FEATURE

Clinical development success rates for investigational drugs

Michael Hay, David W Thomas, John L Craighead, Celia Economides & Jesse Rosenthal

The most comprehensive survey of clinical success rates across the drug industry to date shows productivity may be even lower than previous estimates.

Since the human genome was sequenced ten years ago, the number of compounds in development has increased 62% and total R&D expenditures have doubled[1–3]. And yet, the average number of new drugs approved by the US Food and Drug Administration (FDA) per year has declined since the 1990s. In 2012, 39 novel drugs classified as new molecular entities (NMEs) and biologic license applications (BLAs) were approved by the FDA[4]. Although this represents the highest number of approvals since 1997 and is nearly 50% above the average of 26 approvals per year over the past decade, 25% fewer NME and BLA drugs were approved on average in the past 10 years compared with the 1990s[5]. Several possible explanations for the divergence of R&D spending and new product approvals have been offered by professionals in the industry, such as unbalanced regulatory risk-benefit assessments, higher regulatory efficacy hurdles, commercial and financial decisions driving project termination, and the increased complexity and cost of clinical trials[6,7].

This article aims to measure clinical development success rates across the industry with a view to strengthening benchmarking metrics for drug development. The study is the largest and most recent of its kind, examining success rates of 835 drug developers, including biotech companies as well as specialty and

Michael Hay and Jesse Rosenthal are at BioMedTracker, Sagient Research Systems, San Diego, California, USA; David W. Thomas and Celia Economides are at the Biotechnology Industry Organization (BIO), Washington, DC, USA; and John L. Craighead is at Biotech Strategy & Analytics, Rockville, Maryland, USA. e-mail: mhay@sagientresearch.com

large pharmaceutical firms from 2003 to 2011. Success rates for over 7,300 independent drug development paths are analyzed by clinical phase, molecule type, disease area and lead versus nonlead indication status.

Our results pinpoint weaknesses along the capital-intensive pathway to drug approval. Our hope is that they will prove useful in informing policy makers where to focus changes in regulation and strengthen valuation models used by industry and the investment community.

Analyzing success

To measure clinical development success rates for investigational drugs, we analyzed phase transitions from January 1, 2003 to December 31, 2011, in the BioMedTracker database. The BioMedTracker data set contained 4,451 drugs with 7,372 independent clinical development paths from 835 companies and included 5,820 phase transitions. The development paths comprised lead (primary) and nonlead (secondary) indications, with roughly 38% designated as nonlead. A more detailed description of the data collection, composition and analysis methodology is described in **Boxes 1–3** (see also **Tables 1** and **2**).

Unlike many previous studies that reported clinical development success rates for large pharmaceutical companies, this study provides a benchmark for the broader drug development industry by including small public and private biotech companies and specialty pharmaceutical firms. The aim is to incorporate data from a wider range of clinical development organizations, as well as drug modalities and targets. Two landmark publications on the subject, DiMasi et al.[6] and Kola et al.[8] use 50 and 10 pharmaceutical company pipelines, respectively, to arrive at their conclusions. An important study published by the US Federal

Trade Commission Bureau of Economics, Abrantes-Metz et al.[9] covered a wide number of drugs over a 14 year period from 1989 to 2002, but did not provide the number or type of companies investigated. Although the impact of company size and experience on R&D productivity has been studied extensively[10–13], success rates established by DiMasi et al.[6], Kola et al.[8] and Abrantes-Metz et al.[9] remain the primary benchmarks for the drug development industry.

We believe it is of great value to report updated success rates that capture the diversity in drug development sponsor types as experience and technology vary widely outside of traditional, large pharmaceutical corporations. Furthermore, the more recent time frame for this study provides insight into the latest industry productivity. A comparison of previously published reports with the current study is summarized in **Table 3** and is discussed below.

One key distinction of the study presented here is our ability to evaluate all of a drug's indications to determine success rates. Danzon et al.[12] first considered success rates at the indication level, recognizing that FDA requires clinical trial evidence to establish efficacy for each approved indication. Although these authors included data from 1988 to 2000, an observation period similar to Kola et al.[8] and Abrantes-Metz et al.[9], their success rates were significantly higher and lacked a characteristic decrease in phase 2 probability reported in previous studies as well as here. Danzon et al.[12] concluded that higher clinical development success rates resulted from the analysis of all indications. Even so, evidence presented here strongly suggests that evaluating all indications results in lower probabilities of success across all phases of drug development.

To illustrate the importance of using all indications to determine success rates, consider this scenario. An antibody is developed in four cancer indications, and all four indications transition successfully from phase 1 to phase 3, but three fail in phase 3 and only one succeeds in gaining FDA approval. Many prior studies reported this as 100% success, whereas our study differentiates the results as 25% success for all indications, and 100% success for the lead indication. Considering the cost and time spent on the three failed phase 3 indications, we believe including all 'development paths' more accurately reflects success and R&D productivity in drug development.

Examining individual drug indications allows us to answer the question: "what is the probability that a drug developed for a specific indication will reach approval?" Whereas, using only the lead or most advanced indication seeks to answer the question: "what is the probability that a drug will reach approval for any indication?" This study addresses both questions with emphasis on the findings of the former. In the following sections, we present the results of our analysis as they relate to overall phase success and likelihood of approval (LOA; see **Box 2**), to the type of therapeutic modality, to the disease being treated and to the type of drug application (whether orphan or Special Protocol Assessment (SPA) pathways).

Phase success and likelihood of approval

We found that approximately one in ten (10.4%, $n = 5,820$) of all indication development paths in phase 1 were approved by FDA (**Fig. 1** and **Table 4**). Examining the individual phase components of this compound probability, phase I success (the number of phase 1 drugs that successfully transitioned to phase 2 divided by the total transitions in phase 1) was 64.5% ($n = 1,918$). Success in phase 2 (32.4%, $n = 2,268$) was substantially lower than in phase 1, but subsequently increased in phase 3 (60.1%, $n = 975$). The probability of FDA approval after submitting a new drug application (NDA) or biologic license application (BLA) was 83.2% ($n = 659$).

Success rates for lead indication development paths were higher than for all indication development paths in every phase. Lead indications had a LOA from phase 1 of 15.3% ($n = 3,688$).

Success rates by drug classification

Drugs in the BioMedTracker data set were annotated by their FDA classification: new molecular entity (NME), non-NME, biologic and vaccine. However, owing to inconsistency in the FDA classifications, we also used our

Box 1 Data collection and composition

BioMedTracker, a subscription-based product of Sagient Research Systems (San Diego) introduced in 2002, tracks the clinical development and regulatory history of novel investigational drugs in the United States. Analysts with advanced degrees in the life sciences and medicine maintain the database using information from company press releases, analyst conference calls, and presentations at investor and medical meetings. BioMedTracker also uses other sources, including regular communication with companies conducting clinical trials, to ensure the accuracy and timeliness of the data.

Data included in this study were selected using BioMedTracker's Probability of Technical Success (PTS) calculator, which identified 5,820 phase transitions from January 1, 2003, to December 31, 2011. Transitions in all phases of development were recorded in the early years of observation and resulted from clinical studies initiated before 2003. The data set contained 4,451 drugs from 835 companies and 7,372 independent clinical development paths in 417 unique indications.

The composition of these novel drug development sponsors included a wide range of company sizes and types (**Table 1**). Emerging biotech represented 85% (712) of the companies, whereas a small number (33) of large firms (4% of total) were responsible for 48% (3,573) of indications and 47% (2,075) of drugs in development. Similarly, private firms represented 49% (412) of the companies and fewer than 20% of indications and drugs included in the study.

These ownership classifications were recorded at the end of the analysis time period and underestimate the number of drugs and indications developed by biotech companies due to licensing and acquisitions during the study time frame. In addition, ownership was assigned to the licensee controlling and funding the majority of development. In cases where development and economics were shared equally, ownership was generally assigned to the larger organization, further contributing to the conservative estimate of drugs developed by small and private biotech companies. Although generic products were not included, generic manufacturers developing novel investigational drugs were represented.

The study also likely tracked a larger percentage of late-stage studies as these programs are more often in the public domain. Even so, small biotech companies often disclose ongoing phase 1 studies and we would expect their substantial representation in this study to partially offset the under-representation of early-stage discontinuation rates. Only company sponsored development paths designed for FDA approval were considered; investigator sponsored studies and combinations with other investigational drugs were excluded in this analysis.

In addition, this study analyzed development paths organized by disease area, biochemical composition, molecular size, FDA classification and regulatory status (SPA and orphan drug status). Given the increasing complexity of ownership and diversity of invention in the drug development industry, the study did not further classify the database on the discovery origin or licensing status of the drug.

