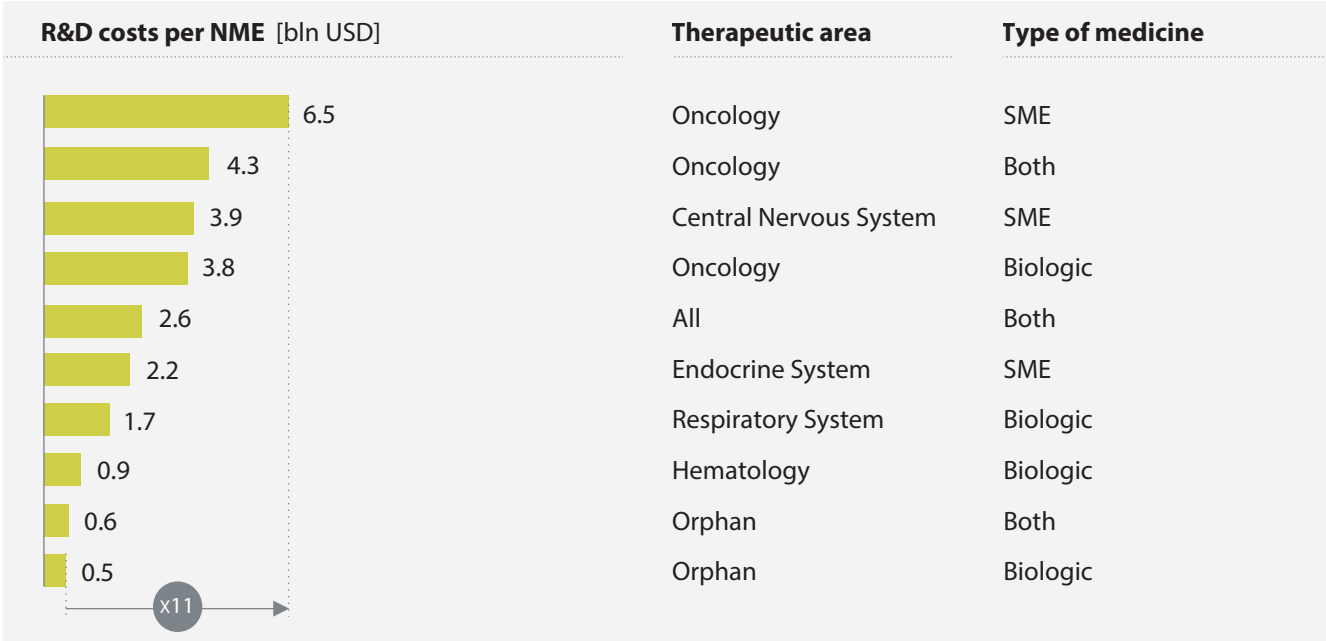


Figure 7. In 2017, R&D costs per NME differed up to a factor 11 between therapeutic areas and types of medicines.[8]

The contribution of the cost components to total R&D costs also differ between therapeutic areas *(Figure 8)*. For example, out-of-pocket failure costs form a much smaller portion of total R&D costs for orphan drugs than for (non-orphan) cancer drugs. This is caused by relatively more relaxed approval paths and a more specific target population, leading to larger expected effect size.

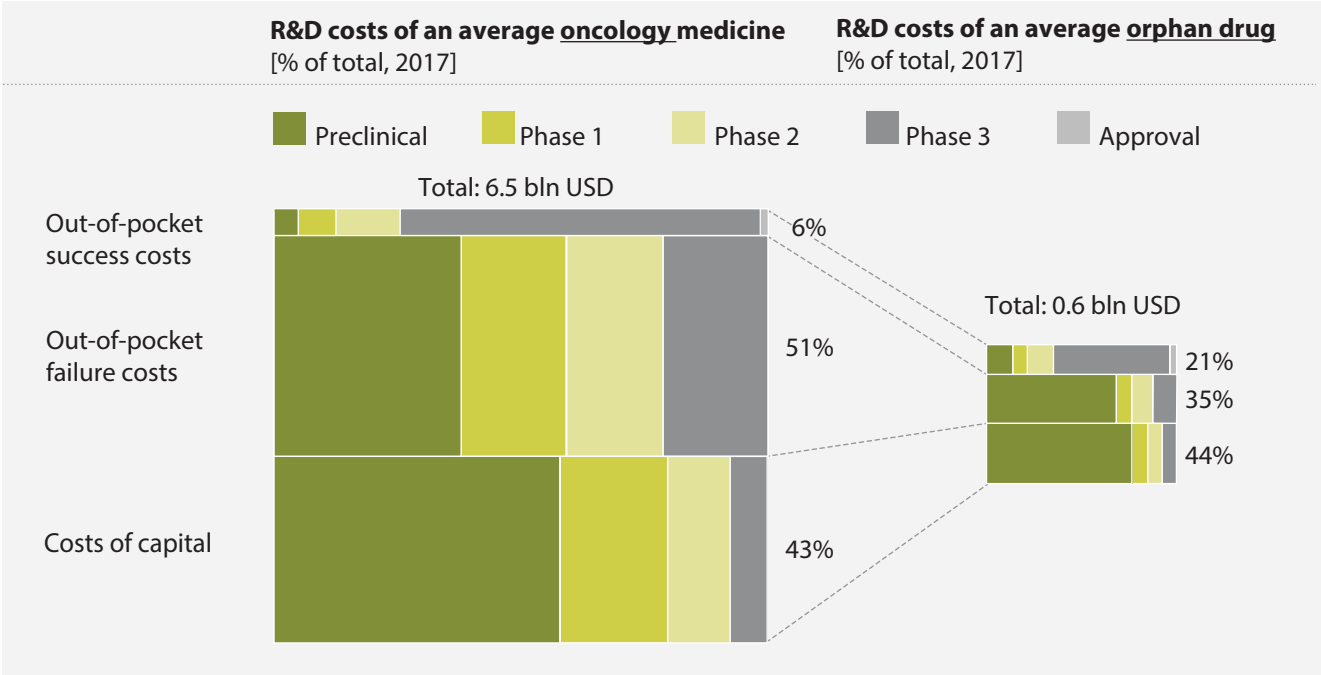


Figure 8. R&D costs of an average oncology medicine and an average orphan drug differ in size as well as in contribution of the three cost components.

R&D costs per NME vary over time

The R&D costs per NME peaked in 2007 up to 3.7 bln USD and subsequently declined to 2.5 bln USD in 2017, which is almost the same amount as in 2000 *(Figure 9)*.

