Trends in Risks Associated With New Drug Development: Success Rates for Investigational Drugs

JA DiMasi[1], L Feldman[1], A Seckler[1] and A Wilson[1]

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.

INTRODUCTION

Numerous studies have found that the drug development process is highly expensive and that these costs have trended significantly upward for decades.[1–6] Many factors affect the cost of drug development, but two of the key basic elements are time and risk. Development times increased substantially from the 1960s through the 1980s but overall remained relatively stable during the 1990s.[7,8] Thus, development times did not directly contribute much to the rapid increase in pharmaceutical R&D costs in the past two decades. However, if clinical trials become larger and more complex, and the costs of inputs to the development process increase faster than inflation, the "time costs" associated with the investment of resources in new drug development will increase in absolute terms, even if development times remain the same. Indeed, there is evidence that the clinical trial process has become more extensive and complex in the past few decades.[4,9] The situation is similar for drug development risks. By development risk, we mean the likelihood that development of a drug will be terminated owing to efficacy, safety, or commercial concerns. High drug failure rates contribute substantially to R&D costs, whether or not these costs are otherwise increasing. Thus, the rate at which pharmaceutical firms successfully develop investigational compounds for marketing approval by regulatory agencies is an important indicator of the effectiveness of the drug development process. Processes and technological innovations that can improve the predictability of outcomes for new compounds can therefore significantly increase the productivity of new drug innovation.[10]

The historical literature focusing specifically on the quantification of drug development risks is fairly robust.[11–20] The aforementioned research on drug development costs includes estimates of drug development risks. Early research on development risks suggested that clinical approval rates for self-originated drugs in the 1960s were in the neighborhood of one in eight.[11] Subsequent studies indicated that development risks fell in the 1970s, with approval rates averaging approximately one in five; the risk levels pertaining to the 1970s remained fairly stable to the mid-1990s.[1,3,14,15]

This study provides updated clinical approval success rates and clinical phase transition analyses for the investigational compounds that entered clinical testing between the mid-1990s and the early 2000s from the 50 largest pharmaceutical firms (as determined by sales). We analyze approval success rates and phase transition rate trends within this period for new compounds as a whole and by therapeutic class. The data are also stratified by product type (large molecule vs. small molecule).

[1]Tufts Center for the Study of Drug Development, Tufts University, Boston, Massachusetts, USA. Correspondence: JA DiMasi (joseph.dimasi@tufts.edu)

Received 9 December 2009; accepted 9 December 2009; advance online publication 3 Febraury 2010. doi:10.1038/clpt.2009.295

The results relating to phase transition rates (or their converse, phase attrition rates) allow us to examine whether pharmaceutical firms are "failing" drugs earlier in the development process and thereby (other factors assumed to be equal) potentially reducing overall development costs.

We examined the investigational drug pipelines of the 50 largest pharmaceutical firms as determined on the basis of sales in 2006. Several data sources were consulted, but the core source for the compound list was the IMS R&D Focus investigational drug pipeline database. We supplemented that database with information from two other commercial pipeline databases (iDdb3 and Pharmaprojects), as well as from Tufts CSDD investigational drug, approved drug, and investigational biopharmaceutical databases that were derived, in part, from confidential company surveys, published regulatory agency documents, online company pipeline lists, and Internet searches.

Inclusion criteria

The resulting database contains information on nearly 4,000 drugs and biologics. For the purpose of simplifying the discussion, we refer to all the compounds analyzed as "new drugs." Our analyses are restricted to the new drugs for which the starting dates for phase I testing were available and for which this phase I testing was initiated anywhere in the world from 1993 through 2004. The dataset used for the analysis contains information on the development histories of 1,738 new drugs. For the purposes of this study, the dataset's key elements include information on the drug's therapeutic class (identified by the major indication pursued), the drug type (small molecule, including synthetic peptides and oligonucleotides, or large molecule, including monoclonal antibodies, recombinant proteins, and other biologics), the clinical phases in which the drug has been tested, whether the drug has been approved for marketing in the United States, the latest phase (clinical or regulatory) that the compound had entered (if research on the drug has been terminated), the sponsor company, and the source of the drug (self-originated, licensed-in, or licensed-out). The bulk of the licensed-in compounds were licensed from firms outside the top 50. A compound was considered licensed-out only if it had been licensed from one of the top 50 firms to a firm outside the top 50. We excluded from analysis diagnostics, vaccines, and new formulations and indications for already-approved drugs. We placed drugs in therapeutic categories according to their classification in the IMS R&D Focus database. The database uses the Anatomical Therapeutic Chemical classification system established by the World Health Organization Collaborating Centre for Drug Statistics Methodology for classifying indications.

