

# Research Synthesis: Time and Success Rates of Pharmaceutical R&D

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## Introduction

The literature on research and development (R&D) timeframes and success rates in the pharmaceutical sector is considerable.\* Most of the literature focuses on the development of drugs and on the clinical development stage of the process. The topic is a key component in pharmaceutical pricing models and current debates on the productivity of R&D.

## Search terms

Pharmaceutical research and development, Pharmaceutical R&D, drug development, medical product development, clinical success rates, transition rates, attrition rates, success rates, likelihood of success, LOA, probability of success, POS, clinical phase length, phase length, phase timelines, clinical timelines.

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

## Synthesis of the literature

Research and development for medical products is a longstanding topic of research. Estimating costs and time to produce new health technologies has wide implications for the pharmaceutical industry, governments, and global health policies as a whole. Accurate estimation of time spent in each development stage as well as success rates could allow actors to be more efficient in their allocation of resources to product development.

This research synthesis examines success rates and timeframes of pharmaceutical R&D<sup>1</sup>. While there is public data available on clinical trial and regulatory approval length, there is a dearth of data on time spent in preclinical development, limiting some of the estimated timeframes. Success rates and timeframes are combined to lay the

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<sup>1</sup> A prior research synthesis focused on costs. See: Knowledge Portal on Innovation and Access to Medicines, Research Synthesis: Costs of Pharmaceutical R&D, available at: <https://www.knowledgeportalia.org/cost-of-r-d>

foundation for predictive models that estimate the cumulative probability of approval for a product – a critical component of product development planning. The main reasons for development termination are also explored.

Though the research is aimed at all health technologies and all organizations conducting product development, the literature is dominated by projects related to the development of new drugs, with some studies providing information disaggregated by therapeutic class, and by pharmaceutical industry data. In addition, the conspicuous absence of research relating to different kinds of organizations, development processes outside the United States, and different products outside of strictly pharmaceuticals are noticeable lacunae in the literature.

Table 1. Summary of recent estimates of success rates and timeframes of new drug development

Study	Sample Size	Time Period	Phase 1	Phase 2	Phase 3	Overall	Phase 1	Phase 2	Phase 3	Overall
			Success rates				Timeframes (in months)			
Kola and Landis (2004)	10 companies	1991 – 2000	68.5%	38.0%	55.0%	11%	-	-	-	-
Abrantes-Metz et al. (2004)	27,987 drug entities	1980 – 2004	80.7%	57.7%	56.7%	26.4%	22.1	34.0	44.9	96.6
Paul et al. (2010)	13 companies	-	54%	34%	70%	-	18	30	30	-
DiMasi et al. (2010)	50 companies	1993 - 2004				19%				
Hay et al. (2014)	850 organizations	2003 - 2011	64.5%	32.4%	60.1%	10.4%	-	-	-	
Smietana et al. (2016)	2,857 products	2012 – 2014	58.0%	39.0%	67.0%	11.6%	-	-	-	
DiMasi et al. (2016)	1,442 compounds from 50 companies	1995 - 2013	59.5%	35.5%	61.9%	11.8%	33.1	37.9	45.1	96.8
Thomas et al. (2016)	7,455 projects, from 1,103 companies	2006-2015	63.2%	30.7%	58.1%	9.6%				
P2I Model (NCE-Simple) (Young et al., 2018)	3,655 candidates	2007 - 2014	60.0%	39.0%	69.0%		30	21.6	40.8	
P2I Model (NCE-Complex)	18,851 candidates	2007 - 2014	57.0%	20.0%	40.0%		34.8	22.8	42	

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Study	Sample Size	Time Period	Phase 1	Phase 2	Phase 3	Overall	Phase 1	Phase 2	Phase 3	Overall
			Success rates				Timeframes (in months)			
(Young et al., 2018)										
Wong, Siah, Lo (2019)	406,038 data points	2005 – 2015	66.4%	48.6%	59.0%	13.8%	19.2	34.8	45.6	-
Dowden and Munro (2019)	30 companies	2010-2017	-	23-25%	49-62%	6-7%				
Pammolli et al. (2020)	50,150 projects	2010-2013	44.5%	19.6%	31.2%	-	5	23	34	-

## Summary of the contents

This research synthesis is organized into the following topics:

- 1) Estimation of historical success rates
  - Overall – new drugs
  - New drugs by therapeutic class
  - Other technology types
- 2) Estimation of historical timeframes
  - Overall – new drugs
  - New drugs by therapeutic class
  - Other technology types
- 3) Main reasons for development termination

### 1) Estimation of historical success rates

#### Overall – new drugs

The literature on success rates in pharmaceutical R&D varies in both its use of terminology and the way in which data are presented. In general, attrition rate is defined as the percentage of projects that entered a particular phase and passed to the subsequent phase, with different papers using different metrics, namely: phase transition rate, approval rate, likelihood of approval, probability of success, and failure rate. While the terminology varies, the methods used to calculate common success metrics have remained similar over time, allowing for historical comparisons. By pooling

the literature, we are able to form a relatively comprehensive picture of the success rate trends from the 1960s through the mid-2010s.

Sheck et al. (1984) wrote a foundational piece detailing the clinical success rates for new chemical entities (NCEs) in the United States for different 3-year cohorts (from January 1st, 1963 through December 31st, 1979) and comparing them. The authors calculated success rates based on the number of drugs that obtained regulatory approval by the FDA in the 8-year period following receipt of permission to start human clinical trials (investigational new drugs - INDs). The results show a cumulative success rate of 9.4% for the period from 1963-65, 8.5% for 1966-1968, 13.7% for 1969-1971, and 9.5% for 1972-1974. The authors note that success rates could, in reality, be higher, as some projects were still under development at the time calculations were made. No cumulative success rates are provided for 1974-1979 as not enough time had elapsed since the IND had been obtained.

Using a similar methodology, DiMasi (2001) looked at roughly the next decade, from 1981 to 1992, using data obtained from a Tufts CSDD database with self-reported data from 24 US pharmaceutical companies. The author divided this period into 4 cohorts, with overall clinical success rates fluctuating between 20.5% and 23.2%, until the final period of 1990-1992, which saw a drop to 17.2%. This drop can mostly be accounted for by the fact that the time between the last IND filed during that period and the paper's publication was significantly less time than it would typically take for an entire cohort of INDs to reach completion (either approval or termination). Because of this, DiMasi writes that *"the results suggest that approval rates have not declined over time, and, quite possibly, have increased."* Clinical success rates are broken down for NCEs that were acquired, self-originated, and self-originated and first tested in humans in the United States, respectively at 33.1%, 16.9% and 8.6%. The results show that licensed-in compounds have higher success rates, and that self-originated compounds first tested outside of the United States are more likely to be successful.

Kola and Landis (2004) investigated the following decade, with data from 1991-2000 for ten big pharmaceutical companies in the United States and Europe. The authors estimated a cumulative success rate from Phase I through registration at 11%, a rate markedly lower than had been estimated for the previous decade by DiMasi (2001), and closer to the estimations by Sheck et al. (1984). The authors also provided figures by stage of development, showing a success rate of 60% for Phase I, 40% for Phase II, 59% for Phase III and 77% for registration. The analysis has a few caveats, namely that the small 4-year difference between the last IND date in the dataset and the publishing of the paper does not seem to be addressed.

Abrantes-Metz et al. (2004) also looked at data from the 1990s, covering a period from 1989 through 2002 using data from Pharmaprojects (a large industry drug development database). The study focuses on "new drugs", including those composed of chemicals, biologicals, and natural products. They used a sophisticated model to calculate the

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success rates of each phase, finding significantly different rates than Kola and Landis (2004), despite covering a similar timeframe. The success rates were estimated at 80.7%, 57.7%, and 56.7% for Phases I, II, and III respectively. It should be noted that the registration is included in Phase III. The cumulative success rate was 26.4%. Figures are also separated by company size, showing higher success rates in Phase I and II for “non-big pharma”, while Phase III has higher success rate for “big pharma”. The study’s estimate does not have the characteristic dip in phase II success rates that appears in other studies, and the reason for the high phase II rate is not explicitly addressed in the paper.

Paul et al. (2010) developed a model of R&D productivity based on assumptions of attrition rates, timeframes, and costs for each phase of discovery and development. The model was constructed using data from 13 large pharmaceutical companies provided by the Pharmaceutical Benchmarking Forum, as well as the authors’ own internal data from Eli Lilly and Company. The probability of successful transition is presented for eight development phases: Target-to-hit: 80%, Hit-to-lead: 75%, Lead optimization: 85%, Preclinical: 69%, Phase I: 54%, Phase II: 34%, Phase III: 70% and Submission to launch: 91%.