Table 1 Analysis of company size and type

	Companies		Indications		Drugs	
	Number	Percentage	Number	Percentage	Number	Percentage
Company size						
Large pharma/biotech (>$5 billion sales)	33	4%	3,573	48%	2,075	47%
Small to mid-sized pharma/biotech ($0.1 billion–$5 billion sales)	90	11%	1,099	15%	724	16%
Emerging biotech (<$0.1 billion sales)	712	85%	2,700	37%	1,652	37%
Total	835	–	7,372	–	4,451	–
Company type						
Private	412	49%	1,269	17%	841	19%
Public	423	51%	6,103	83%	3,601	81%
Total	835	–	7,372	–	4,451	–

> ## Box 2 Metrics of success: 'Phase Success' and 'Likelihood of Approval'
>
> There are two different types of success rates reported in this study: 'Phase Success' and 'Likelihood of Approval' (LOA). 'Phase Success' is calculated as the number of drugs that moved from one phase to the next phase divided by the sum of the number of drugs that progressed to the next phase and the number of drugs that were suspended. The n value associated with the Phase Success represents the number of drugs that have advanced plus the number of drugs that have been suspended, which we label as phase transitions. For example, if there were 100 drugs in phase 2 development and 50 transitioned to phase 3, 20 were suspended and 30 remained in phase 2 development, the phase 2 Phase Success would be 71.4% (50/70; $n = 70$).
>
> Our second metric, LOA, denotes the probability of reaching FDA approval from the current phase, and is also expressed as a percentage. LOA is calculated as the product of each Phase Success probability leading to FDA approval. The n value associated with LOA is the sum of the n values for each Phase Success included in the LOA calculation. For example, if a drug is currently in phase 2, and the Phase Success for phase 2 is 30% ($n = 20$), phase 3 is 50% ($n = 10$), and FDA approval is 80% ($n = 5$), then the LOA for the phase 2 drug would be 12% ($30\% \times 50\% \times 80\% = 12\%$, $n = 35$). This calculation is illustrated in **Supplementary Figure 2**.

data to annotate drugs by their biochemical composition (e.g., peptide, nucleic acid, monoclonal antibody (mAb)) and molecular size (i.e., large and small molecules). For example, FDA often designates large-molecule biologics, such as proteins and peptides, as NMEs. Indeed, large molecules, as defined by the BioMedTracker biochemical categories, comprise 13% of the NME data set, making direct FDA NME to biologic classification comparisons somewhat imprecise. FDA's biologic classification comprises a wider group that includes the Center for Drug Evaluation and Research (CDER) regulated products, such as antibodies, cytokines, growth factors and enzymes, as well as the Center for

Biologics Evaluation and Research (CBER) regulated products including blood isolates, gene therapies and cell therapy.

FDA's non-NME classification often includes drugs with the same molecular properties as NMEs, but which are frequently reformulations or combinations of approved products. The majority of non-NMEs also use the 505(b)(2) pathway to gain FDA approval. Vaccines were also treated as a separate class in this analysis, and generic and over-the-counter drugs were not included. A comparative analysis of FDA classifications and BioMedTracker categories can be found in **Supplementary Table 1**. The metrics for the different therapeutic modality types is provided in **Table 4**.

NMEs were found to have the lowest success rates in every phase of development; biologics had nearly twice the LOA from phase 1 (14.6%, $n = 1,173$) as NMEs (7.5%, $n = 3,496$) for all indications (**Table 4**). Similar results are seen when the data are reclassified into large-molecule (excluding low molecular weight chemicals and steroids) and small-molecule NMEs: 13.2% ($n = 1,834$) and

7.6% ($n = 3,029$), respectively. In addition, the LOA from phase 1 for mAbs (14.1%, $n = 639$), a good proxy for CDER-regulated biologics, was also consistent with these broader definitions of biologics.

Non-NMEs had the highest LOA from phase 1 of 20.0% ($n = 855$), with success rates well above those of the NME and biologic classifications in every phase. However, many non-NMEs begin development in phase 2 or phase 3, so the actual approval rate is likely higher (assuming that successful phase 1 outcomes would contribute positively to the LOA from phase 1).

When analyzing lead indications only (i.e., on a per drug basis), we find similar rankings for NME, biologic and non-NME, but at much higher success rates. The LOA from phase 1 for biologics and non-NMEs are near one in four and NMEs approach one in eight (12.0%, $n = 2,124$), almost twice what was found when all indications were considered.

Success rates by disease
We found substantial variation in success rates among disease, as listed in **Table 5** from highest to lowest LOA from phase 1. Oncology drugs had the lowest LOA from phase 1 at 6.7% ($n = 1,803$). Drugs for the 'other' disease group, which combined allergy, gastroenterology, ophthalmology, dermatology, obstetrics-gynecology and urology indications due to small sample size, had the highest LOA from phase 1, at 18.2% ($n = 720$). Drugs for infectious disease and autoimmune-immunology groups had the next two highest LOAs from phase 1, at 16.7% ($n = 537$) and 12.7% ($n = 549$), respectively.

On a lead indication basis, also in **Table 5**, we found that cardiovascular drugs had the lowest LOA from phase 1 at 8.7% ($n = 318$) and the 'other' disease category again had the highest success rate at 24.5% ($n = 499$). The largest difference between lead and all-indication for LOA from phase 1 was observed in oncology: 6.7% ($n = 1,803$) for lead indication and 13.2% ($n = 796$) for all indications. Oncology drugs also had the most nonlead indications (56% of all development paths compared with 28% of non-oncology indications) as a result of the large number of cancers investigated using the same drug. Unfortunately, in oncology, when all indications are considered, only around 1 in 15 drugs entering clinical development in phase 1 achieves FDA approval compared with close to 1 in 8 using the lead indication methodology. As noted above, the result for lead indications represents the most successful development path for a particular compound, thereby addressing LOA on a per drug
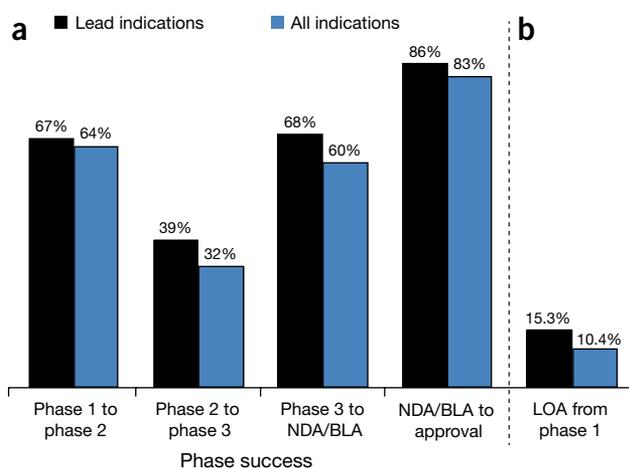

Figure 1 Phase success and LOA rates. (**a**) Phase success rates for lead and all indications. The rates represent the probability that a drug will successfully advance to the next phase. (**b**) LOA from phase 1 for lead and all indications. Rates denote the probability of FDA approval for drugs in phase 1 development.

Box 3 Methods used in this study

Data used for this study were extracted from BioMedTracker using a probability of technical success (PTS) tool, which identified all 'Advanced' and 'Suspended' drugs by development phase from January 1, 2003, to December 31, 2011. BioMedTracker tracks the clinical development and regulatory history of investigational drugs to assess its Likelihood of Approval (LOA) from phase 1 by the FDA. The database is populated in near real-time with updated information from press releases, corporate earnings calls, investor and medical meetings, and numerous other sources. These data are recorded in BioMedTracker and tagged with a date.

Phase is defined as the stage of clinical development in the United States (**Table 2**). Although it is rare, drugs that were removed from development in the United States, but approved in Europe (e.g., vildagliptin for type II diabetes) were considered 'suspended' for the sake of our analysis. In this time period, 7,372 development paths were analyzed, encompassing 4,451 unique compounds. 5,820 unique phase transitions were used to determine the reported success rates. **Table 4** includes the number of observed transitions by phase (a description of the success rate analysis is described). Phase 2 transitions accounted for the highest percentage of the data set with 39% ($n = 2,268$), compared with 33% in phase 1 ($n = 1,918$), 17% in phase 3 ($n = 975$) and 11% in NDA/BLA ($n = 659$). Nonlead indications comprise 38% ($n = 2,132$) of the 5,820 total transitions and success rates by phase can be found in **Supplementary Table 2**.

Development paths track a specific indication for each drug. For example, Rituxan (rituximab) in non-Hodgkin's lymphoma qualifies as a development path different from Rituxan in multiple sclerosis (MS). BioMedTracker assigns a unique internal identifier that can be used to isolate all development paths. In addition to tracking the phase of development, BioMedTracker assigns 'lead' status to certain development paths. This is used to denote the most advanced indication in clinical development for a specific drug. Drugs can only have one lead development path, except in specific circumstances where two development paths are being developed simultaneously (e.g., type I and type II diabetes). For example, the Avastin (bevacizumab) colorectal cancer development path was marked as a 'lead' indication, and other Avastin development paths were labeled 'nonlead'. Using this metric, Avastin clinical development can more accurately be viewed as a series of successes and failures, as opposed to simply one success and no failures. However, a drug's lead indication may also change if it fails in development in the lead indication. The lead indication success rate will therefore be higher due to selection bias than the nonlead success rate. This bias does not affect the LOA from phase 1 rate for all indication development paths.