R&D costs per NME per average year of research
[bln USD 2017, 1990-2017]

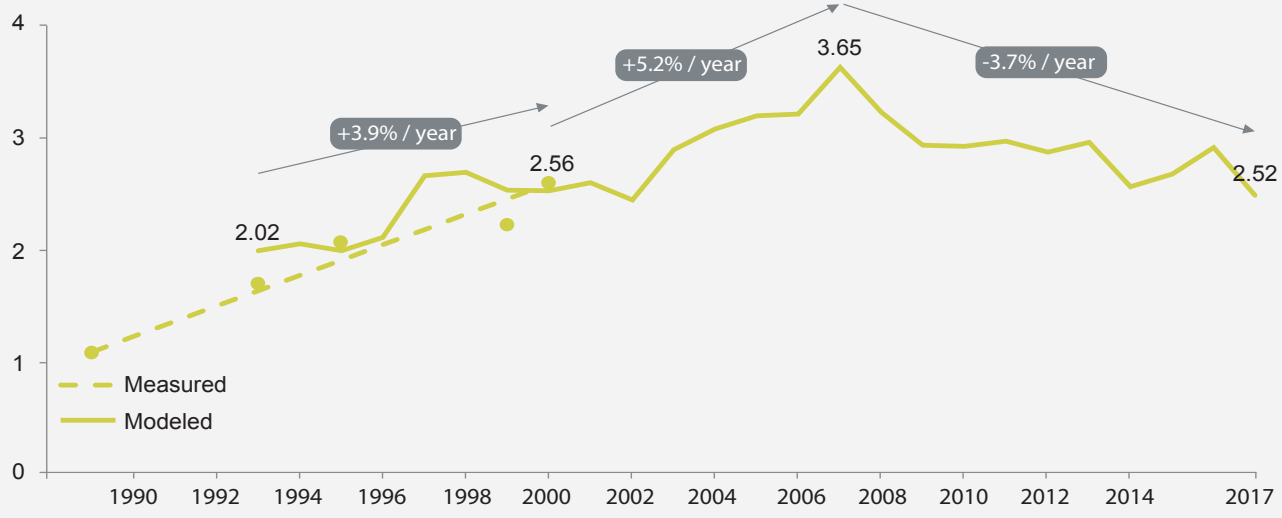


Figure 9. R&D costs per NME peaked in 2007 and subsequently declined to approximately the same amount as in 2000 (measured = datapoints from published studies described in figure 4

R&D costs are affected by four cost drivers: trial size, trial duration, success rate and WACC. In *Figure 10*, we show the development of these factors over time.

Development of cost drivers of pharmaceutical R&D costs
[Indexed to 2000; red drivers lead to cost increase between 2000 and 2017, green drivers to cost decrease]

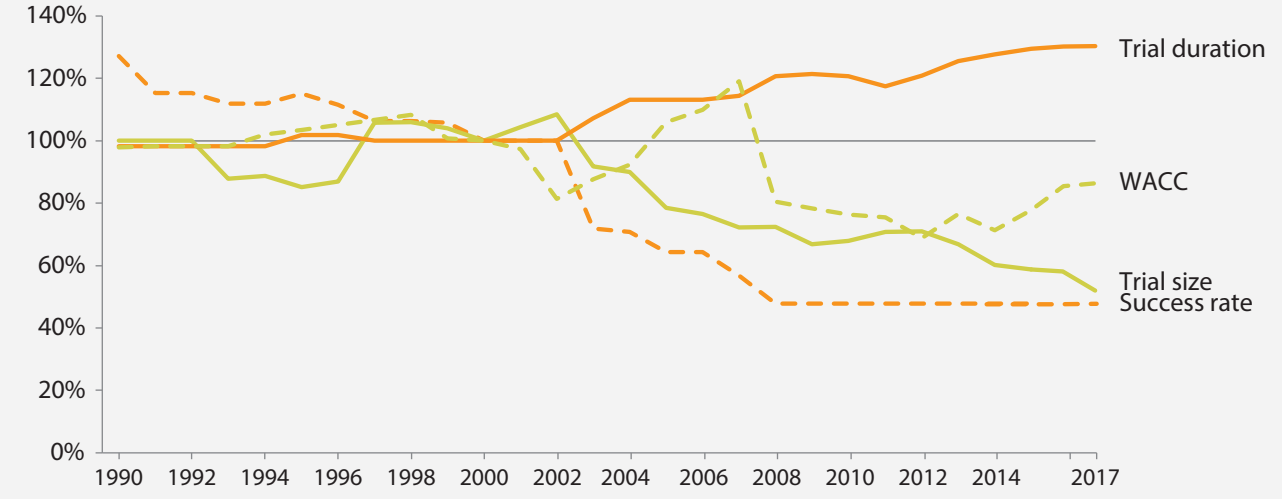


Figure 10. The four cost drivers show opposite effects on total R&D costs over time: trials took longer and success rates went down, leading to a negative effect on R&D costs (i.e. costs potentially went up), whereas trial size and WACC decreased (indexed for 2000), leading to a positive effect on R&D costs (i.e. costs potentially went down). See Appendix for absolute development of individual cost drivers.

Here, we briefly summarize the key trends observed for the four cost drivers:

- Average trial duration has steadily increased since 2002; this observation is consistent with observations by others[9] and possibly reflects increasing protocol complexity and treatment duration to demonstrate efficacy.
- Success rates steadily declined between 1990 and 2009; the declining success rate may reflect the concept of diminishing return: as more treatment options become available, it becomes increasingly more difficult to demonstrate incremental improvement. Furthermore, it can be attributed to more intense rules and regulations following several terrible real-life outcomes of medicines after market entry (such as Softenon and Vioxx[10]).
- Average trial size increased until 2002, but declined rapidly since; we believe the decline is a result of the changing pharmaceutical landscape, in which more orphan drugs are being developed, for which trial sizes are smaller by definition.
- WACC decreased rapidly after the financial crisis in 2007 and has stabilized since.

In *Figure 11*, we show the extent to which each of these trends impacted total R&D costs per NME.

Relative contribution of cost drivers to overall development of R&D cost per NME
[bln USD per NME, 1990-2017]

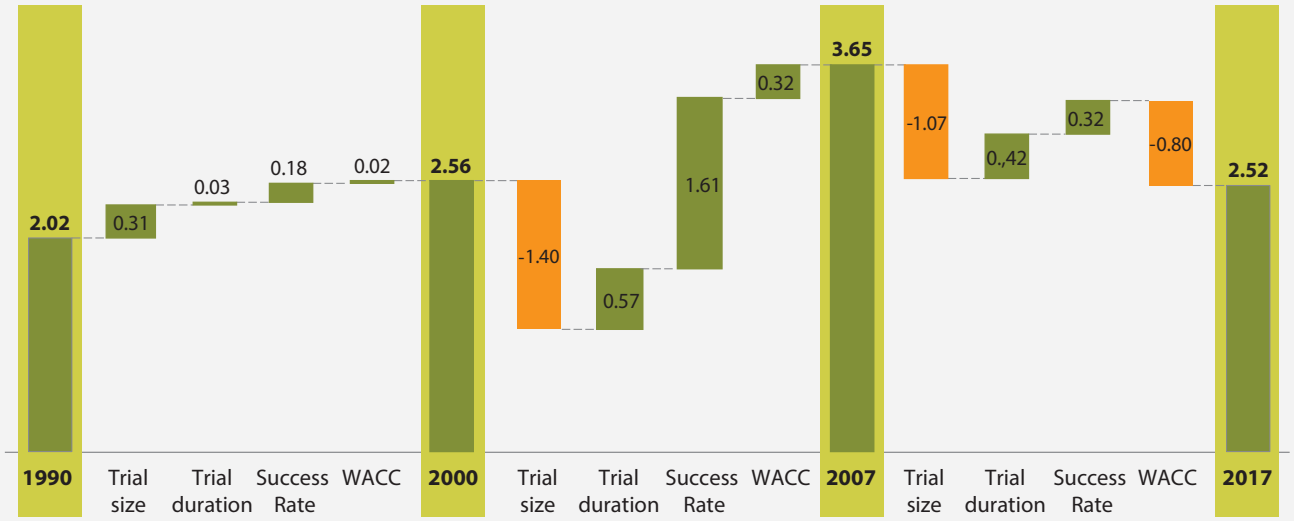


Figure 11. Reduced trial size and lower WACC are the principal drivers of recent decline in R&D costs.