DiMasi et al. (2010) also looked at the decade from 1993 to 2009 to estimate clinical approval probabilities using data from the 50 largest pharmaceutical firms (by sales). The authors found that clinical success rates began to drop in the mid-1990s and estimated an overall success rate of 19% for the entire period for all compounds and 16% if considering only self-originated drugs (compared to 11% for Kola and Landis, 2004). The paper details several interesting features of the data. For example, despite the two half-decade periods in the study having similar success rates from phase I to approval, the later cohort had lower success rates in earlier phases (I and II). The authors argued that clinical testing has become more complex, potentially explaining higher failure rates for earlier phases due to a higher standard of success in general during these phases. Another finding is that licensed-in compounds have higher success rates, since typically licensed-in compounds have already undergone some screening or testing prior to licensing.

Arrowsmith (2011a, 2011b and 2013) investigated success/failure rates in phase II, phase III and submission in the period from 2008 to 2012 in a series of three papers. The first (Arrowsmith 2011a) focused on phase II success rates from 2008 to 2010 and found that phase II has lower success rates than any other phase of development, as also found in previous studies. The author provided figures from previous periods analysed by the Centre for Medical Research (CMR) that show success rates for phase II at 28% for 2006-2007 and 18% for 2008-2009. The second paper (Arrowsmith 2011b) looked at Phase III success rates from 2007 to 2010. The success rates were around 50% (actual figure is not provided), a decline from previous years. The third article (Arrowsmith and Miller, 2013) looked at phase II and phase III failures together from 2011-2012. The paper states that Phase II success rates for new projects remained below 20%, but Phase III rates have improved 7% from 2009-2011 compared to 2007-2009 (actual figures are not provided).

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The authors concluded that the figures “may be an indication that the industry, as a whole, is designing Phase II programmes that are able to support early termination decisions and thereby avoiding a number of costly Phase III failures”.

Hay et al. (2014) similarly conducted a study from 2003 through 2011, continuing chronologically from where Abrantes-Metz et al. (2004) and DiMasi et al. (2010) ended. The study uses significantly more companies (850 compared with 50 for DiMasi, 10 for Kola and Landis, and an unknown number for Abrantes-Metz). The results show a clinical likelihood of approval (LOA) rate of 10.4%, comparable to Kola and Landis (2004). Hay et al. also found a dip in the probability of Phase II success (32.4% compared to 64.5% for Phase I and 60.1% for Phase III). Hay also calculated rates for lead indications and finds that a lead indication has a LOA rate of 15.3%, and compared this to lead indication rates of 19% for DiMasi, 11% for Kola and Landis, and 26.4% for Abrantes-Metz. Importantly, a lead indication may be changed, meaning that if a lead indication were to fail in Phase I testing, if another indication transitioned from Phase I to Phase II, the lead indication would then change to the second indication. This means that lead indication rates will always be greater than or equal to overall rates, causing upward bias.

Smietana et al. (2016), also using data from the Pharmaprojects database for a total of more than 9,200 compounds, calculated the cumulative success rates from Phase I to launch for five cohorts between 1996 and 2014. The LOA percentage dropped each period until 2011, and rebounded for the 2012-2014 cohort to reach 11.6% (1996-99: 16.4%; 2000-03: 10.8%; 2004-07: 10.0%; 2008-2011: 7.5%). The paper also finds Phase II success rates to be significantly lower than either Phase I or III, never crossing the 50% threshold (Phase I hovers around 65%; Phase III fluctuates between 55% and 70% across the five cohorts). For the last cohort (2012-2014), Phase I success rate is estimated at 58%, Phase II at 39% and Phase III at 67%. The study also separated probability of success for in-licensed and “non-partnered” compounds for the five cohorts, showing higher likelihood of approval for licensed-in compounds across the entire period (for the last period from 2012-2014, licensed-in compounds had 20% cumulative success rates from Phase I to launch versus 12% for non-partnered compounds. In comparison, for the first period from 1997-1999, it was 54% for in-licensed versus 13% for non-partnered).

Following their 2010 study, DiMasi et al. (2016) estimated phase transition probabilities (success rate) based on 1,442 compounds (first tested in humans from 1996 to 2007) self-originated from the top 50 pharmaceutical companies. Phase I to Phase II transition was estimated at 59.52%, Phase II to III at 35.52%, Phase III to submission at 61.95%, and submission to approval at 90.35%. The overall probability of success was estimated to be 11.83%. The authors concluded that “This success rate is substantially lower than the rate of 21.50% estimated for the previous study, but consistent with several recent studies of clinical success rates.”

Thomas et al. (2016), on a BIO, Biomedtracker and Amplion report, tracked pharmaceutical clinical success rates from 2006 through 2015 using data from 7,455

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development programs, across 1,103 companies in the Biomedtracker database. The key findings of the report are a total cumulative success rate of 9.6% for the entire period (11.9% for non-oncology drugs). Consistent with other studies, the study found that Phase II success rate (at 30.7 percent) was lower than those of the other phases (63.2% for Phase I; 58.1% for Phase III).

Wong, Siah, and Lo (2019) conducted a study to calculate rates of success using a larger dataset and a new way to calculate success rates by phase. This study is a significant contribution to the literature because it incorporates big data, dwarfing datasets used by Kola and Landis, DiMasi, and others, and because the authors propose a new measure of phase success to account for missing information that should be counted as a success. For example, consider a drug that has a completed Phase I trial recorded on clinicaltrials.gov, and is listed in ongoing Phase III trials. If there is no Phase II trial available, under normal circumstances, the drug will not count as having passed Phase II. Because the typical “phase-to-phase” success rate is calculated as the cumulative number of drugs which advance from phase  $x$  to phase  $x+1$  divided by the total number of drugs which entered phase  $x$ , missing data are not counted. However, it is a fairly common occurrence that drugs will have missing data or special regulatory pathways; in these instances, using standard approaches, successes will not be counted towards the aggregate total of success from these periods. In contrast, Wong, Siah, and Lo would interpolate a Phase II success in this example, recognizing that there is no way that a drug would have made it to Phase III while failing testing in Phase II (i.e., given the binary nature of trial outcomes, this can justifiably be recorded as a success). The authors also move away from a simple “phase-to-phase” calculation of probability of success (POS), which is common in the literature. The standard calculation defines POS as the product of each individual phase success (i.e., the probability of passing Phase I multiplied by the probability of passing Phase II, and so forth for each phase). The authors instead propose a “phase-by-phase” calculation, wherein all possible drug paths (each unique indication being tested for a particular drug constitutes one “path”) are measured and the proportion of paths that pass from Phase I to approval are counted as one success. Given the methodological differences between the authors and the established literature, success rates would be expected to be higher, and this is, in fact, the case. Wong et al.’s estimates are notably higher than the generally cited 10% figure for Phase I-to-approval success rates. The authors found rates of 66.4%, 48.6%, and 59.0% for Phase I, II, and III trials, respectively, and a rate of 13.8% for all drugs entering Phase I testing.

Dowden and Munro (2019) presented and analysed data for new active substances (including chemicals and biologicals) from CMR International (which operates a consortium of about 30 innovative biopharmaceutical, including large, mid-sized and small companies) for the period of 2010 to 2017. The study shows probability of success from each phase to launch (Phase I to launch, Phase II to launch, and Phase III to launch) and Phase II to Phase III for every two years of the period of the study. For the first period (2010-2012), Phase I to launch is estimated at 6% and for the last period (2015-2017) at 7%. Phase II to Phase III varies from 23% (2010-2012) to 25% (2015-2017).

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In a recently published study, Pammolli et al. (2020) investigated drug development projects using an extensive data set of more than 50,000 projects between 1990 and 2017 from R&D Focus, a proprietary database. Only projects started in the US, Europe or Japan were included. Similar to Wong et al. (2019), if information was missing for one phase of the development process but there was information on a more advanced phase, it was counted as success. The authors found that attrition rates have been decreasing at all stages of clinical research in recent years, though they are still higher than in the decades spanning 1990-1999. Pammolli et al. (2020) also found a reduction in attrition rates over time for the preclinical stage. For the final period of 2010-2013, the estimated attrition rates (failures) for each development phase were: Preclinical: 89.5%, Phase I: 55.5%, Phase II: 80.4%, Phase III: 68.8% and Registration 28.7%. For comparison with other studies in this synthesis, we present these as success rates instead: Preclinical: 10.5%, Phase I: 44.5%, Phase II: 19.6%, Phase III: 31.2% and Registration: 71.3%. The success rates estimated by Pammolli et al. are significantly lower than other estimations available in the literature.