BioMedTracker also records a number of other variables including the following:
- FDA classification (e.g., NME, non-NME, biologic or vaccine)
- Biochemical profile (e.g., small molecule, monoclonal antibody, antisense)

Table 2 Definitions of terms used in this study

BioMedTracker term	Description for purposes of this study
I	Drug is currently in phase 1
I/II, II, IIb	Drug is currently in phase 2
II/III, III	Drug is currently in phase 3
NDA/BLA	Application for approval has been submitted to the FDA and is currently under review
Approved, withdrawn from market, approved (Generic competition)	Drug has been approved for marketing in the United States
Suspended	Drug is no longer in development
Approved in Europe, Approved in other than US/EU, Development, Development outside US	The company developing this drug does not plan to market it in the United States

- Disease area (e.g., autoimmune, cardiovascular, oncology)
- Indication (e.g., diabetes, acute coronary syndrome)

In contrast with many earlier studies, which included only a limited sample of drugs from large companies, the current study included BioMedTracker data from small biotech companies as well as specialty and large pharmaceutical firms.

Phase success and LOA rates calculation. A common method of determining drug development success rates detailed in DiMasi et al.[6] and Abrantes-Metz et al.[9] was used in this study. Phase Success, defined as the probability of a drug moving from phase X to phase X + 1, was used as the basis for all analyses. To arrive at this value, the following questions are used to categorize each drug development path: first, was the drug development path ever in phase X? Second, if so, did it advance to phase X + 1? And third, was it 'Suspended'? After categorizing all drug development paths, Phase Success is calculated by dividing the number of development paths that advanced from phase X to phase X + 1 by the sum of the number of development paths that advanced from phase X to phase X + 1 and the number of development paths that were suspended from phase X – Advanced/(Advanced + Suspended) = Phase Success.

Using this method, we arrived at the probabilities of an 'average' drug advancing from phase 1 to phase 2, from phase 2 to phase 3, from phase 3 to filing the NDA/BLA and from filing the NDA/BLA to FDA approval. We then compounded these probabilities to determine the probability (LOA) that a drug in phase X is approved. For example, the LOA for a drug which has entered phase 2 is the product of the phase success rates from phase 2, phase 3 and NDA/BLA. An example calculation is illustrated in **Supplementary Figure 2**.

For purposes of this analysis, all indications that were advanced or suspended in any phase during our collection time frame were included. In practice, this means a drug that 'entered' the analysis in 2003 in phase 2, and later advanced to phase 3, was included in the study. This method was selected because there are relatively few drugs that entered development in phase 1 in the range of years analyzed and have subsequently progressed through final FDA review, and there is less disclosure of drugs in phase 1 development. Abrantes-Metz et al.[9] also used a similar method and stated, "We did it this way because the data set has very few drugs with complete information for all... phases." Drugs that remained in the same phase were censored, as were those that moved back a phase but were not suspended[9].

Table 3 Comparison of our study with previous drug development success rate studies

	This study (2013) all indications		This study (2013) lead indications		DiMasi et al.[6] lead indications		Kola et al.[8] lead indications		Abrantes-Metz et al.[9] lead indications	
	Phase success	Phase LOA	Phase success	Phase LOA	Phase success	Phase LOA	Phase success	Phase LOA	Phase success	Phase LOA
Phase 1 to phase 2	64.5%	10.4%	66.5%	15.3%	71%	19%	68%	11%	80.7%	NA
Phase 2 to phase 3	32.4%	16.2%	39.5%	23.1%	45%	27%	38%	16%	57.7%	NA
Phase 3 to NDA/BLA	60.1%	50.0%	67.6%	58.4%	64%	60%	55%	42%	56.7%	NA
NDA/BLA to approval	83.2%	83.2%	86.4%	86.4%	93%	93%	77%	77%	NA	NA
LOA from phase 1[a]		10.4%		15.3%		19%		11%	26.4%[c]	NA
Number of drugs in sample advanced or suspended[b]	5,820		4,736		1,316		NA		2,328	
Dates of source data (duration)	2003–2011 (9 years)				1993–2009 (17 years)		1991–2000 (10 years)		1989–2002 (14 years)	
Number of companies	835				50		10		NA	

[a]Probability of FDA approval for drugs in phase 1 development. [b]Total number of transitions used to calculate the success rate (the *n* value noted in the text). [c]Abrantes-Metz, et al.[9] reported 26.4% from phase 1 to phase 3. If we were to conservatively apply the 83.2% NDA/BLA success rate found in this study, Abrantes-Metz would yield the highest LOA from phase 1 (21%). NA, data not available.

basis. Using the lead indication methodology to determine success rates, the scope of the challenge in oncology drug development would be dramatically underestimated.

The largest variation in success rates across disease groups was observed in phase 2. In **Table 5** all-indication phase 2 success rates ranged from 26.3% (for cardiovascular) to 45.9% (for infectious disease). In phase 3, all indication success rates ranged from 45.2% (for oncology) to 71.1% (for other). In contrast, phase 1 and NDA/BLA (As only one application, NDA or BLA, will be filed for any single indication, rates are given below for NDA/BLA.) filing success rates were more consistent across disease groups. All indication data from **Table 5** are charted in **Figure 2** to illustrate the large differences in phases 2 and 3 and LOA from phase 1 success rates across disease areas.

Figure 2 Phase success and LOA from phase 1 by disease for all indications. The bars represent phase 2 and phase 3 success rates and the line represents LOA from phase 1.

The development paths with the two lowest rates of phase 3 success were oncology and cardiovascular disease, with 45.2% (*n* = 221) and 52.8% (*n* = 89), respectively. **Figure 2** also highlights the large step-up in success rates from phase 2 to phase 3 for autoimmune, endocrine and respiratory diseases, increasing from 34% to 68%, 34% to 67%, and 28% to 63%, respectively. The low LOA from phase 1 in oncology rate results primarily from the lack of such a step-up, with a low phase 2 rate of 28.3% (*n* = 827), followed by a phase 3 success rate of only 45.2% (*n* = 221).

Success rates for oncology and non-oncology drugs. As oncology drugs made up the largest portion of the total data set (31.0% of all transitions) and had the lowest LOA from phase 1 (6.7%, *n* = 1,803), we investigated their contribution to success rates for the entire data set. To accomplish this, we removed all oncology drug development paths and compared these results to the full data set and oncology development paths alone. **Table 6** shows phase success and LOA rates for drugs for all disease groups, oncology and non-oncology development paths. The LOA from phase 1 across non-oncology indications is nearly twice that for oncology alone, 12.1% (*n* = 4,017)

versus 6.7% (*n* = 1,803), respectively, reducing the probability of FDA approval in the full data set from nearly one in eight to over one in ten. Interestingly, the LOA from phase 1 for small-molecule NMEs was similar for oncology (6.6%, *n* = 1,163) and non-oncology (7.9% *n* = 2,333) indications, and biologics and non-NMEs accounted for much of the difference. For example, oncology biologics had a 7.3% (*n* = 429) LOA from phase 1 compared with 19.4% (*n* = 744) for non-oncology biologics.

Table 7 shows phase success and LOA rates in subcategories of cancer type for oncology drugs. Although a high number of transitions in all phases were seen for the solid tumor (*n* = 1,358) and hematological (*n* = 409) subgroups, further classification of oncology indications results in low numbers of transition from phase 3 to NDA/BLA. As is true of the full data set, drugs in phase 2 for oncology subgroups display more transitions and represent the strongest data for specific-indication success rate analysis. Oncology phase 2 success rates ranged from 50.0% (*n* = 12) in head and neck cancer to 20.9% (*n* = 24) in prostate cancer; however, the phase 2 rank order by tumor type was uncorrelated with LOA from phase 1 (linear regression, $R^2 = 0.26$). On average, phase 2 success rates were higher in hematological tumors (34.6%, *n* = 179) than in solid tumors (26.3%, *n* = 636). Only two phase 3 oncology indications had more than 20 transitions: breast cancer (*n* = 25) and non–small cell lung cancer (*n* = 23), which together accounted for ~28% of the solid tumor phase 3 transitions (*n* = 172). Because of even smaller sample sizes, cancer type success rates were not analyzed by lead indication.