8 Obviously, 'orphan' is not a real therapeutic area, however no data is a available to significantly separate these drugs into different therapeutic areas.

9 http://www.appliedclinicaltrialsonline.com/oncology-trials-are-taking-longer

10 Krumholtz (2007), Volkskrant (2012).

Implications

The insights of this study can help substantiate discussions on R&D costs with facts. When referring to R&D costs, it is important to use an unequivocal definition and up-to-date results. As shown in the previous chapter, R&D costs of an NME were 2.5 bln USD in 2017. The breakdown of these R&D costs into their underlying components may help pharmaceutical companies, academic researchers and policymakers in their quest to increase the efficacy of R&D expenditure. While there is no low-hanging fruit, conceptually, this could be achieved in several ways:

Reduce the costs of capital

Given that this is the largest contributor to R&D costs, it makes sense to explore options for reducing the COC. We see 3 avenues to influence these costs:

- *Reducing the time that capital is needed:*
  Policymakers or private-public initiatives can search for ways to reduce time to market, for example by allowing pharmaceutical companies in certain instances to access the market already after phase 2. *Figure 6* shows that a large proportion of COC are incurred during phase 3, so a measure like this would have substantial impact. In more extreme variants of this line of thinking, phase 3 trials could transform into 'real world evidence' gathering[11]. This may improve the quality of evidence generated on efficacy, but the benefits should be weighed against the potential downside of patients being exposed to medicines from which they may not benefit.
- *Reducing the amount of funds that are capitalized:*
  Preclinical research is often executed at universities, which then sell assets to pharmaceutical companies for further development. Policymakers could look for ways to entice (or require) universities, when auctioning their assets, not to consider the costs incurred or the future (potential) market value of the medicine. In the most extreme variety, the transfer price should be zero, since the assets are already paid for with public funding. Instead, auction criteria could be based on, for example, the quality of the proposed development plan, guarantees on future pricing, etcetera. While the actually incurred costs of preclinical research are relatively small, the COC are very high (34% of total development costs, see *Figure 5*) because the capital is fixed for such a long period of time. The impact of a measure like this is therefore potentially very large.
- *Reducing the rates of return on capital:*
  By using public finances to fund a larger proportion of the development cycle, COC would come down. Governments could fund universities and encourage them to execute a larger proportion of the cycle, e.g. by doing more phase 1 or 2 trials. This would only be beneficial if pricing of transfer to pharmaceutical companies for further development would be based on costs incurred, not future (potential) market value of the medicine. Taking it to the extreme, governments could consider setting up public investment funds to finance pharmaceutical R&D. This would be rooted in the idea that capital for medicine development might be considered a public facility much like, for example, public infrastructure such as a telecoms network.

Reduce development costs of medicines that do not reach the market

Out-of-pocket failure costs form a substantial part of total R&D costs per medicine. Therefore, reducing these costs has a considerable impact on total R&D costs. We see different opportunities to do so:

- *Increasing efficiency of investment decisions:*
  Failure rates vary widely across therapeutic areas. This difference may reflect aspects intrinsic to each therapeutic area (e.g. availability of reliable preclinical research models) or more efficient investment decisions being made in one area versus the other. It is, for example, likely that criteria to invest in certain fields, like oncology or Alzheimer's disease, with huge potential markets if successful, are weighted differently than in fields with smaller potential markets, such as hematology. Potentially, pharmaceutical companies could drive down R&D costs by optimizing investment criteria
- *Reconsider criteria for approval:*
  The lower failure rates of medicines for orphan diseases, for which approval paths are relatively more relaxed, suggest that there is substantial potential gain if regulating authorities were to critically seek for opportunities to loosen approval requirements for non-orphan disease medicines. This would require that determination of efficacy is left to a greater extent to the post-marketing phase, placing more responsibility in the hands of, for example, universities to study efficacy in clinical trials and guideline boards to weigh the evidence. As pointed out above, this may improve the quality of evidence generated on efficacy, but the benefits should be weighed against the potential downside of patients being exposed to medicines from which they may not benefit.

Reduce development costs of medicines that reach the market

The out-of-pocket success costs are only a small component of the total R&D costs. Moreover, the execution and management of clinical trials has already been commoditized and is typically outsourced in a competitive market of clinical research organizations. We therefore conclude that the potential impact of reducing these costs is small. For example, a 10% improvement in these costs, which would be significant, would lead to an impact of < 0.02 bln USD per NME. ■

11 See, for example: https://www.healthaffairs.org/do/10.1377/hblog20171030.999857/full/

Appendix

Description of the model

Our model deaverages R&D costs over time and type of medicines, starting off with the average R&D costs in 2000[12]. The top-down model uses changes in and variation of principal cost drivers to forecast total R&D costs. The model consists of five elements *(Figure 12)*:

1) *Output of the model* – We define R&D costs of an NME as the sum of out-of-pocket success costs, out-of-pocket failure costs and costs of capital over the full development cycle.
2) *Drivers of R&D costs per NME* – We include trial size, trial duration, success rate and WACC as the principal drivers of R&D costs.
3) *Relationship between cost drivers and R&D costs per NME* – We determine the mathematical relationship between each principal cost driver and R&D costs for each phase of the R&D cycle.
4) *Definition of model inputs that determine the value of cost drivers* – We include three factors in the model: year of R&D, therapeutic area and type of medicine.
5) *Relationship between model inputs and cost drivers* – We assess the relationship between model inputs and cost drivers based on data of 70,000 trials and a meta-analysis of existing literature on such relationships.