Pammolli et al. (2020) also investigated attrition rates across different organization types classified as “pharmaceutical”, “biotech” and “non-industrial” institutions. The calculations showed that “non-industrial” have higher attrition rates (lower success rates) across all development phases (except at registration), followed by “biotech” and “pharmaceutical.” The authors concluded that “biotechnology companies have reached levels of productivity in project development that are equivalent to those of large pharmaceutical companies.”

### New drugs by therapeutic class

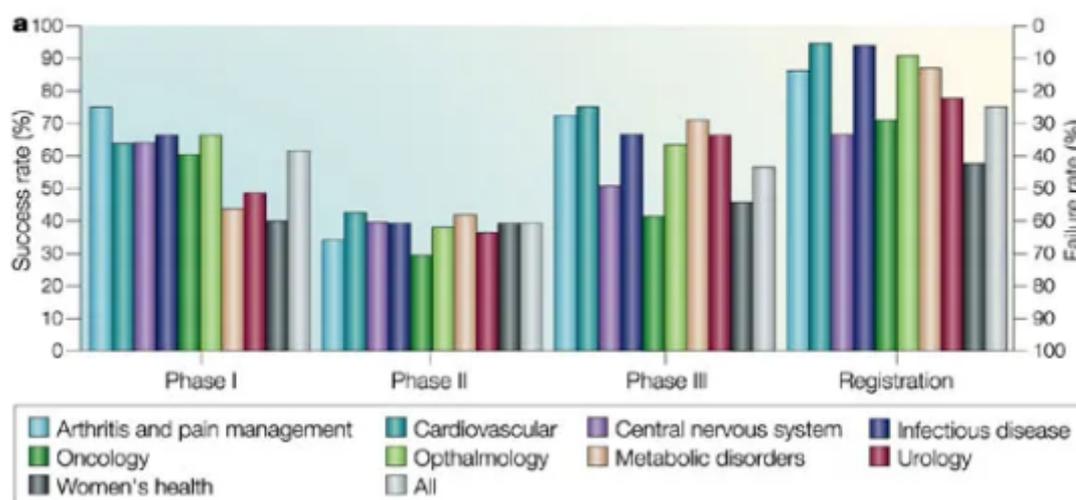
The literature shows that success rates can vary substantially according to therapeutic class. Several different papers disaggregate success rates for different therapeutic class and compare them to a baseline, showing that certain areas have higher success rates than others. All studies mention therapeutic class and disease type as important factors in the efficacy of the research and development process.

DiMasi (2001) found varying success rates among 10 different therapeutic classes. Analgesic/anaesthetic, anti-infective, and gastrointestinal candidates each had success rates above 20%, while candidates with respiratory, central nervous system, and immunologic indications had success rates around 15%. Anti-infectives had the highest success rate (28.1%); respiratory (12%) and miscellaneous (7%) had the lowest. According to the author, some of the variance in success rates can be explained by differences in the way regulatory standards are satisfied by different disease types. For example, efficacy endpoints may be less concrete for certain diseases, or surrogate endpoints may be used.

Kola and Landis (2004) disaggregated success rates by nine therapeutic classes and found considerable variation between them. Cardiovascular candidates had the highest

rate of success (20%), followed by those for arthritis and pain (17%) and infectious diseases (16%), whereas central nervous system (8%), oncology (5%) and women’s health (4%) had the lowest. The study provided information by therapeutic class for each development stage (Phase I, Phase II, Phase III and registration), as shown in the figure below:

**Figure 2: Success rate by phase of development and by therapeutic area.**



Source: Kola and Landis (2004)

Abrantes-Metz et al. (2004) provide success rates disaggregated by therapeutic area and type of technology. The authors found that biologicals had a success rate of 90% in Phase I, 67% in Phase II and 70% in Phase III; that chemicals had a success rate of 84% in Phase I, 66% in Phase II and 66% in Phase III; and that natural products had a success rate 90% in Phase I, 77% in Phase II and 61% in Phase III. The study also provides success rates for 14 therapeutic areas, varying between 70% (transdermal) and 97% (parenteral – subcutaneous) in Phase I; 43% (respiratory) and 81% (parenteral – subcutaneous) in Phase II, and 33% (anti-Alzheimer’s Disease) and 94% (anti-HIV/AIDS) in Phase III. As noted above, the authors included registration as part of Phase III.

DiMasi et al. (2010) ran a similar analysis, finding variance in phase transition rates and LOA rates between eight therapeutic classes. The rates were extremely low for therapies with small N, given that the time period for entering product development (1993-2004) was only 6 years prior to publishing. Nevertheless, the phase transition probabilities offer some insight into which types of therapies tend to perform more effectively than others in clinical testing. Immunologic drugs, for example, had a maximum success rate of 36%; the next highest class was about 20%. Musculoskeletal and miscellaneous drugs had estimated LOA rates of about 20%, while cardiovascular, CNS, GI/metabolism, and respiratory classes had estimated rates around 9%. The study also estimated clinical success rates for self-originated compounds classified by small and large molecules and

found that, over the entire study period, 13% of small molecules and 32% of large molecules succeeded.

Hay et al. (2014) addressed the differences in phase transition and LOA rates based on indication and disease type. They too found large differences in rates depending on the class of drugs, with infectious disease, autoimmune, and endocrine classes with the highest LOA rates (12-17%). On the other hand, neurology, cardiovascular, and oncology drugs had significantly lower success rates, from 7-9%. Oncology drugs in particular were shown to have a very low probability of success.

Additionally, the report by Thomas et al. (2016) found several differences in therapeutic class, specifically that oncology consistently had lower transition rates, going so far as to calculate the cumulative rates with and without oncology included (the LOA for all candidates was 9.6%, and 11.9% for all candidates except those with oncology indications). Of 14 major disease areas, the authors found that haematology (26.1%), infectious diseases, and ophthalmology had the highest cumulative success rates, while psychiatry, cardiovascular disease and oncology (5.1%) had the lowest.

The above-mentioned study by Smietana et al. (2016) provides disaggregated data for small molecules and biologic drugs. The authors found that cumulative success rates remain consistently higher for biologics across the entire period of the study (1996-2014), fluctuating from 5% to 16% for small molecules and 12% to 18% for biologics.

Wong, Siah, and Lo (2019) also disaggregate by class, finding a 3.4% probability of success for oncology candidates. Autoimmune and genitourinary candidates had the next lowest rates at around 15% each. Ophthalmology candidates and vaccines performed extremely well with a roughly 33% probability of success for each.

Dowden and Munro (2019) disaggregated their late-stage development success rate for new active substances targeting rare versus non-rare indications. There are some fluctuations across the study period (2010-2017), but in the initial and final periods, success rates for both indications were found to be very similar (2010-2012: 50% for rare and 49% for non-rare; 2015-2017: 61% for rare and 63% for non-rare). Data are also provided for seven different therapeutic areas, with anti-infectives showing the highest overall probability of success from Phase I to launch (16%) and nervous system candidates the lowest (3%).

Pammolli et al. (2020) disaggregated their data into 13 therapeutic classes and calculated average phase-by-phase attrition rates for 2000-2009 and 2010-2013. Taking Phase II as an example, in the second period, the therapeutic class with the highest attrition rate (i.e., the lowest success rate) was “genito-urinary system and sex hormones” and the one with lowest attrition rate (highest success rate) was “antiparasitic products, insecticides and repellents”.

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Looking at product development for anti-malarial medicines at the Medicines for Malaria Venture (MMV), a non-profit organization, Burrows et al. (2017) estimated success rates in product development by phase from 2009–2014 for MMV and compared to benchmark data for anti-infectives. The authors conclude that “malaria drug discovery has an attrition rate that is no better and no worse than that in the pharmaceutical industry for anti-infectives overall, and significantly better than for other therapeutic areas, such as neurology and oncology”. Success rates for MMV were estimated at: Preclinical: 50%, Phase I: 70%, Phase IIa: 78%, Phase IIb: 75%, Phase III: 67% and Registration: 100%.

## Other technology types

Davis et al. (2011) investigated the differences in success rate between prophylactic vaccines and pharmaceuticals overall. They found that, for the 1995 cohort of IND application submissions, the ratio of failures to successes was 8.3 in prophylactic vaccines and 7.7 in other drugs.