Clinical approval success rates are defined in terms of US regulatory approval for marketing. Current success rates for the compounds were examined through June 2009. Analyses were conducted for the entire study period (1993–2004) and also separately for two subperiods (1993–1998 and 1999–2004). Data on more recent investigational drugs were available, but, given the length of the new drug development process, we judged them too recent to be included in a comprehensive analysis of success rates.

Calculation of success-rate estimates

The dataset used contains information on the latest phase (development or regulatory) of the abandoned drugs at the time they were terminated. These data allow us to estimate the likelihood that an investigational drug will proceed from one clinical phase to the next as well as the distribution of research terminations by phase. They also, in aggregate, permit us to estimate the probability of approval for new drugs that enter the clinical pipeline. Specifically, we estimate the proportion of new drugs that transition from phase i to phase i + 1 as the ratio:

> No. of new drugs that proceeded to phase i + 1/total no. of new drugs that entered phase i
>
> The denominator in the ratio includes only drugs that either proceeded thereafter to phase i + 1 or were terminated in phase i.

We estimate the clinical approval success rate as the product of the individual phase transition probabilities. These transition probability estimates will be unbiased estimates of the population transition probabilities if the drugs that are still active in a phase are, on average, no different (in terms of the likelihood of proceeding to the next phase) from the set of drugs that either have been terminated in the phase or have moved on to the next phase. There are likely to be variable time lags as to when new information on the status of a drug is available in a database. However, if a database firm has not been able to obtain an update on the status of a drug over a set period of time (e.g., 18 months for R&D Focus), it will show that no development activity has been reported for the drug. For purposes of analysis, we assumed that the drug was discontinued in the latest phase that it had entered if no development activity was subsequently reported. Therefore our transition probability estimates may be underestimated; however, even if this is so, the downward bias is probably small.

As noted above, we utilized information from more than half a dozen databases and other sources. We recognized that, among the databases (pipeline-based or survey-based) and other sources that we used, no single source would have the most recent information for all drugs. For our study, we took the earliest date recorded for the start of phase I testing as the date on which clinical testing of the drug began, and the latest available development or regulatory phase as its current status. For example, if one database had information to the effect that a drug has entered phase III while other databases and sources showed its status at phase II, we assumed that the drug has proceeded to phase III. We thus made use of the most recent information available from the multiple sources regarding the status of an investigational drug.

For the entire study period, 70% of the new drugs in our dataset were self-originated (**Table 1**). We found that the proportion of all new drugs that were licensed out to firms outside of the top 50 pharmaceutical companies was small. These shares were similar for the 1993–1998 subperiod. For the full study period, we determined a final outcome (success or failure) for 76% of all the drugs analyzed; for self-originated drugs, this figure was 81%. As expected, the percentage of drugs for which a final outcome was available was higher for the earlier period. For example, final outcomes were reported for 88% of all drugs and 92% of

Table 1 Current and maximum-possible success rates by source of molecule for compounds first tested in humans from 1993 to 2004

Source	*n*	Approved molecules	Open molecules[a]	Percentage completed (%)[a]	Current success rate (%)[a]	Maximum-possible success rate (%)[b]
1993–2004						
Self-originated	1,225	87	239	80.5	7.1	26.6
Licensed-in	412	41	141	65.8	10.0	44.2
Licensed-out	101	10	42	58.4	9.9	51.5
All	1,738	138	422	75.7	7.9	32.2
1993–1998						
Self-originated	584	64	48	91.8	11.0	19.2
Licensed-in	180	32	30	83.3	17.8	34.4
Licensed-out	57	9	21	63.2	15.8	52.6
All	821	105	99	87.9	12.8	24.8

[a]Through June 2009. [b]Assumes that all open compounds will eventually be approved.