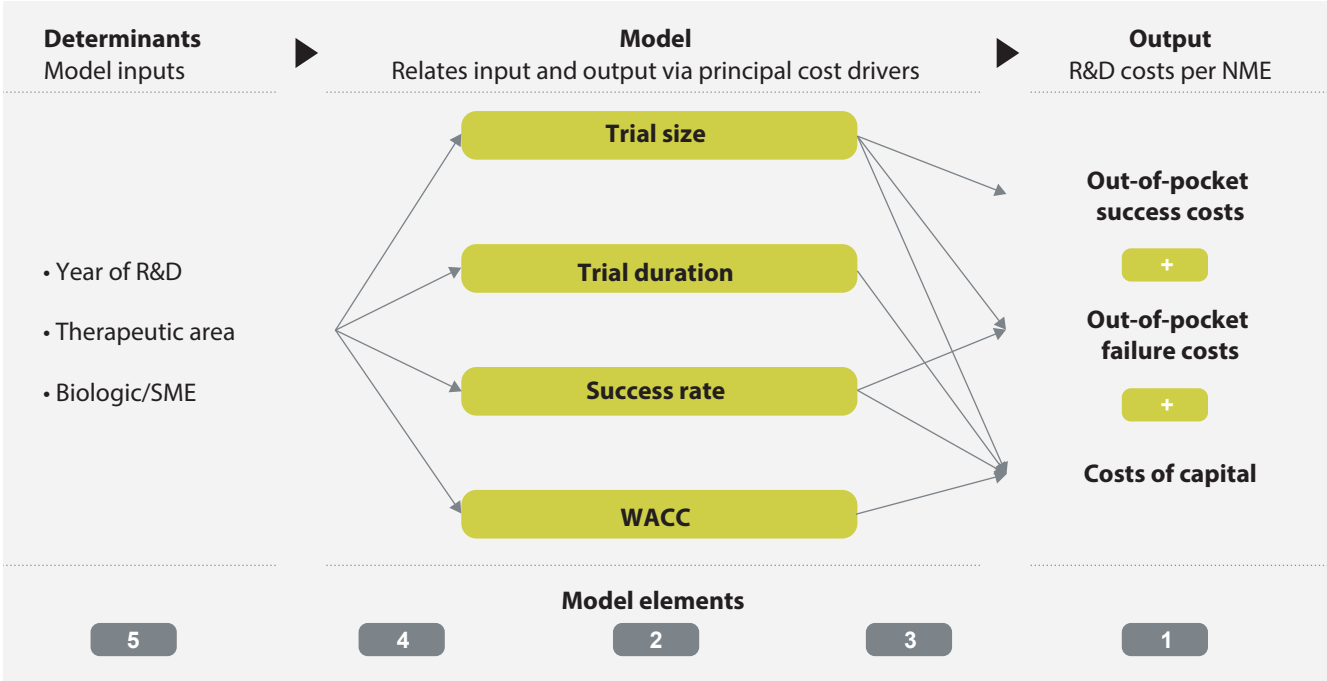


Figure 12. Graphical representation of the cost driver model.

1) Output of the model

We define R&D costs of an NME as the sum of all costs directly attributable to research of that NME (out-of-pocket success costs), the costs of failure (out-of-pocket failure costs) and financing (costs of capital).

In this study we do not differentiate between R&D settings (e.g. academia or small biotech companies) or ways of cost accounting. For example, if a medicine is discovered in academia or a small biotech company, R&D costs are reported in the income statement of this institute. When another company acquires a license to market this medicine, costs of this transaction

are reported in the balance sheet, but subsequent R&D costs will again be reported in their income statement. However, irrespective of how these costs are accounted for, they all constitute R&D expenditure.

- *Out-of-pocket success costs:* this study examines the overall costs of R&D until market introduction. Development of a new medicine can be divided in the preclinical phase, three clinical phases and the post marketing phase *(Figure 13)*. The model in this study includes all R&D costs made in preclinical and clinical phases, so before the market entry of the new medicine.

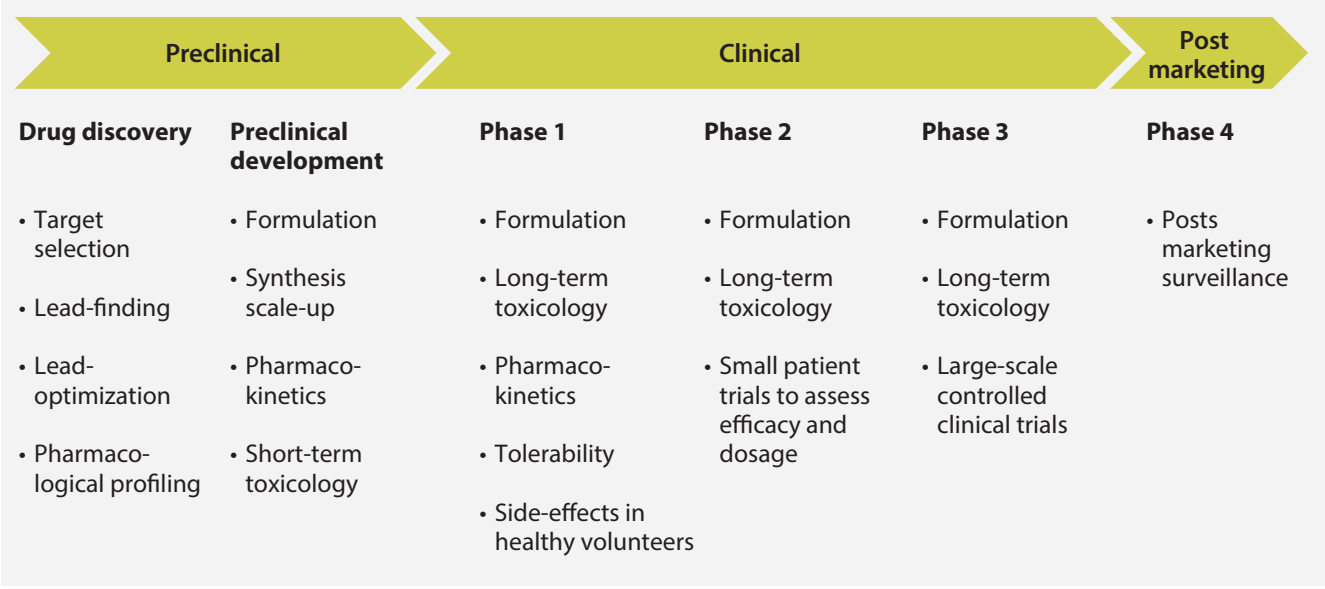


Figure 13. R&D of medicines consists of a preclinical phase and three clinical phases before market introduction.

- *Out-of-pocket failure costs:* many medicines fail before market entry, for example if a lead in the preclinical phase does not successfully reach the predefined target or the efficacy of the medicine is lower than expected in phase 3.
  The accounting of R&D costs of failures is a widely discussed topic. In this report, we consider the bigger picture: the global R&D costs. Since the R&D costs of failures have indeed been incurred, revenue is required to pay for these costs. The exact number of failures in non-successful companies is unknown, since failed medicines are not acquired by other companies. However, shareholders invest in these failed medicines and their investments need to be earned back by successful companies.
- *Costs of capital:* finally, the out-of-pocket costs (both success and failure) need to be financed. These COC can be divided into costs of debt (interest) and costs of equity. These funds could have otherwise been invested in another project, but now cannot be used until the medicine has been brought to market and revenue has been generated. These costs are the return on investment for the investors and are time dependent. The earlier in the development process an investment is made, the higher the COC will be.