Terry et al. (2018) developed a modelling 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. Young et al. (2018) further refined the P2I Model. A summary of the success rates per archetype using version 2 of the P2I Model is provided in the figure below.

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Archetype	Probability of success (%)			
	Predclinical	Phase 1	Phase 2	Phase 3
Simple vaccine	41.0	68.0	46.0	71.0
Complex vaccine	41.0	50.0	22.0	64.0
Unprecedented vaccine	41.0	50.0	5.0	40.0
Simple NCE	65.0	60.0	39.0	69.0
Simple NCE for TB	65.0	60.0	39.0	50.0
Complex NCE	55.0	57.0	20.0	40.0
Simple repurposed drug	75.0	59.0	46.0	68.0
Complex repurposed drug	75.0	59.0	46.0	68.0
Simple biologic	41.0	68.0	46.0	70.0
Simple biologic for TB	41.0	68.0	46.0	55.0
Complex biologic	41.0	50.0	22.0	40.0
	<b>Concept and Research</b>	<b>Feasibility and Planning</b>	<b>Design and Development</b>	<b>Clinical Validation and Launch Readiness</b>
Diagnostic, assay development	71	71	100	100
Diagnostic, simple platform development	71	71	75	100
Other products	87	87	95	80

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

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

## 2) Estimation of historical timeframes

### Overall

The literature on phase lengths is more recent than that on success rates, becoming a recognized aspect of pharmaceutical development in the early 2000s. Earlier papers used survival analyses to understand development time, typically noting the cumulative proportion of products that reached an event (FDA approval) over some period of time. These calculations are still commonplace and are an important aspect of predicting overall success rates for drugs, but individual phase lengths have helped elucidate specific areas for improvement in the R&D process.

One of the first papers to look at phase lengths was Reichert (2003), which divided the total time spent in development into clinical and approval time. Historically, regulatory time averaged about 2 years in the 1970s, increasing to a high of 37 months in 1984-1985. The regulatory time then decreased steadily during the 1990s, to a low of 12.7 months in 1998-1999. Clinical time followed a similar pattern, taking about 50 months during the 1970s, increasing to about 75 months in the 1980s, and remaining high throughout the

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1990s, reaching an apex of 92.5 months in 1994-1995, before decreasing steadily to a low of 63 months in 2000-2001. Consistent with literature on success rate, times also varied widely depending on therapeutic categories, but over the 4-year intervals there was no clear pattern for certain therapeutics taking more or less time compared to the other categories. The author also analysed the trends for approval times in view of three major pieces of legislature implemented in the U.S. in the 1980s: the Bayh-Dole Act, Orphan Drug Act, and Hatch-Waxman act. The patterns suggest that the legislative pieces succeeded at shortening FDA approval time.

Keyhani et al. (2006) investigated development times and the claim that rising drug prices in the US were justified because of longer development times. They investigated 168 drugs approved between 1992 and 2002 using data from publicly available sources (the authors highlight that most of the previous studies had been based on proprietary data). They found that the median clinical trial period was 5.1 years (61.2 months) and that the medial regulatory review period was 1.2 years (14.4 months). The authors concluded that “clinical trial periods have not increased during this time frame, and regulatory review periods have decreased. Therefore, it is unlikely that longer clinical trial times are contributing to rising prescription drug prices”.

The above-mentioned Abrantes-Metz (2004) paper also estimated phase duration in addition to success rates. The authors found mean duration times of 22.1, 34, and 44.9 months for Phase I, II, and III and, an expected duration of 96.6 months for successful drugs. They provided information disaggregated by successful and failed drugs, showing that Phase I and Phase II duration are significantly lower for successful drugs and Phase III duration is lower for failed drugs. They also presented data separated by size of the developer, showing that “big pharma” has longer development rates in Phase I, but lower rates in Phases II and III in comparison to “non-big pharma.”

The R&D model developed by Paul et al. (2010) includes assumptions of cycle times for eight different phases of the development process. Original cycle times were provided in years, but are presented here in months to allow for comparison with other estimates. Target-to-hit: 12, Hit-to-lead: 18, Lead optimization: 24, Preclinical: 12, Phase I: 18, Phase II: 30, Phase III: 30, and Submission to launch: 18.

Pregelj, Verreyne, and Hine (2015) conducted a linear regression analysis of clinical trial lengths, including disaggregation by phase. The study looked at 14,319 Phase I, II, and III trials between 2005 and 2009. Ultimately the regression suggested that the estimated marginal means of trial lengths are reduced from about 25 months (all phases clustered between 23-26 months) to around 20 months, with Phase I tests dropping precipitously to about 15 months. The study found notable differences between originating firms and development times. Industry-originated products were consistently faster to advance through clinical trials, while U.S. Federal backed products were slower and “other” firms were in the middle.

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DiMasi et al. (2016) detailed the cost of producing a new drug, in which capitalized costs play a key role. Timeframes are a major component of calculating capitalized costs, so a key focus of the paper is the length of each phase of clinical testing and regulatory approval time. The paper found that the mean phase lengths are 33.1, 37.9, and 45.1 months for Phase I, II, and III, respectively. The authors also found an average gap of 19.8, 30.3, and 30.7 months after each phase of testing was completed. They found an average time of 31.2 months from synthesis to first human testing, down considerably from 52.0 months in a previous study. The regulatory phase was estimated to take 16.0 months. Overall, the expected time from the beginning of clinical trials to regulatory submission was 80.8 months (96.8 months for time from testing to approval). Note that these figures are not a sum of individual phase times and phase gaps, as there are overlaps across phases and phase gaps.

Martin (2017) investigated phase lengths across clinical trials looking at the decade from 2006-2015 across 3-year periods (overlapping 1 year between each two cohorts) and found increasing phase lengths across the decade, especially for Phase II and Phase III trials. Phase I trials had a median length of 31 months in 2006 before dipping to a low of 27 months for the 2010-2012 period. The final period showed clinical trial lengths of 32 months, a modest increase over the 10-year period. For Phase II trials, trial times have increased gradually from 2006 – 2009, and have increased by 5 months over the second half of the decade to a median of 39 months from 33 months in 2006. For Phase III trials, lengths went from 33 months in 2006 to a high of 42 for the 2011-2013 period, and have since dipped to a median of 40 months, remaining substantially higher than in 2006. The author proposed several potential reasons for these increases, including that companies seem to be changing trial design strategies and have been creating more complex late-stage trials. In addition, trial size has increased in Phase II studies, moving from a median of 88 participants from 2005-2007 to 108 from 2013-2015. Phase III trials, however, saw a reduction in participants over the same period, from 408 to 347. Treatment cycles also increased, and were 23% longer in 2013-2015 than 2010-2012.

Wong, Siah, and Lo (2019) estimated phase lengths in their analysis. They found that during the period from 2005-2015, trial lengths were 1.6, 2.9, and 3.8 years (19.2, 34.8, and 45.6 months) for Phase I, II, and III testing, respectively. The authors also analysed the difference between terminated and successful projects and found that Phase II trials tend to conclude 8.1 months earlier for candidates that do not advance to Phase III testing. Phase III trials concluded 3.2 months later in successful candidates. Differences in Phase I times were insignificant.

Pammolli et al. (2020) also investigated timeframes in their above-mentioned study. The authors calculated median phase duration per each phase of development in 3-years intervals (1990-1999, 2000-2009 and 2010-2013). Phase III had longer duration across the entire period and registration the shortest. For the last interval, phase lengths were estimated at: Preclinical: 19 months, Phase I: 5 months, Phase II: 23 months, Phase III: 34

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months and Registration: 3 months. It should be noted that these estimates are much lower than other estimates available in the literature.

### New drugs by therapeutic class

Abrantes-Metz et al. (2004) provided estimates for development times by phase, disaggregated by type of compound and therapeutic area. For successful drugs, they show that biologicals have an average duration of 17.87 months in Phase I, 31.87 months in Phase II and 45.63 months in Phase III; chemicals have an average duration of 19.63 months in Phase I, 29.41 months in Phase II and 47.74 months in Phase III, and natural products have an average duration of 21.5 months Phase I, 19.44 months in Phase II and 46.14 months in Phase III. The study also disaggregates phases by 14 therapeutic areas, demonstrating variations between 10.73 months (anti-hypertension) and 22.43 months (transdermal) in Phase I; 21.57 months (anti-HIV/AIDS) and 46.11 months (anti-Alzheimer's Disease) in Phase II, and 24.31 months (anti-HIV/AIDS) and 63.4 months (anti-Parkinson's Disease) in Phase III. As noted above, the authors included registration as part of Phase III. There are also estimations provided for failed projects.