Success rates for neurology, autoimmune and endocrine disease drugs. Neurology and autoimmune/immunology disease groups are
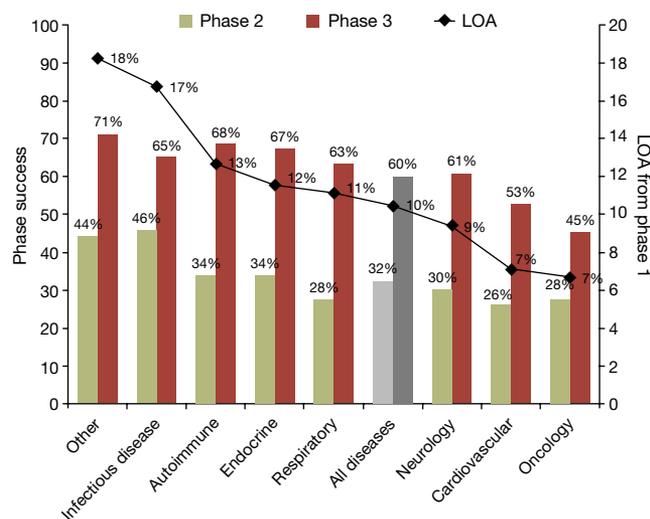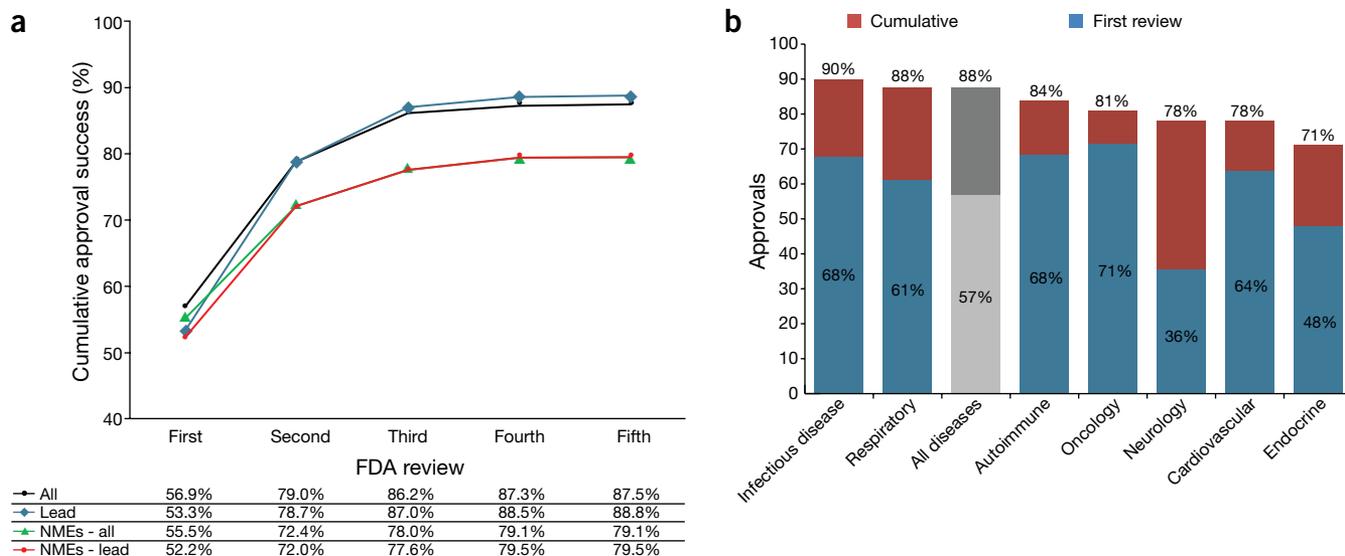
Figure 3 NDA/BLA success rates. (**a**) Cumulative approval rates by FDA review from 2005 to 2011 (914 reviews). (**b**) Cumulative and first FDA approval rates by disease.

well represented, comprising 17% and 9% of the data set, respectively. We subcategorized neurology into pain and psychiatric disorders, the two main therapeutic areas representing 51% of all neurology indications (**Table 8**). Analyzing all development paths, pain indications had a 10.7% ($n = 231$) LOA from phase 1 compared with 7.2% ($n = 294$) for psychiatric disorders. Other neurology indications, mainly representing neurodegenerative diseases, had a 9.8% ($n = 452$) LOA from phase 1.

An autoimmune subset analysis reveals that biologics had more than five times the LOA from phase 1 (22.5%, $n = 288$) than NMEs (5.2%, $n = 202$). **Table 8** also includes success rates for the type II diabetes and rheumatoid arthritis indication subcategories. Although rheumatoid arthritis had a 100% ($n = 5$) NDA/BLA submission success, the LOA from phase 1 was only 10.3% ($n = 130$) due to one of the lowest phase 2 success rates in this study (15.9%, $n = 63$). Diabetes also displayed lower-than-average

success rates in all phases, except for NDA/BLA submissions, at 86.4% ($n = 22$).

Regulatory pathway success rates
To investigate the influence of regulation on clinical success we looked at two important pathways for drug oversight: the SPA and orphan drug designation.

SPA success rates. Similar to other analyses, we looked at phase success and LOA rates for drugs with an SPA (**Table 9**). Before

Table 4 Phase success and LOA by drug class

	Phase 1 to phase 2				Phase 2 to phase 3				Phase 3 to NDA/BLA				NDA/BLA to approval			
	Total in phase[a]	Advanced or suspended[b]	Phase success[c]	Phase LOA[d]	Total in phase[a]	Advanced or suspended[b]	Phase success[c]	Phase LOA[d]	Total in phase[a]	Advanced or suspended[b]	Phase success[c]	Phase LOA[d]	Total in phase[a]	Advanced or suspended[b]	Phase success[c]	Phase LOA[d]
FDA classification[e]																
All indications	2,541	1,918	64.5%	10.4%	3,743	2,268	32.4%	16.2%	1,554	975	60.1%	50.0%	908	659	83.2%	83.2%
NMEs	1,585	1,218	64.2%	7.5%	2,375	1,470	28.6%	11.6%	831	515	53.2%	40.7%	425	293	76.5%	76.5%
Biologics	572	411	68.4%	14.6%	819	464	37.9%	21.3%	320	182	63.2%	56.1%	159	116	88.8%	88.8%
Non-NMEs	218	168	66.7%	20.0%	355	226	45.1%	29.9%	321	234	75.6%	66.3%	293	227	87.7%	87.7%
Lead indications	1,770	1,336	66.5%	15.3%	2,070	1,247	39.5%	23.1%	1,009	633	67.6%	58.4%	664	472	86.4%	86.4%
NMEs	1094	848	65.2%	12.0%	1,275	791	36.4%	18.3%	497	300	61.7%	50.3%	283	185	81.6%	81.6%
Biologics	362	257	75.1%	20.8%	403	216	44.0%	27.7%	182	106	71.7%	63.1%	106	75	88.0%	88.0%
Non-NMEs	167	124	66.9%	23.2%	232	153	49.0%	34.6%	254	186	79.0%	70.7%	246	189	89.4%	89.4%
Biomedtracker product category[f]																
Small molecule NMEs	1,335	1,033	65.4%	7.6%	2,053	1,283	29.0%	11.6%	725	449	52.3%	39.8%	369	264	76.1%	76.1%
Large molecules	912	658	65.8%	13.2%	1,279	714	37.7%	20.1%	511	296	60.1%	53.3%	244	166	88.6%	88.6%
mAbs	329	234	70.1%	14.1%	458	268	38.1%	20.1%	147	84	60.7%	52.7%	65	53	86.8%	86.8%
non-mAb proteins	192	151	58.9%	13.1%	280	170	35.3%	22.3%	150	87	69.0%	63.1%	93	59	91.5%	91.5%
Vaccines	121	57	67.1%	14.9%	160	79	44.3%	22.2%	67	34	50.0%	50.0%	23	20	100.0%	100.0%

[a]Number of indications identified. [b]Total number of transitions used to calculate the success rate, the n value noted in the text. The difference between 'Total in phase' and 'Advanced or suspended' is the number of indications that remain in development. [c]Probability of successfully advancing to the next phase. [d]Probability of FDA approval for drugs in this phase of development. [e]FDA NME, biologic and non-NME classifications as defined in the results section. Data are presented for all and lead indication development paths. [f]BioMedTracker classification of small-molecule NMEs and large-molecule drugs. Large molecules are further stratified by biochemical profile.