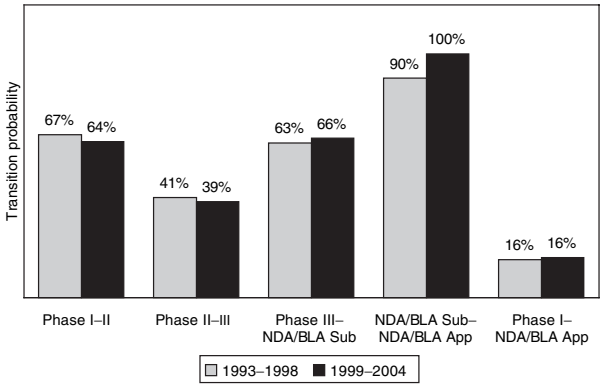

Figure 1 Phase transition probabilities and clinical approval success probabilities for self-originated compounds by period of first-in-human testing. BLA, biologics license application; NDA, new drug application.

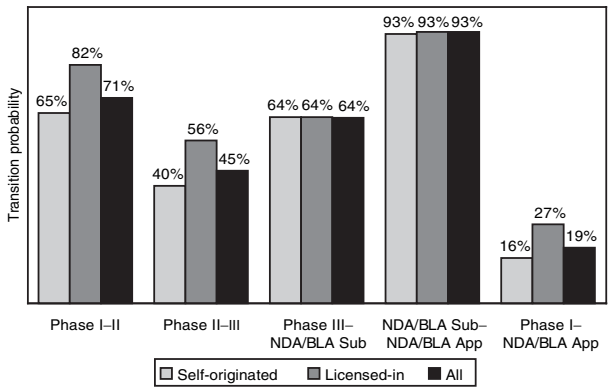

Figure 2 Phase transition probabilities and clinical approval success probabilities by source of compound, for compounds first tested in humans from 1993 to 2004. BLA, biologics license application; NDA, new drug application.

self-originated drugs that commenced clinical trials during the 1993–1998 subperiod. Given that the data are censored (some drugs are still active), we show both the current and maximum-possible US clinical approval success rates. These rates were higher for licensed-in than for self-originated drugs.

Success-rate trends

Figure 1 shows estimated phase transition probabilities and the overall clinical approval success rates for the 1993–1998 and the 1999–2004 subperiods. The results do not suggest any trend in the overall clinical approval success rates for new drugs over this period; estimates showed that approximately one in six new drugs that entered clinical testing during each of these subperiods was eventually approved for marketing. However, there were small differences between the two subperiods with respect to the estimated clinical phase transition rates. The results suggest that the failures occurred somewhat earlier in the clinical trial process (phases I and II) for drugs initiated into clinical trials during the later subperiod.

There are at least two good reasons for the generally higher clinical approval success rates for licensed-in compounds. First, these compounds have generally undergone some screening or testing prior to licensing and have been shown to be promising candidates for marketing approval. Thus, there may be a screening effect for new drugs that are licensed-in. Second, it is likely that many of these licensed-in drugs were acquired after some clinical testing had been done on them. Although drugs may be licensed-in at any point during the development process, including during the preclinical period, later clinical phases are associated with higher approval rates. We do not have data on when in the development process each of the licensed-in drugs was acquired, but if, for example, the average licensed-in drug was acquired at phase II, then we would expect higher clinical approval success rates for the licensed-in group for that reason alone.

Figure 2 shows estimated phase transition probabilities and clinical approval success rates by source of the compound. As expected, the estimated overall clinical approval success rate is substantially higher for the licensed-in drugs than for self-originated drugs (27 vs. 16%). However, the estimated transition probabilities for phase III and regulatory review are identical for licensed-in and self-originated drugs. The higher estimated clinical approval success rate for licensed-in drugs derives from higher transition probabilities at phases I

and II. This suggests that many of the licensed-in drugs were acquired after phase I or phase II testing had already been conducted by the licensor.

Success rates by therapeutic class

Prior research has shown that success rates for new drugs vary by therapeutic class.[3,5,14–16] Table 2 shows current and maximum-possible success rates and the percentage of self-originated drugs that have had a reported final outcome by therapeutic class. Given that the number of compounds available for analysis is greatly reduced when the data are stratified into therapeutic categories, the entire study period (1993–2004) is used. Explicit results are reported for the seven therapeutic classes with the most new drugs taken into clinical testing over the study period (≥80 compounds). These seven classes account for 85% of all self-originated drugs that were included for analysis. The proportion of drugs in these classes that have reached a final outcome varied from 71% for antineoplastic/immunologic drugs to 89% for systemic anti-infectives.