2) Drivers of R&D costs per NME

Literature analysis shows that R&D costs are driven by four principal drivers: trial size, trial duration, success rate and WACC.

- *Trial size:* trial size is defined as the number of participants per phase. The number of participants and the cost per participant influence trial costs. Variation in number of participants is driven by statistics: an adequate sample size is required to demonstrate a clinically meaningful and statistically significant treatment effect on the chosen endpoint.
- *Trial duration:* trial duration is defined as the time between the start of one clinical phase and the next. Phase 1 usually takes several months, phase 2 can last up to two years and phase 3 can take up to four years. In this report we assume trial duration in preclinical phase to be constant, while trial duration of phase 1, 2 and 3 can vary.
- *Success rate:* success rate is defined as the chance that a molecule will successfully pass a trial phase. Not all clinical trials have a positive outcome. Medicines that are not brought to market are called failures. Failure can occur in every stage of the process, from preclinical up to the moment of approval.

  WACC: the final cost driver is the WACC. Like any economic sector, the pharmaceutical industry is dependent on the worldwide market for capital supplied by investment banks, shareholders and other investors. Depending on the risk profile of a sector, the expected return on investment (ROI) varies. For high risk investments, expected ROI is higher than for more secure investments. This report uses WACC as a measure for the expected annual ROI. WACC is a weighted average of cost of debt and cost of equity. R&D in pharmacy usually takes 10-15 years per NME, so investments are long term.

3) Relationship between cost drivers and R&D costs per NME

The four cost drivers (trial size, trial duration, success rate and WACC) each have an individual effect on R&D costs *(Figure 14)*.

R&D costs per NME per average year of research

	Trial size	Trial duration	Success rate	WACC
Out-of-pocket success costs	Larger trials have higher costs			
Out-of-pocket failure costs	Larger failed trials have higher costs		More failed trials (lower success rate) result in higher failure costs	
COC	Larger trials with higher costs result in higher COC	Longer trials require longer term investments and higher COC	More failed trials (lower success rate) with higher costs result in higher COC	Higher WACC result in higher COC

Figure 14. R&D costs of medicines are driven by trial size, trial duration, success rate and WACC.

For each phase of the R&D cycle, we define the mathematical relationship between each principal cost driver and R&D costs *(Figure 15)*.

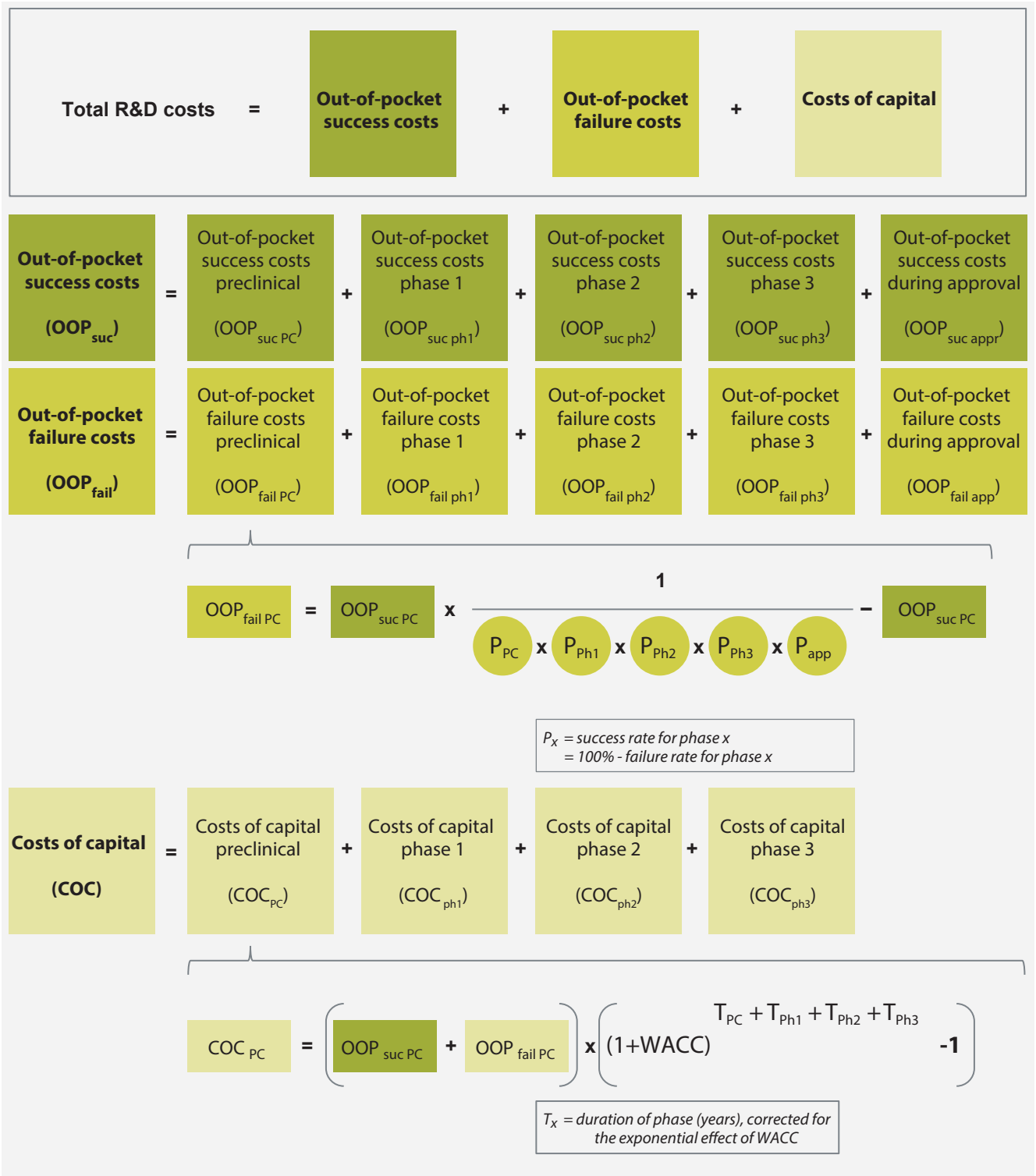


Figure 15. Mathematical relationship between cost drivers and R&D costs.

4) Definition of model inputs that determine the value of cost drivers

This study focuses on three factors that determine the value of cost drivers: the year in which R&D took place, the therapeutic area and the type of medicine. These are three factors that vary over historically reported R&D costs and are therefore individually considered in the model.

- *Year:* R&D of an NME takes place over a long period of time (10-15 years). In the model we use the average year of research as a proxy for the period of R&D. For example, when R&D took place between 2000-2014, the average year of research is 2007.