In the study by Martin (2017), the author conducted a regression analysis and found that trials of large molecules took more time than those of small molecules, even when accounting for variations in study size and disease complexity. Conversely, Beall et al. (2019) investigated the difference in development times between biologic (large molecules) and chemical drugs (small molecules) and found no significant difference. Looking at US Patent and Trademark Office (USPTO) and Merck Index data, the study found that median total development times were about 12 years from first filing to FDA approval for each method (12.1 USPTO and 12.4 Merck Index). The development times between small molecules and biologics were not significantly different in either regression (despite being slightly shorter for biologics in the Merck Index).

### Other technology types

Davis et al. (2011), in the above-mentioned study investigating the differences between prophylactic vaccines and pharmaceuticals overall, found that clinical development times were not significantly different between vaccines and other drugs. There was, however, a significant difference in pre-clinical development time, with prophylactic vaccines taking 3.7 years and other drugs taking 2.8 years. Aside from this, there were no notable differences in phase lengths.

The above-mentioned Portfolio-To-Impact (P2I) Model (Terry et al. 2018, Young et al. 2018) also contains assumptions for time length for each development phase, summarized in the table below for different types of technologies included in the model ("archetypes").

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Archetype	Length of phase (years)			
	Preclinical	Phase 1	Phase 2	Phase 3
Simple vaccine	3.4	1.6	2.2	2.3
Complex vaccine	3.3	2.0	3.7	3.5
Unprecedented vaccine	3.3	2.0	3.7	3.5
Simple NCE	2.5	1.8	3.4	3.2
Simple NCE for TB	2.5	1.8	3.4	3.2
Complex NCE	2.9	1.9	3.5	2.8
Simple repurposed drug	2.3	1.6	2.1	2.1
Complex repurposed drug	2.3	1.6	2.1	2.1
Simple biologic	3.4	1.6	2.2	3.1
Simple biologic for TB	3.4	1.6	2.2	3.1
Complex biologic	3.3	2.0	3.7	2.8
	<b>Concept and Research</b>	<b>Feasibility and Planning</b>	<b>Design and Development</b>	<b>Clinical Validation and Launch Readiness</b>
Diagnostic, assay development	0.5	0.5	2.0	1.3
Diagnostic, simple platform development	0.5	0.5	2.5	2.0
Other products	0.5	0.5	1.0	1.0

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

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

Using the P2I Model to analyse the vaccine portfolio of the European Vaccine Initiative (EVI), a not-for-profit organization, Gunn et al. (2019) provide information on timeframes for the historical development of vaccines within the organization. The portfolio includes candidates for various diseases of poverty and emerging infectious diseases at different stages of development. The preclinical phase was estimated at 36 months, Phase I at 17.4 and Phase II at 22.5.

### 3) Main reasons for development termination

The above-mentioned paper by DiMasi (2001) investigated the reasons for termination of projects under clinical development, in two cohorts of 5-year periods (from 1981-1986 and 1987-1992). Results for each period, respectively, are 29.8%/33.8% for economic reasons, 33.0%/37.6% for efficacy, 21.4%/19.6% for safety, and 15.8%/9.0% for other reasons.

Kola and Landis (2004) also investigated the reasons for failure and point out that over the course of the decade, the reasons for failure shifted from primarily pharmacokinetic/bioavailability reasons (~40% in 1991) to commercial (20%), toxicology (20%), and cost of goods (9%) reasons (which notably was not mentioned as a reason for failure in 1991) in 2000. Clinical safety and efficacy as causes of failure stay roughly constant between 1991 and 2000 (10-12% and 30-28%, respectively). Overall, the 1990s are seen as a time of sea change, in which clinical success rates plummeted and never fully recovered. The authors suggest that this could be the result of several factors, including the targeting of more complex diseases in clinical trials, competing with enhanced standards of care, and more demanding regulatory authorities.

The trio of Arrowsmith papers published by Thomson Reuters (Arrowsmith 2011a, 2011b and 2013) also outlined major causes for failure in Phase II and Phase III tests. For Phase III tests, the major reasons for failure from 2007-2010 were efficacy (66%), safety (21%), and commercial (7%). For Phase II tests from 2008-2010, the four major factors in failure were efficacy (51%), strategic (29%), safety (19%), and pharmacokinetics/bioavailability (1%). Therapeutic area also played a role, with cancer and alimentary drugs failing more often than other those in areas. The final study for Phase II and III studies from 2011-2012 found that the primary factors for failure were efficacy (56%), safety (28%), and strategic (7%). The 2013 study showed that, of the 83 failures in Phase III trials, 28% were cancer drugs, 18% were nervous system and 13% were alimentary/metabolism (including obesity and diabetes). One conclusion was that large numbers of failures occurred in drugs with novel mechanisms of action in areas of unmet need.

Harrison (2016) found similar results for the time period between 2013-2015. Looking at Phase II and Phase III failures, the primary factors in failure were efficacy (52%), safety (24%), strategy (15%), commercial (6%), and operational (3%). Strategic reasons were a significantly higher cause of failure in Phase II (21%) than Phase III (14%). The highest percentage of failures were in oncology (32%) and CNS (17%), confirming that certain therapeutic areas are more difficult than others.

Hwang et al. (2016) explored failures of investigational drugs in Phase 3 trials across several countries from January 1<sup>st</sup>, 1998 – December 31<sup>st</sup>, 2008, with follow up in 2015. The study included the United States, Canada, Australia, Switzerland, and the EU. Of 640 novel drugs and biologics, 53.8 were unapproved and 46.2% were approved (35.9% in the United States). Approximately 30% were biologics and 70% were pharmacologic. Of drugs that were not approved, 56.7 were not approved due to lack of efficacy, 17.2% due to lack of safety, and 21.5% for commercial reasons. In only 4.7% were the reasons for a lack of approval unknown. Commercial reasons were significantly more likely to be the cause of failure for small and medium sized enterprises ( $P < .001$ ). A major drawback to the study is that it relied on publicly available information. This may cause bias since the FDA's response letters denying a drug approval are not required to explain precise reasons for failure.

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Schumacher et al. (2016) examined changing R&D models in the pharmaceutical industry and broad organizational archetypes for future development. Laying out the argument for a changing R&D model, the authors included a list of issues impacting pharmaceutical R&D. They identified various reasons for high attrition rates, including a lack of reliability in published data; biopharmaceutical issues including PK; poor predictive models in discovery and preclinical research; target-based drug discovery and advanced complexity of target selection; competition for proprietary target; complex process for target validation; complexity of clinical trials in treating chronic diseases; increasing demands from regulatory authorities and funders; and a lack of knowledge in small organizations resulting in lower PTRS from phase I to submission than for large organizations. Whereas many of the issues identified in the literature are specific to clinical trials, Schumacher includes many issues that affect pre-clinical development and drug discovery. While the broader focus of the paper is innovative R&D strategies, these issues continue to plague health product development in this potential transition period.

Dahlin et al. (2016) examined the types of pharmaceutical product development strategies that are most likely to reach market from a sample of 2,562 clinical trials conducted in 406 US pharmaceutical companies between 1993 and 2004. Product development strategies were categorized into 4 distinct paths: (i) a novel strategy – indicating that the firm was undertaking product development for a drug and indication that they had no prior experience conducting clinical trials for; (ii) a drug experience strategy – combining previous drug development expertise with a new indication; (iii) an indication experience – showing previous clinical trial experience with an indication but for a new drug; and, (iv) a combined experience strategy – denoting prior expertise conducting clinical trials for the drug and indication. The results, amongst other things, show that combined experience strategies were the most successful (and least likely to be utilized), followed by drug experience strategies, with novel strategies trailing closely, and, finally, indication experience strategies being the least successful means to get a product to market.

Lauer et al. (2017) investigated the effect that costs and attrition rates have on the development of cardiovascular medicines. Many of the factors that have been found to be increasing prices and lowering success rates overall in pharmaceuticals are also potential drivers of costs for cardiovascular medicines specifically. The study cites several issues, including complex trial design, restrictive inclusion and exclusion criteria, strict regulations, excessive source-data verification, and the effect of clinical conduct on workflow. There is a lengthy explanation of barriers to cost-efficient clinical trials, which traverses several responsible parties for increased prices. Sponsor-induced risk aversion may lead to extraneous steps and longer protocols. A disconnect between research and care may cause inefficiencies because healthcare professionals are unable to interpret clinical research methods. Regulatory boards are decentralized and less efficient than they could be. Trial regulations are antiquated and are designed for smaller trials. There

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are a plethora of other causes and actors, but the takeaway is that there are many complex and diverse barriers to improving clinical R&D processes.