Table 5 Phase success and LOA by disease[a]

	Phase 1 to phase 2				Phase 2 to phase 3				Phase 3 to NDA/BLA				NDA/BLA to approval			
	Total in phase[b]	Advanced or sus-pended[c]	Phase success[d]	Phase LOA[e]	Total in phase[b]	Advanced or sus-pended[c]	Phase success[d]	Phase LOA[e]	Total in phase[b]	Advanced or sus-pended[c]	Phase success[c]	Phase LOA[e]	Total in phase[b]	Advanced or sus-pended[c]	Phase success[d]	Phase LOA[e]
All indications																
Other[f]	254	198	72.2%	18.2%	419	251	44.2%	25.3%	252	159	71.1%	57.1%	169	112	80.4%	80.4%
Infectious disease	247	196	65.8%	16.7%	288	157	45.9%	25.4%	159	98	65.3%	55.4%	115	86	84.9%	84.9%
Autoimmune	241	178	68.0%	12.7%	350	215	34.0%	18.7%	149	95	68.4%	55.0%	88	61	80.3%	80.3%
Endocrine	223	180	58.3%	11.6%	293	198	33.8%	19.8%	147	95	67.4%	58.5%	91	61	86.9%	86.9%
Respiratory	110	90	66.7%	11.1%	193	120	27.5%	16.7%	58	30	63.3%	60.8%	33	25	96.0%	96.0%
Neurology	389	298	62.4%	9.4%	520	348	30.2%	15.0%	285	188	60.6%	49.9%	192	152	82.2%	82.2%
Cardiovascular	158	127	60.6%	7.1%	229	152	26.3%	11.7%	121	89	52.8%	44.6%	78	58	84.5%	84.5%
Oncology	919	651	63.9%	6.7%	1,451	827	28.3%	10.5%	383	221	45.2%	37.0%	142	104	81.7%	81.7%
Total	2,541	1,918	64.5%	10.4%	3,743	2,268	32.4%	16.2%	1,554	975	60.1%	50.0%	908	659	83.2%	83.2%
Lead indications																
Other[f]	193	146	75.3%	24.5%	273	157	50.3%	32.5%	174	115	74.8%	64.6%	122	81	86.4%	86.4%
Infectious disease	228	181	66.9%	19.3%	248	135	45.9%	28.8%	127	76	69.7%	62.8%	94	70	90.0%	90.0%
Respiratory	79	66	63.6%	16.3%	120	76	31.6%	25.6%	40	20	85.0%	81.0%	29	21	95.2%	95.2%
Autoimmune	165	127	67.7%	15.4%	178	102	37.3%	22.8%	77	52	80.8%	61.1%	56	37	75.7%	75.7%
Endocrine	188	152	61.2%	14.5%	226	155	38.1%	23.8%	122	78	69.2%	62.4%	78	51	90.2%	90.2%
Oncology	489	334	68.9%	13.2%	527	298	42.3%	19.1%	193	106	54.7%	45.3%	85	58	82.8%	82.8%
Neurology	301	228	62.7%	12.3%	339	218	34.4%	19.6%	191	124	66.9%	56.8%	137	106	84.9%	84.9%
Cardiovascular	127	102	62.7%	8.7%	159	106	27.4%	13.8%	85	62	56.5%	50.6%	63	48	89.6%	89.6%
Total	1,770	1,336	66.5%	15.3%	2,070	1,247	39.5%	23.1%	1,009	633	67.6%	58.4%	664	472	86.4%	86.4%

[a]Categories are listed from highest to lowest LOA from phase 1 for all indications (lead and nonlead). [b]Number of indications identified. [c]Total number of transitions used to calculate the success rate, the n value noted in the text. The difference between 'Total in phase' and 'Advanced or suspended' is the number of indications that remain in development. [d]Probability of successfully advancing to the next phase. [e]Probability of FDA approval for drugs in this phase of development. [f]Includes allergy, gastroenterology, ophthalmology, dermatology, obstetrics/gynecology and urology.

initiating a pivotal phase 3 program, companies can submit the protocol to the FDA to obtain the agency's agreement that the trial(s) are adequate to meet its scientific and regulatory requirements. At the same time, these trials are often more complex and investigate treatments for less well understood diseases. This latter point is evident from our analysis: NDA/BLA success rates for SPA-designated drugs are slightly below average at 80.0% ($n = 45$) compared with 83.2% ($n = 659$) for all drugs. On the other hand, phase 3 success rates are nearly identical at 60.0% ($n = 110$) for SPA-designated drug indications compared with 60.1% ($n = 975$) for all drugs.

Orphan drug pathway success rates. A company may request that FDA grant the orphan designation for a drug being studied in a rare disease or condition. This is intended for indications affecting fewer than 200,000 people in the United States. Orphan drug designation was designed to reduce development costs and provide financial incentives (e.g., an extended exclusivity period) to encourage development in these indications. **Table 9** shows that although drugs for orphan indications have high rates of phase 1 and 2 success, phase 3 and NDA/BLA success rates are similar to all indications. Even so, it is important to note that orphan designations can be granted at any point in the clinical development

process and are most often received when a drug is in phase 2. Orphan drugs in our data set received orphan status at all stages of development: preclinical (9%), phase 1 (22%), phase 2 (45%), phase 3 (16%) and NDA/BLA (2%). This distribution introduces a positive bias in early development success rates as some trials are not annotated as orphan until later phases. In contrast, by phase 3, 82% of indications that end up with the orphan designation have been annotated. Indeed, orphan indication phase 1 and 2 success rates were well above average at 86.8% ($n = 136$) and 70.0% ($n = 190$), respectively. Orphan phase 3 success rates (66.9%, $n = 148$) also compared favorably with all indications (60.1%, $n = 975$) and orphan NDA/BLA approvals were lower, 81.0% ($n = 84$) compared with 83.2% ($n = 659$), respectively. A subgroup analysis of phase 3 and NDA/BLA stage orphan drugs by indication reveals that oncology success rates were lower than non-oncology drugs, a result that is consistent with these categories in the full data set.

NDA/BLA success rates
To complement the NDA/BLA phase success rates gathered above, we examined 910 FDA decisions from 2005 to 2011 and classified each as 'Approved' or 'Not Approved.' In addition, we determined at which FDA review each decision occurred (i.e., the first, second,

third, fourth or fifth time the agency reviewed the specific application). **Figure 3a** shows the cumulative success rates for NDA/BLA filings in the all, lead and NME drug classifications. Only 56.9% of all applications were approved on the first NDA/BLA submission, whereas 86.2% were approved by the third submission. After the third submission, there was only a marginal increase in the cumulative approval percentage, as there were few drugs with more than three regulatory reviews. For all NMEs, we found similar first submission success rates, yet fewer than 80% of these drugs were approved by FDA in subsequent submissions.

Analysis of first review approval success rates by disease reveals a variation inconsistent with cumulative approval rates. For example, **Figure 3b** shows that although oncology drugs had a median NDA/BLA success rate (81%), the chances of a first review approval were the highest, at 71%. Neurology drugs, on the other hand, had the lowest first review approval rate at 36%, but the cumulative approval rate reached 78%.

We also examined 304 first review FDA complete response letters and approvable letters issued for approved and suspended drugs. For approved drugs, 46% of the letters to the sponsor cited manufacturing or labeling issues and 47% cited efficacy or safety. In contrast, for suspended drugs, only 2% cited manufacturing or labeling issues and

Table 6 Phase success and LOA for oncology and non-oncology disease groups

	Phase 1 to phase 2				Phase 2 to phase 3				Phase 3 to NDA/BLA				NDA/BLA to approval			
	Total in phase[a]	Advanced or suspended[b]	Phase success[c]	Phase LOA[d]	Total in phase[a]	Advanced or suspended[b]	Phase success[c]	Phase LOA[d]	Total in phase[a]	Advanced or suspended[b]	Phase success[c]	Phase LOA[d]	Total in phase[a]	Advanced or suspended[b]	Phase success[c]	Phase LOA[d]
FDA classification[e]																
All indications	2,541	1,918	64.5%	10.4%	3,743	2,268	32.4%	16.2%	1,554	975	60.1%	50.0%	908	659	83.2%	83.2%
Total oncology	919	651	63.9%	6.7%	1,451	827	28.3%	10.5%	383	221	45.2%	37.0%	142	104	81.7%	81.7%
Oncology NMEs	574	402	65.9%	6.6%	948	534	27.5%	10.0%	245	150	46.0%	36.4%	101	77	79.2%	79.2%
Oncology biologics	244	177	61.6%	7.3%	346	193	30.6%	11.9%	83	41	43.9%	39.0%	24	18	88.9%	88.9%
Oncology non-NMEs	53	39	69.2%	9.4%	76	50	22.0%	13.6%	26	17	70.6%	61.8%	16	8	87.5%	87.5%
Total non-oncology	1622	1267	64.8%	12.1%	2,292	1,441	34.8%	18.7%	1,171	754	64.5%	53.8%	766	555	83.4%	83.4%
Non-oncology NMEs	1011	816	63.4%	7.9%	1,427	936	29.3%	12.4%	586	365	56.2%	42.4%	324	216	75.5%	75.5%
Non-oncology biologics	328	234	73.5%	19.4%	473	271	43.2%	26.4%	237	141	68.8%	61.1%	135	98	88.8%	88.8%
Non-oncology non-NMEs	165	129	65.9%	22.7%	279	176	51.7%	34.5%	295	217	76.0%	66.7%	277	219	87.7%	87.7%
BioMedTracker product category[f]																
All indications	2,541	1,918	64.5%	10.4%	3,743	2,268	32.4%	16.2%	1,554	975	60.1%	50.0%	908	659	83.2%	83.2%
Total oncology	919	651	63.9%	6.7%	1,451	827	28.3%	10.5%	383	221	45.2%	37.0%	142	104	81.7%	81.7%
Oncology small molecule NMEs	492	346	66.5%	7.2%	830	466	28.8%	10.9%	219	136	45.6%	37.8%	93	70	82.9%	82.9%
Oncology mAbs	175	125	68.0%	9.3%	245	140	29.3%	13.7%	55	30	50.0%	46.9%	21	16	93.8%	93.8%
Oncology proteins/peptides	68	50	48.0%	3.4%	108	57	31.6%	7.1%	34	16	37.5%	22.5%	8	5	60.0%	60.0%
Oncology vaccines	41	28	50.0%	1.6%	73	43	39.5%	3.3%	28	12	8.3%	8.3%	1	1	100.0%	100.0%
Total non-oncology	1622	1267	64.8%	12.1%	2,292	1,441	34.8%	18.7%	1,171	754	64.5%	53.8%	766	555	83.4%	83.4%
Non-oncology small molecule NMEs	843	687	64.9%	7.7%	1,223	817	29.1%	11.9%	506	313	55.3%	40.7%	276	194	73.7%	73.7%
Non-oncology mAbs	154	109	72.5%	19.3%	213	128	47.7%	26.6%	92	54	66.7%	55.9%	44	37	83.8%	83.8%
Non-oncology proteins/peptides	228	178	65.7%	18.0%	321	198	42.4%	27.4%	191	118	69.5%	64.7%	125	72	93.1%	93.1%
Non-oncology vaccines	82	57	71.9%	21.8%	87	38	47.4%	30.3%	44	25	64.0%	64.0%	22	19	100.0%	100.0%