- *Therapeutic area:* to deaverage the R&D costs over therapeutic areas we differentiate between the following therapeutic areas:
  - Cardiovascular System
  - Central Nervous System
  - Dermatology
  - Endocrine System
  - Gastrointestinal System
  - Genitourinary System
  - Hematology
  - Immunology
  - Infectious Diseases
  - Oncology
  - Ophthalmology
  - Pain and Anesthesia
  - Respiratory System
  - Rare diseases (orphan medicines)[13]

- *Type of medicine:* to deaverage the R&D costs over type of medicines, we differentiate between the following types:
  1. SME (Small Molecular Entity)
  2. Biologica

5) Relationship between model inputs and cost drivers

The relationship between model inputs and cost drivers is assessed based on data of 70,000 trials (registered in ClinicalTrials.gov) and a meta-analysis of existing literature on such relationships. These data points are used to scale the cost drivers to the right year, therapeutic area and type of medicine.

Relationship between year and cost drivers

Trial size

In this report, we assume costs per participant to be equal over time. Therefore, we scale trial size over time by number of participants. Average number of participants is based on data of clinical trials. Number of subjects is averaged and summed for phase 1-3 to correct for outliers and for trials running multiple years: we use the reported start of the trial as the year of input and a moving average over 3 years for the sum of phase 1-3.

In addition, we assume costs per participant to be independent of year of trial start. For each year, we calculate the average number of participants per trial phase, for all trials started that year. We subsequently sum these participants over all three trial phases. In *Figure 16*, we report the moving average over 3 years of these summed participants.

Number of subjects per successful medicine
[moving average over 3 years, sum of phase 1-3, start of trials: 1993-2017]

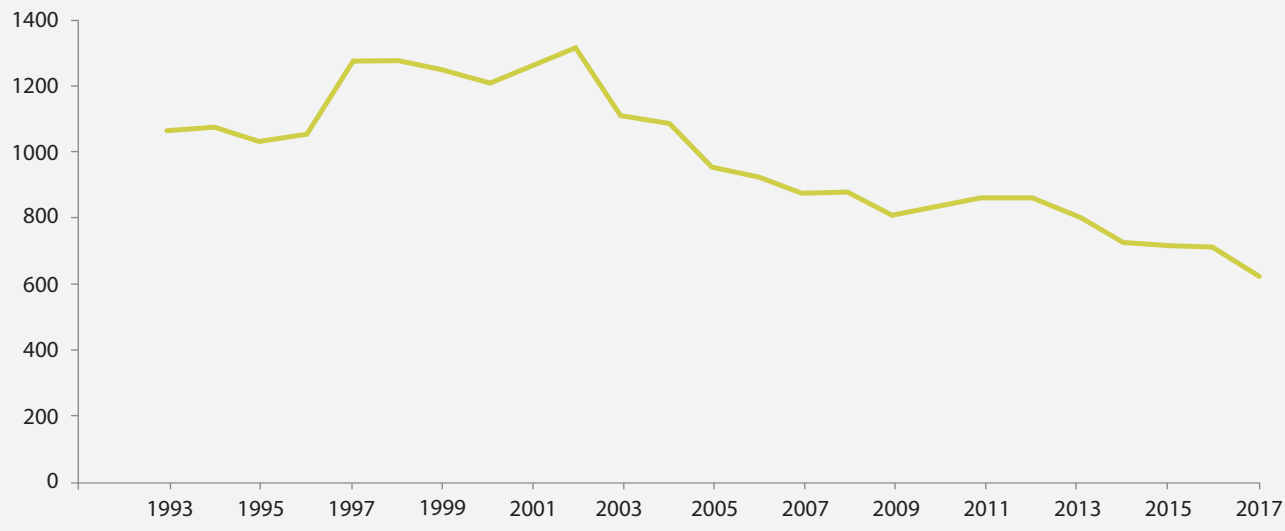


Figure 16. After a peak in 2002, average trial size declined in the last 15 years. Note: only trials with > 15 subjects were included[14].

Trial duration

The reported increase in trial duration over time is based on meta-analysis of existing studies on this topic. For each year, we averaged the reported trial duration (sum of duration of phase 1, 2 and 3) for all started trials *(Figure 17)*. The number of studies that reported trial durations for separate phases was insufficient to accurately determine changes in trial duration over time for separate phases.

Development of trial duration of new medicines
[number of months for phase 1-3, start of trials: 1989-2015]

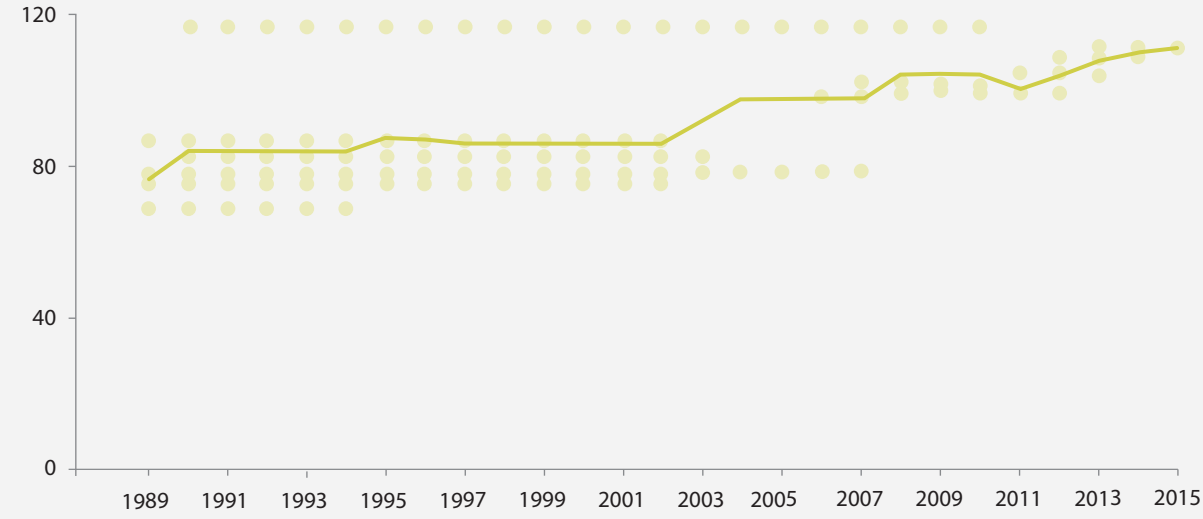


Figure 17. Average trial duration increased by 62% between 1989 - 2015. Note: individual samples of a period are represented by a dot per year, averages were calculated over all available samples per year[15].

Success rate

Variation in success rate over time is based on a meta-analysis of existing studies. For each year, we averaged the reported success rates (from phase 1 till approval) for that year *(Figure 18)*. The number of studies that report success rates for separate phases was insufficient to accurately determine changes in success rates over time per phase.