### Research gaps

- Insufficient number of estimates of early discovery and preclinical phase lengths and/or success rates
- Insufficient data on R&D of health technologies, other than new molecular entities (NMEs)
- Insufficient data on R&D conducted outside of the United States, Europe, and Japan
- Insufficient information on product development by organizations other than pharmaceutical and biotech companies
- Insufficient number of studies using big data techniques; most of the literature is based on limited data sets

### Cited papers with abstracts

Abrantes-Metz, Rosa M., Christopher Adams, and Albert D. Metz. 2004. "Pharmaceutical Development Phases: A Duration Analysis." *SSRN Electronic Journal*, 2004. <https://doi.org/10.2139/ssrn.607941>.

Abstract: This paper estimates a duration model of late stage drug development in the pharmaceutical industry using publicly available data. The paper presents descriptive results on the estimated relationship between a particular drug's characteristics such as therapy category, route of administration and originator's size, and that drug's pathway through the three stages of human clinical trials and regulatory review. The results suggest that drugs with longer durations are less likely to succeed, drugs from larger firms are more likely to succeed and faster in the later phases of development, and that durations fell between 1995 and 2002.

Arrowsmith, John. 2011. "Phase III and Submission Failures: 2007–2010." *Nature Reviews Drug Discovery* 10 (2): 87–87. <https://doi.org/10.1038/nrd3375>.

Abstract: not available.

Arrowsmith, John. 2011. "Phase II Failures: 2008–2010." *Nature Reviews Drug Discovery* 10 (5): 328–29. <https://doi.org/10.1038/nrd3439>.

Abstract: not available.

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Arrowsmith, John, and Philip Miller. 2013. "Phase II and Phase III Attrition Rates 2011–2012." *Nature Reviews Drug Discovery* 12 (8): 569–569. <https://doi.org/10.1038/nrd4090>.

Abstract: not available.

Beall, Reed F., Thomas J. Hwang, and Aaron S. Kesselheim. 2019. "Pre-Market Development Times for Biologic versus Small-Molecule Drugs." *Nature Biotechnology* 37 (7): 708–11. <https://doi.org/10.1038/s41587-019-0175-2>.

Abstract: not available.

Burrows, Jeremy N., Stephan Duparc, Winston E. Gutteridge, Rob Hooft van Huijsduijnen, Wiweka Kaszubska, Fiona Macintyre, Sébastien Mazzuri, Jörg J. Möhrle, and Timothy N. C. Wells. 2017. "New Developments in Anti-Malarial Target Candidate and Product Profiles." *Malaria Journal* 16 (1): 26. <https://doi.org/10.1186/s12936-016-1675-x>.

Abstract: A decade of discovery and development of new anti-malarial medicines has led to a renewed focus on malaria elimination and eradication. Changes in the way new anti-malarial drugs are discovered and developed have led to a dramatic increase in the number and diversity of new molecules presently in pre-clinical and early clinical development. The twin challenges faced can be summarized by multi-drug resistant malaria from the Greater Mekong Sub-region, and the need to provide simplified medicines. This review lists changes in anti-malarial target candidate and target product profiles over the last 4 years. As well as new medicines to treat disease and prevent transmission, there has been increased focus on the longer term goal of finding new medicines for chemoprotection, potentially with long-acting molecules, or parenteral formulations. Other gaps in the malaria armamentarium, such as drugs to treat severe malaria and endectocides (that kill mosquitoes which feed on people who have taken the drug), are defined here. Ultimately the elimination of malaria requires medicines that are safe and well-tolerated to be used in vulnerable populations: in pregnancy, especially the first trimester, and in those suffering from malnutrition or co-infection with other pathogens. These updates reflect the maturing of an understanding of the key challenges in producing the next generation of medicines to control, eliminate and ultimately eradicate malaria.

Dahlin, E., G. M. Nelson, M. Haynes, and F. Sargeant. 2016. Success rates for product development strategies in new drug development. *J Clin Pharm Ther*, 41: 198-202. doi:[10.1111/jcpt.12362](https://doi.org/10.1111/jcpt.12362)

Abstract: What is known and objective: While research has examined the likelihood that drugs progress across phases of clinical trials, no research to date has examined the types of product development strategies that are the most likely to be successful in clinical trials. This research seeks to identify the strategies that are most likely to reach

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the market—those generated using a novel product development strategy or strategies that combine a company's expertise with both drugs and indications, which we call combined experience strategies. Methods: We evaluate the success of product development strategies in the drug development process for a sample of 2562 clinical trials completed by 406 US pharmaceutical companies. To identify product development strategies, we coded each clinical trial according to whether it consisted of an indication or a drug that was new to the firm. Accordingly, a clinical trial that consists of both an indication and a drug that were both new to the firm represents a novel product development strategy; indication experience is a product development strategy that consists of an indication that a firm had tested previously in a clinical trial, but with a drug that was new to the firm; drug experience is a product development strategy that consists of a drug that the firm had prior experience testing in clinical trials, but with an indication that was new to the firm; combined experience consists of both a drug and an indication that the firm had experience testing in clinical trials. Success rates for product development strategies across clinical phases were calculated for the clinical trials in our sample. Results and discussion: Combined experience strategies had the highest success rate. More than three and a half percent (0.036) of the trials that combined experience with drugs and indications eventually reached the market. The next most successful strategy is drug experience (0.025) with novel strategies trailing closely (0.024). Indication experience strategies are the least successful (0.008). These differences are statistically significant. What is new and conclusion: The primary contribution of this study is that product development strategies combining experience with drugs and indications strategies are the most likely to reach the market, even though they are least common strategy. Therefore, combined experience strategies remain underutilized. The findings also suggest a promising path for pursuing combined experience strategies: gaining expertise with drugs is likely to be a more effective path to gaining the expertise necessary for developing subsequent recombination strategies.

Davis, Matthew M., Amy T. Butchart, John R.C. Wheeler, Margaret S. Coleman, Dianne C. Singer, and Gary L. Freed. "Failure-to-Success Ratios, Transition Probabilities and Phase Lengths for Prophylactic Vaccines versus Other Pharmaceuticals in the Development Pipeline." *Vaccine* 29, no. 51 (November 2011): 9414–16. <https://doi.org/10.1016/j.vaccine.2011.09.128>.

Abstract: Research and development of prophylactic vaccines carries a high risk of failure. In the past, industry experts have asserted that vaccines are riskier to produce than other pharmaceuticals. This assertion has not been critically examined. We assessed outcomes in pharmaceutical research and development from 1995 to 2011, using a global pharmaceutical database to identify prophylactic vaccines versus other pharmaceuticals in preclinical, Phase I, Phase II, or Phase III stages of development. Over 16 years of follow-up for 4367 products (132 prophylactic vaccines; 4235 other pharmaceuticals), we determined the failure-to-success ratios for prophylactic vaccines versus all other products. The overall ratio of failures to successes for prophylactic

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vaccines for the 1995 cohort over 16 years of follow-up was 8.3 (116/14) versus 7.7 (3650/475) for other pharmaceuticals. The probability of advancing through the development pipeline at each point was not significantly different for prophylactic vaccines than for other pharmaceuticals. Phase length was significantly longer for prophylactic vaccines than other pharmaceuticals for preclinical development (3.70 years vs 2.80 years;  $p < .0001$ ), but was equivalent for all 3 human clinical trial phases between the two groups. We conclude that failure rates, phase transition probabilities, and most phase lengths for prophylactic vaccines are not significantly different from those of other pharmaceutical products, which may partially explain rapidly growing interest in prophylactic vaccines among major pharmaceutical manufacturers.

DiMasi, J. "Risks in New Drug Development: Approval Success Rates for Investigational Drugs." *Clinical Pharmacology & Therapeutics* 69, no. 5 (May 2001): 297–307. <https://doi.org/10.1067/mcp.2001.115446>.

Abstract: not available.

DiMasi, J A, L Feldman, A Seckler, and A Wilson. "Trends in Risks Associated With New Drug Development: Success Rates for Investigational Drugs." *Clinical Pharmacology & Therapeutics* 87, no. 3 (March 2010): 272–77. <https://doi.org/10.1038/clpt.2009.295>.