[a]Number of indications identified. [b]Total number of transitions used to calculate the success rate, the *n* value noted in the text. The difference between 'Total in phase' and 'Advanced or suspended' is the number of indications that remain in development. [c]Probability of successfully advancing to the next phase [d]Probability of FDA approval for drugs in this phase of development. [e]Oncology and non-oncology disease groups and FDA NME, biologic, and non-NME classifications. Data are presented for all indication development paths. [f]Oncology and non-oncology disease groups and BioMedTracker biochemical categories.

83% cited efficacy or safety. Furthermore, we analyzed the time to drug approval after receiving a first complete response letter and found a 15-month average delay across all diseases with a setback of over one year for all diseases except (**Supplementary Fig. 1**) infectious disease (**Supplementary Fig. 2**).

Lead and nonlead indication success rates
Classifying drugs by lead and nonlead indications results in a selection bias favoring lead indication success rates. For lead indications that are suspended, and have a nonlead development path in-progress, the nonlead indication is redefined as the lead indication. The most advanced nonlead indications therefore becomes the lead indications once the initial lead is suspended. The BioMedTracker database is maintained as such for real-time viewing of pipelines, where it is critical to identify a company's lead program for each compound.

This lead indication annotation methodology tracks the most successful development path, and closely resembles the best case scenario for a specific drug. On the other hand, nonlead indication success rates understate the importance of lead indications that were previously designated as nonlead. Nonlead indication success rates are included in **Supplementary Table 2**, and, as expected, have a much lower success rate across all phases. For nonlead indications, the LOA from phase 1 was 4.9% (*n* = 2,132) compared with 15.3% (*n* = 3,688) for lead indications. The most pronounced deviation was found in phase 3, where lead indications had a 67.6% (*n* = 633) success rate, whereas nonlead indications had a 46.2% (*n* = 342) probability of advancing to NDA/BLA. The disparity between lead and nonlead success rates is noteworthy, and the accuracy of nonlead rates must

be viewed in the context of the selection methodology.

DISCUSSION
During the time frame of this study, approximately one development path in ten (10.4%) that enters clinical development in phase 1 is expected to advance to FDA approval. We also analyzed lead indication data and found nearly a one-in-six (15.3%) probability a drug will advance from phase 1 to FDA approval. We believe that the lower success rate for all-indication development paths more accurately reflects drug development success rates in industry and is particularly important when considering the cost and time of unsuccessful clinical trials.

One limitation of this study is the direct comparison of these data and methodology on a year-by-year or decade-by-decade basis. For example, a program was designated as
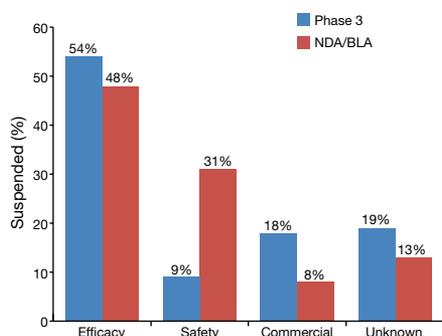
Figure 4 Root-cause analysis for 359 phase 3 and 95 NDA/BLA suspended programs. A program was designated as 'suspended' when conclusive evidence had been gathered regarding a company's plans to discontinue development or communications with regulators were not reinitiated for several years.

'suspended' when conclusive evidence had been gathered regarding a company's plans to discontinue development, or communications with regulators were not reinitiated for several years. Unfortunately, the timing of annotating suspended indications and drugs is not precise enough to analyze yearly changes in success rates. Furthermore, real-time data collection was initiated in 2003; thus, we cannot directly compare prior decades using these data and must rely on results published in the literature.

Many previous studies considered only a drug's most advanced indication to determine drug development success rates. Most published data from the 1960s to present reported success rates ranging from one in five to one in eight[14–19]. For comparison with more recent findings, we summarize in **Table 3** the results from DiMasi *et al.*[6], Kola *et al.*[8] and Abrantes-Metz *et al.*[9]. The most recent publication on the subject, from DiMasi *et al.*[6], reports a nearly one-in-five LOA from phase 1 (19%, *n* = 1,316) from 1993 to 2009. In Kola *et al.*[8], the authors found an LOA from phase 1 of 11%, close to the 10.4% reported here for all indications. However, given the small number of company pipelines (10 versus 835 reported here) and lack of information about the number of drugs advanced or suspended in this study, these results were inconclusive. In addition, the Abrantes-Metz *et al.*[9] data covered a similar period as Kola *et al.*[8], 1989 to 2002 versus 1991 to 2000, respectively, but did not report NDA/BLA success rates. If we were to conservatively apply the 83.2% NDA/BLA success rate found in this study, Abrantes-Metz *et al.*[9] would yield the highest LOA from phase 1 (21%), again near one in five.

Comparing the phase transitions, phase 2 success rates were consistently lower than phase 1, with phase 1 ranging from 65% to 81%, and phase 2 from 32% to 58%. In this study, and in DiMasi *et al.*[6] and Kola *et al.*[8],

a step-up in phase 3 success rates from phase 2 rates was observed. Only Abrantes-Metz *et al.*[9] reported a phase 2 success rate (57.7%) in-line with phase 3 (56.7%), a result that was 20 percentage points higher than the phase 2 success rate in Kola *et al.*[8] (38%) for a similar time period (**Table 3**). There are fewer data available to compare NDA/BLA success rates, but our result of 83.2% is similar to that of Kola *et al.*[8] (77%) and 10% lower than that of DiMasi *et al.*[6].

For lead indication success rates, our results are similar to that found by DiMasi *et al.*[6]. Although our LOA from phase 1 for lead indications (15.3%) is below DiMasi *et al.*'s[6] 19% result, it is close to their 16% result for self-originated drugs. We also note that the 16% success rate for self-originated drugs held over multiple time frames (1993–1998 and 1999–2004) in their studies. One possible explanation is that success rates for self-originated drugs at large pharmaceutical companies are less prone to selection bias compared with late-stage, in-licensed drugs.

Factors contributing to lower success rates found in this study include the large number of small biotech companies represented in the data, more recent time frame (2003–2011) and higher regulatory hurdles for new drugs. Small biotech companies tend to develop riskier, less validated drug classes and targets, and are more likely to have less experienced