Development of success rate of new medicines
[success rate (% of phase 1 medicines that are successfully approved), start of trials: 1989 -2010]

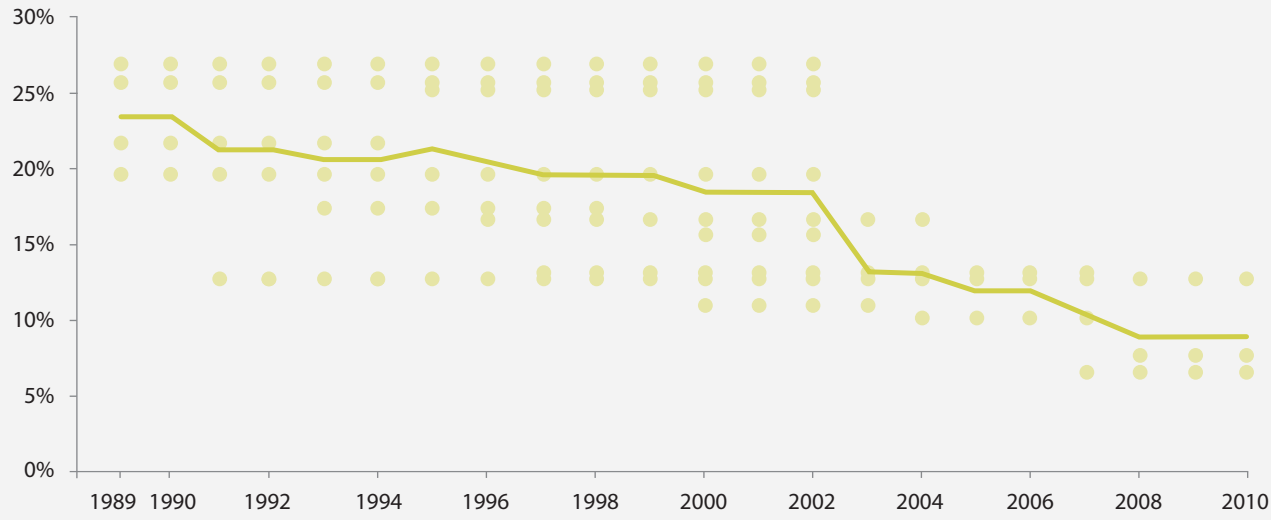


Figure 18. Success rates showed a marked decline, particularly between 2000 and 2010.[16]

WACC

COC for the pharmaceutical industry is based on public data that calculates WACC for the pharmaceutical industry *(Figure 19)*.

WACC of pharmaceutical industry
[%, 1983-2017]

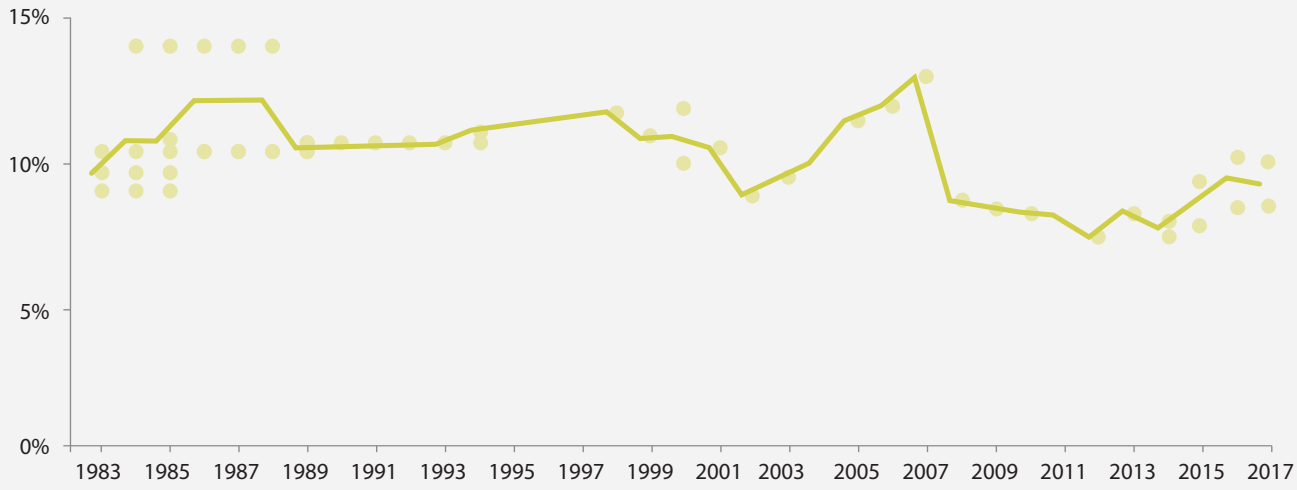


Figure 19. WACC for the pharmaceutical industry declined markedly since the financial crisis in 2007. Note: individual samples are represented by a dot per year, average calculated over available samples per year[17].

Relationship between therapeutic area and type of medicine, and cost drivers

Trial size

As a proxy for trial size by therapeutic area, we use published estimates of trial costs per phase and per therapeutic area *(Figure 20)*. For orphan medicines, trial costs are only 35% of the average trial costs, due to a lower number of participants[18].

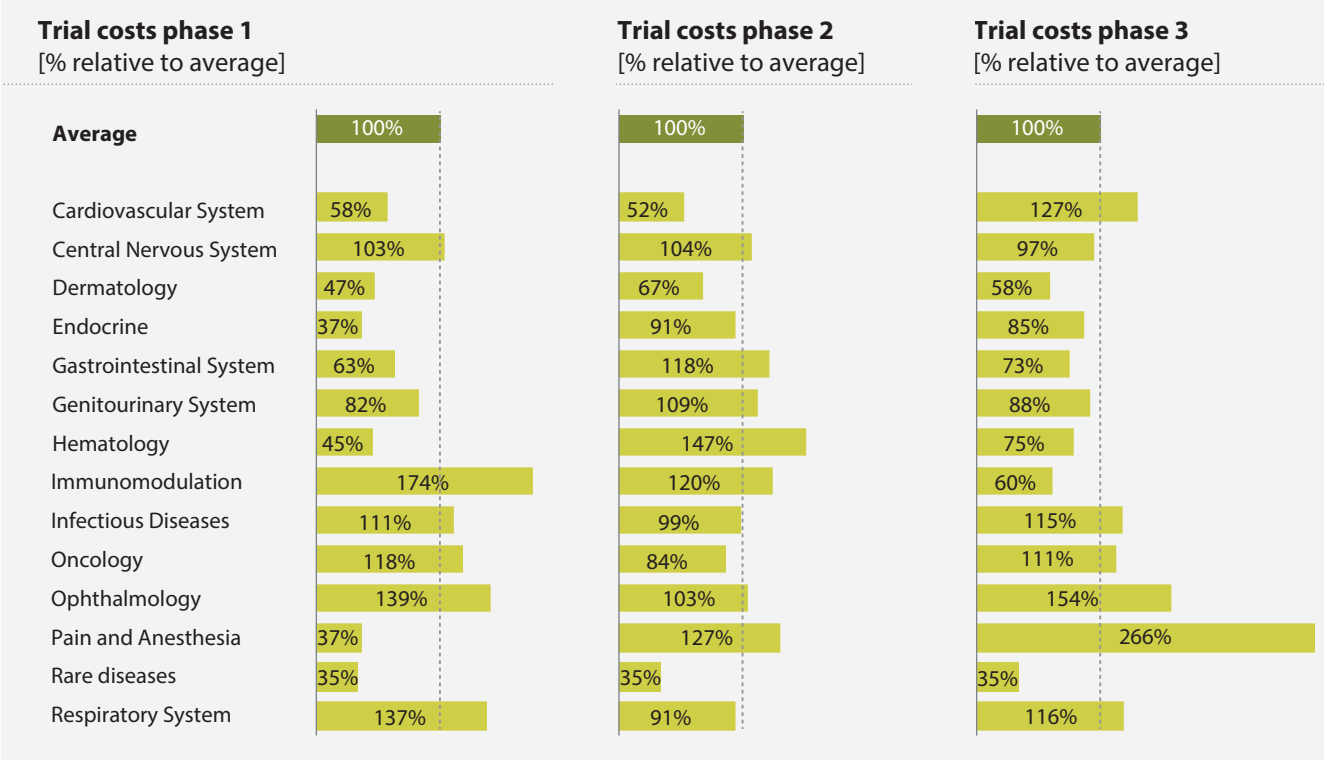


Figure 20. Phase 3 trials are most expensive for Pain and Anesthesia; rare diseases are less expensive than other therapeutic areas.[19]