Abstract: This study utilizes both public and private data sources to estimate clinical phase transition and clinical approval probabilities for drugs in the development pipelines of the 50 largest pharmaceutical firms (by sales). The study examined the development histories of these investigational compounds from the time point at which they first entered clinical testing (1993–2004) through June 2009. The clinical approval success rate in the United States was 16% for self-originated drugs (originating from the pharmaceutical company itself) during both the 1993–1998 and the 1999–2004 subperiods. For all compounds (including licensed-in and licensed-out drugs in addition to self-originated drugs), the clinical approval success rate for the entire study period was 19%. The estimated clinical approval success rates and phase transition probabilities differed significantly by therapeutic class. The estimated clinical approval success rate for self-originated compounds over the entire study period was 32% for large molecules and 13% for small molecules. The estimated transition probabilities were also higher for all clinical phases with respect to large molecules.

DiMasi, Joseph A., Henry G. Grabowski, and Ronald W. Hansen. "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs." *Journal of Health Economics* 47 (May 2016): 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

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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).

Dowden, Helen, and Jamie Munro. 2019. "Trends in Clinical Success Rates and Therapeutic Focus." *Nature Reviews Drug Discovery* 18 (7): 495–96. <https://doi.org/10.1038/d41573-019-00074-z>.

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.

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Harrison, Richard K. 2016. "Phase II and Phase III Failures: 2013–2015." *Nature Reviews Drug Discovery* 15 (12): 817–18. <https://doi.org/10.1038/nrd.2016.184>.

Abstract: not available.

Hay, Michael, David W Thomas, John L Craighead, Celia Economides, and Jesse Rosenthal. "Clinical Development Success Rates for Investigational Drugs." *Nature Biotechnology* 32, no. 1 (January 2014): 40–51. <https://doi.org/10.1038/nbt.2786>.

Abstract: not available.

Hwang, Thomas J., Daniel Carpenter, Julie C. Lauffenburger, Bo Wang, Jessica M. Franklin, and Aaron S. Kesselheim. 2016. "Failure of Investigational Drugs in Late-Stage Clinical Development and Publication of Trial Results." *JAMA Internal Medicine* 176 (12): 1826–33. <https://doi.org/10.1001/jamainternmed.2016.6008>.

Abstract: Importance: Many investigational drugs fail in late-stage clinical development. A better understanding of why investigational drugs fail can inform clinical practice, regulatory decisions, and future research. Objective: To assess factors associated with regulatory approval or reasons for failure of investigational therapeutics in phase 3 or pivotal trials and rates of publication of trial results. Design, Setting, and Participants: Using public sources and commercial databases, we identified investigational therapeutics that entered pivotal trials between 1998 and 2008, with follow-up through 2015. Agents were classified by therapeutic area, orphan designation status, fast track designation, novelty of biological pathway, company size, and as a pharmacologic or biologic product. Main Outcomes and Measures: For each product, we identified reasons for failure (efficacy, safety, commercial) and assessed the rates of publication of trial results. We used multivariable logistic regression models to evaluate factors associated with regulatory approval. Results: Among 640 novel therapeutics, 344 (54%) failed in clinical development, 230 (36%) were approved by the US Food and Drug Administration (FDA), and 66 (10%) were approved in other countries but not by the FDA. Most products failed due to inadequate efficacy (n=195; 57%), while 59 (17%) failed because of safety concerns and 74 (22%) failed due to commercial reasons. The pivotal trial results were published in peer-reviewed journals for 138 of the 344 (40%) failed agents. Of 74 trials for agents that failed for commercial reasons, only 6 (8.1%) were published. In analyses adjusted for therapeutic area, agent type, firm size, orphan designation, fast-track status, trial year, and novelty of biological pathway, orphan-designated drugs were significantly more likely than nonorphan drugs to be approved (46% vs 34%; adjusted odds ratio [aOR], 2.3; 95% CI, 1.4-3.7). Cancer drugs (27% vs 39%; aOR, 0.5; 95% CI, 0.3-0.9) and agents sponsored by small and medium-size companies (28% vs 42%; aOR, 0.4; 95% CI, 0.3-0.7) were significantly less likely to be approved. Conclusions and Relevance: Roughly, half of investigational drugs entering late-stage clinical development fail during or after pivotal clinical trials, primarily because of

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concerns about safety, efficacy, or both. Results for the majority of studies of investigational drugs that fail are not published in peer-reviewed journals.

Keyhani, Salomeh, Marie Diener-West, and Neil Powe. "Are Development Times For Pharmaceuticals Increasing Or Decreasing?" *Health Affairs* 25, no. 2 (March 2006): 461–68. <https://doi.org/10.1377/hlthaff.25.2.461>.

Abstract: This study examines trends in drug development times. Longer clinical trial times have been described as one factor leading to higher drug prices. Previous reports on development times have been based on proprietary data. We examined trends in development times for 168 drugs with data collected from publicly available sources. The median clinical trial and regulatory review periods for drugs approved between 1992 and 2002 were 5.1 and 1.2 years, respectively. Clinical trial periods have not increased during this time frame, and regulatory review periods have decreased. Therefore, it is unlikely that longer clinical trial times are contributing to rising prescription drug prices.

Kola, Ismail, and John Landis. "Can the Pharmaceutical Industry Reduce Attrition Rates?" *Nature Reviews Drug Discovery* 3, no. 8 (August 1, 2004): 711–16. <https://doi.org/10.1038/nrd1470>.

Abstract: The pharmaceutical industry faces considerable challenges, both politically and fiscally. Politically, governments around the world are trying to contain costs and, as health care budgets constitute a very significant part of governmental spending; these costs are the subject of intense scrutiny. In the United States, drug costs are also the subject of intense political discourse. This article deals with the fiscal pressures that face the industry from the perspective of R&D. What impinges on productivity? How can we improve current reduced R&D productivity?

Lauer, Michael S., David Gordon, Gina Wei, and Gail Pearson. 2017. "Efficient Design of Clinical Trials and Epidemiological Research: Is It Possible?" *Nature Reviews Cardiology* 14 (8): 493–501. <https://doi.org/10.1038/nrcardio.2017.60>.

Abstract: Randomized clinical trials and large-scale, cohort studies continue to have a critical role in generating evidence in cardiovascular medicine; however, the increasing concern is that ballooning costs threaten the clinical trial enterprise. In this Perspectives article, we discuss the changing landscape of clinical research, and clinical trials in particular, focusing on reasons for the increasing costs and inefficiencies. These reasons include excessively complex design, overly restrictive inclusion and exclusion criteria, burdensome regulations, excessive source-data verification, and concerns about the effect of clinical research conduct on workflow. Thought leaders have called on the clinical research community to consider alternative, transformative business models, including those models that focus on simplicity and leveraging of digital resources. We present some examples of innovative approaches by which some investigators have successfully conducted large-scale, clinical trials at relatively low cost. These examples

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include randomized registry trials, cluster-randomized trials, adaptive trials, and trials that are fully embedded within digital clinical care or administrative platforms.

Martin, Linda, Melissa Hutchens, and Conrad Hawkins. "Clinical Trial Cycle Times Continue to Increase despite Industry Efforts." *Nature Reviews Drug Discovery* 16, no. 3 (March 2017): 157–157. <https://doi.org/10.1038/nrd.2017.21>.

Abstract: One key issue facing pharmaceutical clinical development organizations has been increasing clinical trial cycle times. Despite substantial effort and attention from the industry on this issue, overall development timelines continue to increase, at both the programme and study levels. Indeed, cycle time continues to be a major area for improvement for drug development, given the current time to market — reported as 13.8 years to go from target identification to first approval in a major market (Pharmaceutical Benchmarking Forum 2016 R&D Performance: Success Rates & Cycle Time, KMR Group, June 2016). Companies that can master the operational challenges and restraints in study design can not only reap rewards of shorter cycle times but can also see first-mover advantages, revenue benefits, longer market protection and improve productivity through reduced expenditure on conducting clinical trials.

Pammolli, Fabio, Lorenzo Righetto, Sergio Abrignani, Luca Pani, Pier Giuseppe Pelicci, and Emanuele Rabosio. 2020. "The Endless Frontier? The Recent Increase of R&D Productivity in Pharmaceuticals." *Journal of Translational Medicine* 18 (1): 162. <https://doi.org/10.1186/s12967-020-02313-z>.