Table 7 Phase success and LOA for oncology subgroups and cancer types

	Phase 1 to phase 2				Phase 2 to phase 3				Phase 3 to NDA/BLA				NDA/BLA to approval			
	Total in phase[a]	Advanced or sus-pended[b]	Phase success[c]	Phase LOA[d]	Total in phase[a]	Advanced or sus-pended[b]	Phase success[c]	Phase LOA[d]	Total in phase[a]	Advanced or sus-pended[b]	Phase success[c]	Phase LOA[d]	Total in phase[a]	Advanced or sus-pended[b]	Phase success[c]	Phase LOA[d]
All indications	2,541	1,918	64.5%	10.4%	3743	2268	32.4%	16.2%	1554	975	60.1%	50.0%	908	659	83.2%	83.2%
Total oncology	919	651	63.9%	5.4%	1451	827	28.3%	8.5%	383	147	36.7%	30.0%	142	104	81.7%	81.7%
Total solid tumors	668	483	66.7%	5.7%	1114	636	26.3%	8.6%	299	172	41.3%	32.7%	88	67	79.1%	79.1%
Renal cell cancer (RCC)	20	15	86.7%	18.4%	54	33	30.3%	21.2%	15	10	70.0%	70.0%	7	6	100.0%	100.0%
Head and neck cancer	6	5	100.0%	14.3%	23	12	50.0%	14.3%	14	7	42.9%	28.6%	3	3	66.7%	66.7%
Hepatocellular (liver) cancer (HCC)	18	15	73.3%	6.6%	39	25	36.0%	9.0%	12	4	25.0%	25.0%	1	1	100.0%	100.0%
Breast cancer	54	47	68.1%	5.7%	119	61	21.3%	8.4%	34	25	56.0%	39.2%	14	10	70.0%	70.0%
Non-small cell lung cancer (NSCLC)	63	55	87.3%	5.7%	161	94	29.8%	6.5%	46	23	26.1%	21.7%	11	6	83.3%	83.3%
Prostate cancer	42	8	71.0%	5.6%	103	24	20.9%	7.8%	25	8	56.3%	37.5%	11	3	66.7%	66.7%
Colorectal cancer (CRC)	45	37	62.2%	5.1%	87	56	21.4%	8.2%	18	13	38.5%	38.5%	4	4	100.0%	100.0%
Ovarian cancer	31	25	68.0%	4.6%	72	37	27.0%	6.8%	15	8	25.0%	25.0%	3	1	100.0%	100.0%
Pancreatic cancer	29	24	75.0%	2.3%	66	36	30.6%	3.1%	19	10	20.0%	10.0%	2	2	50.0%	50.0%
Total hematological tumors	216	152	58.6%	9.9%	317	179	34.6%	16.9%	78	45	55.6%	48.8%	48	33	87.9%	87.9%
Multiple myeloma (MM)	43	29	69.0%	9.7%	48	30	23.3%	14.0%	13	5	60.0%	60.0%	5	4	100.0%	100.0%
Non-Hodgkin's lymphoma (NHL)	38	28	57.1%	8.5%	62	35	40.0%	14.8%	19	9	44.4%	37.0%	8	6	83.3%	83.3%
Chronic lymphocytic leukemia (CLL)	17	12	50.0%	7.3%	41	24	29.2%	14.6%	10	8	62.5%	50.0%	7	5	80.0%	80.0%
Myelodysplastic syndrome (MDS)	12	7	71.4%	4.8%	22	9	33.3%	6.7%	6	5	20.0%	20.0%	4	3	100.0%	100.0%

[a]Number of indications identified. [b]Total number of transitions used to calculate the success rate, the *n* value noted in the text. The difference between 'Total in phase' and 'Advanced or suspended' is the number of indications that remain in development. [c]Probability of successfully advancing to the next phase. [d]Probability of FDA approval for drugs in this phase of development.

Table 8 Phase success and LOA for neurology and autoimmune diseases (broken further into rheumatoid arthritis and type II diabetes)

	Phase 1 to phase 2				Phase 2 to phase 3				Phase 3 to NDA/BLA				NDA/BLA to approval			
	Total in phase[a]	Advanced or suspended[b]	Phase success[c]	Phase LOA[d]	Total in phase[a]	Advanced or suspended[b]	Phase success[c]	Phase LOA[d]	Total in phase[a]	Advanced or suspended[b]	Phase success[c]	Phase LOA[d]	Total in phase[a]	Advanced or suspended[b]	Phase success[c]	Phase LOA[d]
All indications	2,541	1,918	64.5%	10.4%	3,743	2,268	32.4%	16.2%	1,554	975	60.1%	50.0%	908	659	83.2%	83.2%
Total neurology	389	298	62.4%	9.4%	520	348	30.2%	15.0%	285	188	60.6%	49.9%	192	152	82.2%	82.2%
Psychiatric disease	97	80	60.0%	7.2%	148	116	23.3%	12.0%	83	49	63.3%	51.6%	57	49	81.6%	81.6%
Pain	96	73	67.1%	10.7%	113	79	27.8%	15.9%	67	46	67.4%	57.2%	42	33	84.8%	84.8%
Other	196	136	58.8%	9.8%	259	153	36.6%	16.7%	135	93	55.9%	45.5%	93	70	81.4%	81.4%
Total autoimmune disease	241	178	68.0%	12.7%	350	215	34.0%	18.7%	149	95	68.4%	55.0%	88	61	80.3%	80.3%
Total autoimmune disease NMEs	111	88	62.5%	5.2%	151	86	22.1%	8.3%	38	20	50.0%	37.5%	16	8	75.0%	75.0%
Total autoimmune disease biologics	116	80	73.8%	22.5%	171	111	45.0%	30.5%	89	56	75.0%	67.7%	53	41	90.2%	90.2%
Total autoimmune disease non-NMEs	10	8	87.5%	7.9%	22	16	25.0%	9.0%	21	18	72.2%	36.1%	18	12	50.0%	50.0%
Total rheumatoid arthritis	65	54	74.1%	10.3%	102	63	15.9%	13.9%	18	8	87.5%	87.5%	10	5	100.0%	100.0%
Rheumatoid arthritis NMEs	30	29	69.0%	NA	46	29	10.3%	NA	4	1	100.0%	NA	2	0	NA	NA
Rheumatoid arthritis biologics	32	24	79.2%	15.9%	49	29	24.1%	20.1%	13	6	83.3%	83.3%	7	5	100.0%	100.0%
Total type II diabetes	110	89	60.7%	9.3%	128	84	29.8%	15.3%	53	37	59.5%	51.4%	31	22	86.4%	86.4%
Diabetes NMEs	83	68	63.2%	7.5%	100	69	29.0%	11.8%	35	25	56.0%	40.7%	15	11	72.7%	72.7%

[a]Number of indications identified. [b]Number of transitions used to calculate the success rate, the *n* value noted in the text. The difference between 'Total in phase' and 'Advanced or suspended' is the number of indications that remain in development. [c]Probability of successfully advancing to the next phase. [d]Probability of FDA approval for drugs in this phase of development. NA, data not available.

development teams and fewer resources than large pharmaceutical corporations. The past nine-year period has been a time of increased clinical trial cost and complexity for all drug development sponsors, and this likely contributes to the lower success rates than previous periods. In addition, an increasing number of diseases have higher scientific and regulatory hurdles as the standard of care has improved over the past decade. More clinical studies are comparative in nature and published data show clinical trials are more complex today than in previous decades[7]. The time frame in this study also coincides with the shift toward greater regulatory uncertainty and stronger emphasis on safety at the FDA since the 2004 Vioxx (rofecoxib) recall. For smaller companies, financing challenges in the past several years have also affected development progression decisions. Phase success rates reported in this study are based on transition rates, not necessarily resulting from safety or efficacy data. Transition rates are negatively affected by early development termination due to commercial and regulatory uncertainty as well as economic and portfolio management decisions.

Lower success rates found when analyzing all indications likely results from including nonlead and/or secondary indications. Nonlead development paths have far lower success rates compared with lead programs. One possible explanation is that many com-

panies first develop drugs in lead indications where the strongest scientific rationale and early efficacy signals are found. Lead indications are also often smaller, better-defined patient populations. After initial success in these populations, companies may decide to investigate nonlead indications, which may not have the same scientific support, homogenous patient population or development and regulatory path as the lead indication. Nonlead success rates are also important to monitor as many of these indications can be moved directly into late-stage trials, where most clinical development costs occur. Furthermore, our research suggests that these late-stage trials for nonlead indications often enroll a greater number of patients than lead indications.

Phase 3 success rates. In **Figures 1** and **2**, we show that phase 3 success rates are 60% for drugs for all indications, but only around 50% in oncology or cardiology. Such low phase 3 success rates for these diseases are concerning as 35% of all R&D spending is now spent on phase 3 development, and phase 3 trials account for 60% of all clinical trial costs[3]. Some of the low phase 3 rates may be attributed to trial design factors and insufficient communication between sponsors and regulators during their end-of-phase-2 meetings. Both oncology and cardiology, for example, now require outcome studies looking for

improved overall survival, but lack well-validated surrogate markers for this outcome. On the other hand, disease areas with validated surrogate markers tend to have higher phase 3 success rates. For example, studies of infectious diseases such as hepatitis C and HIV that use viral load as a primary endpoint as well as glycosylated hemoglobin (HbA1c) in diabetes show higher success rates.

Oncology is a particularly challenging disease area in which to achieve phase 3 success. The FDA requires overall survival as the primary endpoint in most pivotal oncology studies. Crossover designs that allow patients who progress on the comparator arm to cross over and receive the investigational drug, or patients receiving additional approved and experimental salvage therapies, also make it more difficult to design well-controlled phase 3 studies with overall survival as a primary endpoint. Furthermore, current animal models (e.g., xenograft tumor models in mice) can be poor predictors of clinical outcomes in humans. Additionally, recent scientific reports show that certain types of cancer, which were previously thought of as one disease, may actually comprise several subtypes of disease with different etiologies. For example, NSCLC is now considered by many oncologists to be at least ten different mutation-specific diseases, and thus it is not surprising that drugs for NSCLC have one of the lowest LOAs from phase 1 of all oncology indications in **Table 7** (ref. 20).