Table 3 shows the estimated phase transition and clinical approval success probabilities for the seven therapeutic classes and one miscellaneous category. There was substantial variability by class for both the phase transition probabilities and the clinical approval success rates. More than 70% of the self-originated drugs in the antineoplastic, musculoskeletal, and respiratory categories moved from phase I testing to phase II testing, whereas fewer than 60% of the self-originated drugs in the systemic anti-infective and central nervous system (CNS) categories did so. One-third or fewer of the self-originated drugs in the respiratory, cardiovascular, and CNS categories proceeded from phase II to phase III testing, but nearly half of the antineoplastic/immunologic drugs moved from phase II trials to much more expensive phase III testing. However, once antineoplastic/immunologic drugs reached phase III, they had a relatively low estimated probability (55%) of having an application for marketing approval submitted to the US Food and Drug Administration. Similarly, only 50% of gastrointestinal/metabolism drugs and 46% of CNS drugs moved from phase III to regulatory review. In contrast, the systemic anti-infective, musculoskeletal, and respiratory drug categories had relatively high estimated probabilities of getting to regulatory review after they had entered phase III (79% or higher).

The estimated clinical approval success rates for self-originated drugs varied substantially by therapeutic class. The CNS (8%), cardiovascular (9%), gastrointestinal/metabolism (9%), and respiratory (10%) categories had relatively low estimated approval

Table 2 Current and maximum-possible success rates by therapeutic class for self-originated compounds first tested in humans from 1993 to 2004

Therapeutic class	*n*	Approved molecules	Open molecules[a]	Percentage completed (%)[a]	Current success rate (%)[a]	Maximum-possible success rate (%)[b]
Antineoplastic/immunologic	254	18	75	70.5	7.1	36.6
Cardiovascular	134	4	24	82.1	3.0	20.9
CNS	235	9	40	83.0	3.8	20.9
GI/metabolism	120	4	28	76.7	3.3	26.7
Musculoskeletal	88	8	18	79.5	9.1	29.5
Respiratory	83	4	15	81.9	4.8	22.9
Systemic anti-infective	122	19	14	88.5	15.6	27.0
Miscellaneous	189	21	25	86.8	11.1	24.3

CNS, central nervous system; GI, gastrointestinal.

[a]Through June 2009. [b]Assumes that all open compounds will eventually be approved.

Table 3 Phase transition and clinical approval probabilities by therapeutic class for self-originated compounds first tested in humans from 1993 to 2004

Therapeutic class	Phase I–II (%)	Phase II–III (%)	Phase III–RR (%)	RR–approval (%)	Clinical approval success rate (%)
Antineoplastic/immunologic	71.8	49.0	55.3	100	19.4
Cardiovascular	62.9	32.4	64.3	66.7	8.7
CNS	59.6	33.0	46.4	90.0	8.2
GI/metabolism	67.5	34.9	50.0	80.0	9.4
Musculoskeletal	72.4	35.2	80.0	100	20.4
Respiratory	72.5	20.0	85.7	80.0	9.9
Systemic anti-infective	58.2	52.2	78.6	100	23.9
Miscellaneous	62.8	48.7	69.8	91.3	19.5

Through June 2009.

CNS, central nervous system; GI, gastrointestinal; RR, regulatory review.

success rates. In contrast, systemic anti-infectives had a relatively high clinical approval success rate (24%). Although the sample sizes are much smaller, the rankings of approval success rates by therapeutic class were generally similar for the two study subperiods.