Trial duration

No studies on trial duration per therapeutic area are known to us. Therefore, we assume trial duration to be constant, irrespective of therapeutic area or type of medicine.

Success rate

The total success rate (from preclinical[20] to approval) varies across therapeutic areas and types of medicine *(Figure 21)*. Oncology is the therapeutic area with the lowest success rate, due to the low success rate in phase 3. The weighted average success rate is highly driven by oncology, since this area accounts for 25% of all NMEs. There is also a substantial difference in success rate between different types of medicine. For example, the success rate of new biologicals is almost twice that of SMEs.

Success rate of preclinical phase is not reported and is assumed to be constant over therapeutic area and medicine type. Furthermore, reported values per therapeutic area are linearly scaled to success rates that coincide with the average R&D costs of 2000. As such, the success rate for a therapeutic area is assumed to be constant over time.

Success rate preclinical → approval		Success rate preclinical	Success rate ph1	Success rate ph2	Success rate ph3	Success rate approval
Average	100%	35%	60%	36%	62%	90%
Cardiovascular System	3%	35%	55%	28%	59%	89%
Central Nervous System	4%	35%	56%	34%	61%	88%
Dermatology	7%	35%	63%	46%	74%	94%
Endocrine	6%	35%	55%	46%	69%	91%
Gastrointestinal System	7%	35%	71%	41%	65%	98%
Genitourinary System	5%	35%	54%	38%	76%	91%
Hematology	11%	35%	69%	65%	80%	89%
Immunomodulation	5%	35%	62%	37%	66%	91%
Infectious Diseases	8%	35%	65%	49%	77%	94%
Oncology	2%	35%	59%	28%	43%	87%
Ophthalmology	7%	35%	80%	52%	62%	82%
Pain and Anesthesia	7%	35%	63%	46%	74%	94%
Rare diseases	11%	35%	72%	58%	78%	94%
Respiratory System	6%	35%	61%	34%	76%	100%

Success rate preclinical → approval		Success rate preclinical	Success rate ph1	Success rate ph2	Success rate ph3	Success rate approval
Biologic	11%	35%	66%	34%	57%	88%
SME	6%	35%	61%	27%	49%	78%

Figure 21. Absolute variation of success rate over therapeutic area as reported over 2006-2015. Oncology is the therapeutic area with the lowest success rate, mainly due to the low success rate in phase 3; SMEs are associated with lower success rates than biologics in every phase [21].

WACC

In general, the WACC is comparable within an industry. Based on public data, it is not possible to account WACC to individual medicines, as this is largely determined by how funds are allocated within companies. For this study, we assume that WACC is equal for all types of medicines and for all types of disease.

Model assumptions

Main assumptions during development of R&D cost model	Model step associated with assumption
1. Failure costs accounted to medicines developed for the same therapeutic area and medicine type	1, 3
2. Trial costs change over time, due to changing number of participants (trial size). This is unaffected by trial duration. Costs per participant indexed over time	2, 3
3. Average R&D costs per NME are2.6 bln USD in 2000	3
4. The R&D costs for in-licensed and self-originated medicines are equal	4
5. R&D costs of 2017 are modelled based on most recent known value per cost driver	4
6. Average year of research determines development of R&D costs over time	1, 2, 5
7. Variation in time scales linear with average year of research	5
8. Trial duration fluctuates over time, but is equal over therapeutic area and type of medicine	5

Figure 22. Main assumptions during development of the R&D cost model.

12 DiMasi (2016).

13 Obviously, 'orphan' is not a real therapeutic area, however no data is a available to significantly separate these drugs into different therapeutic areas.

14 ClinicalTrials.gov, EvaluatePharma.

15 DiMasi (2003, 2007, 2016); Abrantes-Metz (2004); Adams (2006, 2010); Paul (2010); KMR-group(2012); Martin (2017).

16 Abrantes-Metz (2004); Adams (2006, 2010); DiMasi (2003, 2010); Gilbert (2003); Hay (2014); KMR-group (2012); Kola (2004); Smietana (2017).

17 Stern School of Business at New York University; Harrington (2009).

18 EvaluatePharma ; ClinicalTrials.gov

19 Sertkaya (2016). ClinicalTrials.gov

20 No variation between therapeutic area or type of medicine over preclinical success rate is known to the authors. Average preclinical success rate of 35% is based on Paul (2010).

21 Clinical Development Success Rates 2006-2015 - BIO, Biomedtracker, Amplion (2016).

List of definitions and abbreviations & sources

List of definitions and abbreviations

Costs of capital (COC)	Costs of debt (interest) and cost of equity. The latter refers to costs that are incurred when R&D is paid for directly from equity of the pharmaceutical company. This equity could have otherwise been invested in another project, but now cannot be used until the medicine has been brought to market and revenue has been generated
Development costs of NME	Sum of out-of-pocket success costs, out-of-pocket failure costs and costs of capital
FDA	US food and drug administration
NME	New molecular entity: a new small molecular entity or a new approved biologic medicine
Orphan disease	A disease that has not been adopted by the pharmaceutical industry because it provides little financial incentive for the private sector to make and market new medications to treat or prevent it. An orphan disease may be a rare disease (USA: <200,000 patients, EU: <5 in 10,000, Japan: <50,000 patients) or a common disease that has been ignored because it is far more prevalent in developing countries than in developed countries
R&D	Research and development
SME	Small molecular entity: a small molecule that has a low molecular weight
Success rate	Rate of molecules that successfully pass a preclinical or clinical phase: measured by percentage of molecules that started the next phase of research
Trial duration	Trial duration is defined as time between start of a clinical phase and start of the next clinical phase
Trial costs	Trial costs are defined as the costs incurred to fulfill a single-phase for a single NME
Trial size	Trial size is defined as the number of participants in a trial
USD	US dollar - Inflation adjusted to 2017
WACC	Weighted average costs of capital: the weighted average of cost of debt and cost of equity
Year of research	R&D of an NME takes place over a long period of time (10-15 year), in the model we use the average year of research as a proxy for the period of R&D. E.g. when R&D took place between 2000-2014, the average year of research is 2007

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