Table 9 Phase success and LOA for drugs receiving a FDA SPA or orphan drug designation

	Phase 1 to phase 2				Phase 2 to phase 3				Phase 3 to NDA/BLA				NDA/BLA to approval			
	Total in phase[a]	Advanced or sus-pended[b]	Phase success[c]	Phase LOA[d]	Total in phase[a]	Advanced or sus-pended[b]	Phase success[c]	Phase LOA[d]	Total in phase[a]	Advanced or sus-pended[b]	Phase success[c]	Phase LOA[d]	Total in phase[a]	Advanced or sus-pended[b]	Phase success[c]	Phase LOA[d]
All indications	2,541	1,918	64.5%	10.4%	3,743	2268	32.4%	16.2%	1,554	975	60.1%	50.0%	908	659	83.2%	83.2%
Total SPAs	42	35	97.1%	45.4%	128	115	97.4%	46.7%	171	110	60.0%	48.0%	73	45	80.0%	80.0%
Total orphans	170	136	86.8%	32.9%	328	190	70.0%	37.9%	237	148	66.9%	54.2%	136	84	81.0%	81.0%
Orphan oncology	85	67	85.1%	23.0%	176	105	61.0%	27.1%	102	63	58.7%	44.4%	54	37	75.7%	75.7%
Orphan non-oncology	85	69	88.4%	44.5%	152	85	81.2%	50.4%	135	85	72.9%	62.1%	82	47	85.1%	85.1%

[a]Number of indications identified. [b]Total number of transitions used to calculate the success rate, the n value noted in the text. The difference between 'Total in phase' and 'Advanced or suspended' is the number of indications that remain in development. [c]Probability of successfully advancing to the next phase. [d]Probability of FDA approval for drugs in this phase of development.

Clinical trials targeting heterogeneous patient populations may have lower success rates than trials identifying responders within a population through the use of biomarkers. As predictability of clinical outcomes increases through the use of molecular diagnostics in earlier testing, it is possible that phase 3 trial success rates will rise. Furthermore, the adoption of adaptive trial design may facilitate the identification of targeted subsets of patient populations before study completion. According to the FDA's draft guidance for industry, issued in February 2010, adaptive trial design may make clinical studies more efficient (e.g., shorter duration and fewer patients), more likely to demonstrate an effect of the drug or more informative (e.g., providing broader dose-response information)[21].

Root causes of phase 3 and NDA/BLA development failures. To gain a better understanding of the causes that lead companies to discontinue drug development, we further analyzed publically available information for the 359 phase 3 and 95 NDA/BLA suspensions included in this study. We classified each discontinued development program into four categories based on the primary reason for suspension including: efficacy, safety, commercial and unknown (**Fig. 4**).

Although it was difficult to objectively determine if a phase 3 study did not reach an endpoint due to poor study design or the drug's biological activity, we found that over half of the 359 suspensions were attributable to some measure of efficacy. Indeed, a detailed analysis of the specific inputs, rationale and history for each program would be needed to identify issues related to poor trial design. Furthermore, public information is not available to assess the degree of communication with regulators, adherence to recommendations, changes to prior standards and input from phase 2 data that would inform the design of a phase 3 study.

We found that 18% of the phase 3 suspensions resulted from a company's commercial decision to not file for approval. We do not know the degree to which regulatory uncertainty factored into these decisions, but recognize its important impact on portfolio management, funding and commercial opportunities due to the increased time and costs of drug development.

Safety was the least likely cause for suspension in phase 3 (9%), perhaps due to significant adverse events identified earlier in drug development. Approximately 20% of the suspensions occurred without publicly available information citing the reason for failure.

We also analyzed the 95 suspended NDA/BLA filings in the data set and found that approximately one-third of failures were attributable to safety concerns raised by regulators compared to only 9% in phase 3. Our analysis also revealed that around half involved cases where the FDA requested additional trials. One interpretation of these data is that sponsors file for regulatory approval believing their drug meets safety guidelines, whereas regulators remain concerned about safety, illustrating insufficient communication between regulators and sponsors. During the period of this study, mainly after the 2004 Vioxx recall, many industry observers have discussed how the benefit-to-risk pendulum has swung toward risk, with a greater focus on safety in the regulatory assessment. Some examples of issues brought forward by regulators were the need for longer-term data, inclusion of additional study arms, inclusion of different patient age and at-risk populations, and increases in the number of patients studied.

Further analysis of failures by lead or non-lead indication, disease, modality and company type were not performed because the small sample size has limitations and subjects the results to molecular and therapeutic class–specific issues. Future studies will allow us to identify trends in failed clinical programs as the sample size becomes more reliable.

Conclusions

The data presented in this study suggest industry-wide productivity may have declined from previous estimates. Achieving FDA approval for only one-in-ten drug indications that enter the clinic is a concerning statistic for drug developers, regulators, investors and patients. We believe progress in clinical science and regulatory risk-benefit assessment can improve success rates. Greater flexibility with alternative surrogate endpoints, the utilization of adaptive clinical trial design and improved methodologies for assessing patient benefit-to-risk are some areas where improvements can be made. In addition, improvements in communication between sponsors and regulators could help reduce regulatory applications that lack safety or efficacy data that are later requested by regulators. Simultaneously, improvements in basic science can enable improvements in success rates. For example, more predictive animal models, earlier toxicology evaluation, biomarker identification and new targeted delivery technologies may increase future success in the clinic.

AUTHOR CONTRIBUTIONS
M.H., D.W.T. and J.L.C. all contributed equally to this work.

1. Lloyd, I., ed. Citeline Drug Intelligence. *Pharma R&D Annual Review 2011*. http://www.citeline.com/

wp-content/uploads/Citleine-Pharma-RD-annual-review-20111.pdf (Citeline Drug Intelligence, 2012).

2. EvaluatePharma. *World Preview 2018: Embracing the Patent Cliff.* http://info.evaluatepharma.com/WP2018_ELS_LP.html (2012).

3. Pharmaceutical Research and Manufacturers of America. *Annual Report 2011.* http://www.phrma.org/sites/default/files/159/phrma_2011_annual_report.pdf (2011).

4. Mullard, A. 2012 FDA drug approvals. *Nat. Rev. Drug Discov.* **12**, 87–90 (2013).

5. Cohen, F.J. Macro trends in pharmaceutical innovation. *Nat. Rev. Drug Discov.* **4**, 78–84 (2005).

6. DiMasi, J.A., Feldman, L., Seckler, A. & Wilson, A. Trends in risks associated with new drug development: success rates for investigational drugs. *Clin. Pharmacol. Ther.* **87**, 272–277 (2010).

7. Kaitin, K.I. & DiMasi, J.A. Pharmaceutical innovation in the 21st century: new drug approvals in the first decade, 2000–2009. *Clin. Pharmacol. Ther.* **89**, 183–188 (2011).

8. Kola, I. & Landis, J. Can the pharmaceutical industry reduce attrition rates? *Nat. Rev. Drug Discov.* **3**, 711–715 (2004).

9. Abrantes-Metz, R., Adams, C. & Metz, A. *Pharmaceutical Development Phases: A Duration Analysis.* Working paper no. 274. http://www.ftc.gov/be/workpapers/wp274.pdf (US Federal Trade Commission: Bureau of Economics, 2004).

10. Henderson, R. & Cockburn, I. Scale, scope, and spill-overs: the determinants of research productivity in drug discovery. *Rand J. Econ.* **27**, 32–59 (1996).

11. Cockburn, I.M. & Henderson, R.M. Scale and scope in drug development: unpacking the advantages of size in pharmaceutical research. *J. Health Econ.* **20**, 1033–1057 (2001).

12. Danzon, P.M., Nicholson, S. & Pereira, N.S. Productivity in pharmaceutical–biotechnology R&D: the role of experience and alliances. *J. Health Econ.* **24**, 317–339 (2005).

13. Arora, A., Gambardella, A., Magazzini, L. & Pammolli, F. A breath of fresh air? Firm type, scale, scope, and selection effects in drug development. *Manage. Sci.* **55**, 1638–1653 (2009).

14. Sheck, L. *et al.* Success rates in the United States drug development system. *Clin. Pharmacol. Ther.* **36**, 574–583 (1984).

15. Tucker, S.A., Blozan, C. & Coppinger, P. The Outcome of Research on New Molecular Entities Commencing Clinical Research in the Years 1976–79 (OPE Study 77). (Office of Planning and Evaluation, US Food and Drug Administration, Rockville, MD, 1988).

16. DiMasi, J.A. Success rates for new drugs entering clinical testing in the United States. *Clin. Pharmacol. Ther.* **58**, 1–14 (1995).

17. DiMasi, J.A. Risks in new drug development: approval success rates for investigational drugs. *Clin. Pharmacol. Ther.* **69**, 297–307 (2001).

18. DiMasi, J.A., Hansen, R.W. & Grabowski, H.G. The price of innovation: new estimates of drug development costs. *J. Health Econ.* **22**, 151–185 (2003).

19. DiMasi, J.A. & Grabowski, H.G. The cost of biopharmaceutical R&D: is biotech different? *Manag. Decis. Econ.* **28**, 469–479 (2007).

20. Edelman, M.J. in *2010 American Society of Clinical Oncology (ASCO) Annual Meeting* (Chicago, IL; 2010).

21. FDA. *Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics.* http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm201790.pdf (FDA, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, 2010).