Abstract: Background: Studies on the early 2000s documented increasing attrition rates and duration of clinical trials, leading to a representation of a "productivity crisis" in pharmaceutical research and development (R&D). In this paper, we produce a new set of analyses for the last decade and report a recent increase of R&D productivity within the industry. Methods: We use an extensive data set on the development history of more than 50,000 projects between 1990 and 2017, which we integrate with data on sales, patents, and anagraphical information on each institution involved. We devise an indicator to quantify the novelty of each project, based on its set of mechanisms of action. Results: First, we investigate how R&D projects are allocated across therapeutic areas and find a polarization towards high uncertainty/high potential reward indications, with a strong focus on oncology. Second, we find that attrition rates have been decreasing at all stages of clinical research in recent years. In parallel, for each phase, we observe a significant reduction of time required to identify projects to be discontinued. Moreover, our analysis shows that more recent successful R&D projects are increasingly based on novel mechanisms of action and target novel indications, which are characterized by relatively small patient populations. Third, we find that the number of R&D projects on advanced therapies is also growing. Finally, we investigate the relative contribution to productivity variations of different types of institutions along the drug development process, with a specific focus on the distinction between the roles of Originators and Developers of R&D projects. We document that in the last decade

Originator–Developer collaborations in which biotech companies act as Developers have been growing in importance. Moreover, we show that biotechnology companies have reached levels of productivity in project development that are equivalent to those of large pharmaceutical companies. Conclusions: Our study reports on the state of R&D productivity in the bio-pharmaceutical industry, finding several signals of an improving performance, with R&D projects becoming more targeted and novel in terms of indications and mechanisms of action.

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 (February): 203. <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.

Pregelj, Lisette, Martie-Louise Verreynne, and Damian Hine. “Changes in Clinical Trial Length.” *Nature Reviews Drug Discovery* 14, no. 5 (May 2015): 307–8. <https://doi.org/10.1038/nrd4611>.

Abstract: not available.

Reichert, Janice M. “Trends in Development and Approval Times for New Therapeutics in the United States.” *Nature Reviews Drug Discovery* 2, no. 9 (September 2003): 695–702. <https://doi.org/10.1038/nrd1178>.

Abstract: The process of clinical development and regulatory review of new therapeutics in the United States was significantly changed by a number of legislative acts passed in the 1980s and 1990s. These acts were designed to encourage the development of innovative products, especially for rare, serious or life-threatening diseases, and to ensure that patients had timely access to these treatments. To assess the effects of the various modifications to the process, the Tufts Center for the Study of Drug Development analysed clinical development and approval data for 554 therapeutics

(504 small molecules, 40 recombinant proteins and 10 monoclonal antibodies) approved in the United States from 1980–2001. Trends in the number of approved products and the clinical development and approval times indicated that the effects of these changes were generally beneficial as of the mid- to late-1990s, but that the gains have not been sustained in the early 2000s. Current efforts by the FDA, and the pharmaceutical and biopharmaceutical industry, to reverse the recent tendency toward fewer new approvals and longer approval times are discussed.

Schuhmacher, Alexander, Oliver Gassmann, and Markus Hinder. 2016. "Changing R&D Models in Research-Based Pharmaceutical Companies." *Journal of Translational Medicine* 14 (1): 105. <https://doi.org/10.1186/s12967-016-0838-4>.

Abstract: New drugs serving unmet medical needs are one of the key value drivers of research-based pharmaceutical companies. The efficiency of research and development (R&D), defined as the successful approval and launch of new medicines (output) in the rate of the monetary investments required for R&D (input), has declined since decades. We aimed to identify, analyze and describe the factors that impact the R&D efficiency. Based on publicly available information, we reviewed the R&D models of major research-based pharmaceutical companies and analyzed the key challenges and success factors of a sustainable R&D output. We calculated that the R&D efficiencies of major research-based pharmaceutical companies were in the range of USD 3.2–32.3 billion (2006–2014). As these numbers challenge the model of an innovation-driven pharmaceutical industry, we analyzed the concepts that companies are following to increase their R&D efficiencies: (A) Activities to reduce portfolio and project risk, (B) activities to reduce R&D costs, and (C) activities to increase the innovation potential. While category A comprises measures such as portfolio management and licensing, measures grouped in category B are outsourcing and risk-sharing in late-stage development. Companies made diverse steps to increase their innovation potential and open innovation, exemplified by open source, innovation centers, or crowdsourcing, plays a key role in doing so. In conclusion, research-based pharmaceutical companies need to be aware of the key factors, which impact the rate of innovation, R&D cost and probability of success. Depending on their company strategy and their R&D set-up they can opt for one of the following open innovators: knowledge creator, knowledge integrator or knowledge leverager.

Sheck, Lorraine, Christopher Cox, Henry T Davis, A Gene Trimble, William M Wardell, and Ronald Hansen. "Success Rates in the United States Drug Development System." *Clinical Pharmacology and Therapeutics* 36, no. 5 (November 1984): 574–83. <https://doi.org/10.1038/clpt.1984.224>.

Abstract: not available.

Smietana, Katarzyna, Marcin Siatkowski, and Martin Møller. "Trends in Clinical Success Rates." *Nature Reviews Drug Discovery* 15, no. 6 (June 2016): 379–80. <https://doi.org/10.1038/nrd.2016.85>.

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**Abstract:** The topic of R&D productivity in the pharmaceutical industry has been discussed for more than 20 years. It has been largely a story of decline. In fact, around 90% of potential drugs that enter Phase I trials are destined to fail, and for more than a decade we have observed a downward trend in clinical success rates at all stages. To update our research, we conducted an outside-in analysis of pharmaceutical development success rates from 1996 until 2014. Using Informa's Pharma projects database, we tracked the clinical and regulatory phase progression of more than 9,200 novel compounds in development (see Supplementary information S1 (box) for details). Our methodology enables success rates for individual development phases to be determined based on the proportion of successful drugs among all compounds exiting that phase in a given time period. Here, we summarize the key trends we observed.

**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: 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.

**Thomas, David W., Justin Burns, John Audette, Adam Carroll, Corey Dow-Hygelund, and Michael Hay. "Clinical Development Success Rates 2006-2015" Biomedtracker Report, 2016. 1-28.**

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**Abstract:** This is the largest study of clinical drug development success rates to date. Over the last decade, 2006-2015, a total of 9,985 clinical and regulatory phase transitions were recorded and analyzed from 7,455 development programs, across 1,103 companies in the Biomedtracker database. Phase transitions occur when a drug candidate advances into the next phase of development or is suspended by the sponsor. By calculating the number of programs progressing to the next phase vs. the total number progressing and suspended, we assessed the success rate at each of the four phases of development: Phase I, II, III, and regulatory filing. Having phase-by-phase data in hand, we then compared groups of diseases, drug modalities and other attributes to generate the most comprehensive analysis yet of biopharmaceutical R&D success. This work was made possible due to the years of clinical program monitoring and data entry by Informa's Biomedtracker service. BIO has long partnered with Biomedtracker to calculate success rates based on this data. More recently, BIO and Biomedtracker partnered with Amplion, the inventors of BiomarkerBase, to analyze the effects of biomarkers in clinical trial success.

Link:

<https://www.bio.org/sites/default/files/legacy/bioorg/docs/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf>

Wong, Chi Heem, Kien Wei Siah, and Andrew W Lo. "Estimation of Clinical Trial Success Rates and Related Parameters." *Biostatistics* 20, no. 2 (April 1, 2019): 273–86. <https://doi.org/10.1093/biostatistics/kxx069>.

**Abstract:** Previous estimates of drug development success rates rely on relatively small samples from databases curated by the pharmaceutical industry and are subject to potential selection biases. Using a sample of 406 038 entries of clinical trial data for over 21 143 compounds from January 1, 2000 to October 31, 2015, we estimate aggregate clinical trial success rates and durations. We also compute disaggregated estimates across several trial features including disease type, clinical phase, industry or academic sponsor, biomarker presence, lead indication status, and time. In several cases, our results differ significantly in detail from widely cited statistics. For example, oncology has a 3.4% success rate in our sample vs. 5.1% in prior studies. However, after declining to 1.7% in 2012, this rate has improved to 2.5% and 8.3% in 2014 and 2015, respectively. In addition, trials that use biomarkers in patient-selection have higher overall success probabilities than trials without biomarkers.

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: 23. <https://doi.org/10.12688/gatesopenres.12817.2>.

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**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.*

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