Success rates by product type

We also analyzed phase transition probabilities and clinical approval success rates by product type. Specifically, we examined outcomes by grouping drugs into small- and large-molecule categories. Large-molecule compounds comprise a minority of the compounds in the pipelines of the 50 largest pharmaceutical firms, but their number is still significant. For all compounds and for the entire study period, large-molecule compounds constituted 15% of the total number of drugs. There was a slight downward trend in that percentage over time, from 17% for the 1993–1998 period to 13% for the 1999–2004 period. Given that large pharmaceutical firms often seek licensing candidates from small biopharmaceutical firms, the percentage of large-molecule compounds was lower (but not much lower) for self-originated drugs. Of the self-originated drugs over the entire study period, 12% were large-molecule compounds (14% for 1993–1998 and 11% for 1999–2004). The large-molecule category is dominated by monoclonal antibodies and recombinant proteins. For self-originated drugs during the entire study period, 47% of the large molecules were monoclonal antibodies, 43% were recombinant proteins, and 10% were other biologics.

Figure 3 shows our results for estimated transition and clinical approval success probabilities by product type. Estimated transition probabilities for all phases were higher for large molecules. The estimated clinical approval success rate for large molecules (32%) was much higher than for small molecules (13%). Studies have indicated that success rates differ within the monoclonal antibody class by type of antibody (murine, chimeric, human, or humanized).[20] However, overall, the estimated clinical approval success rates for recombinant proteins and monoclonal antibodies did not differ by much (34% for recombinant proteins and 36% for monoclonal antibodies for self-originated drugs). The large-molecule subtypes, however, did vary somewhat

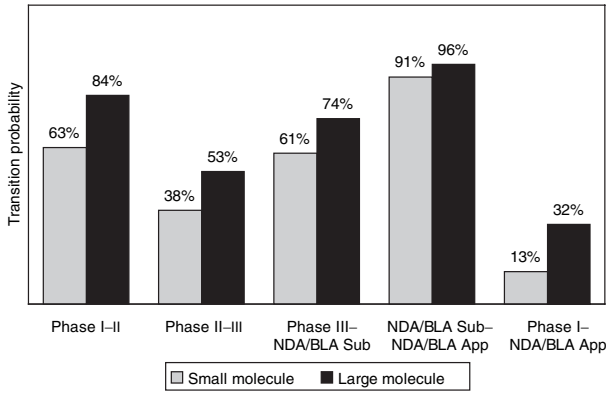

Figure 3 Phase transition probabilities and clinical approval success probabilities by type of compound, for self-originated compounds first tested in humans from 1993 to 2004. BLA, biologics license application; NDA, new drug application.

in their estimated phase transition probabilities. Specifically, recombinant proteins had higher phase transition rates for the early clinical phases but a lower estimated phase transition probability for phase III to regulatory review (66% for recombinant proteins and 87% for monoclonal antibodies).

SUMMARY

We estimated phase transition probabilities and clinical approval success rates for drugs in the pipelines of the 50 largest pharmaceutical firms by sales. These firms are likely to represent very large proportions of the total number of investigational drugs and of aggregate industry R&D expenditures. For self-originated new drugs that first entered clinical testing in 1993–2004 and were observed through mid-2009, the results indicated that approximately one in six drugs that enter the clinical testing pipeline will eventually obtain approval for marketing in the United States. The data did not support the hypothesis of a within-period trend, but the overall estimated clinical approval success rate is lower than it has been for prior periods.[1,4,11–15] Although the overall success rate was fairly constant over the study period, we did find that the failures occurred somewhat earlier in the clinical process for the latter half of the study period. This has implications for the average cost of new drug development.[10] However, the reduction in cost because of a relatively modest improvement in the speed at which firms identify failures may easily be more than offset by increases over time in the out-of-pocket costs of conducting clinical trials. There is evidence to show that clinical trials have become more complex, and therefore probably costlier, in recent years.[9] In addition, when viewed against the background of reported costs of new drug development in earlier periods, the increasing complexity of clinical trials and the overall drop in clinical approval success rates strongly suggest that new drug R&D costs have continued to increase at a high rate in recent years.

We also found, as we have in the past, that clinical approval success rates differ by therapeutic class in any given period. Our analysis of self-originated drugs found estimated clinical approval success rates that varied from 8% for CNS drugs to 24% for systemic anti-infectives. This variability in success rates by therapeutic class might be explained, at least partially, by differences in the uncertainty (inherent in the differing scientific objectives and underlying science knowledge base) about the regulatory standards that must be satisfied for different drug classes. For example, efficacy end points for antibiotics are often clearly defined and can be assessed in a relatively straightforward way. In contrast, it can often be difficult to prove the efficacy of psychotropic compounds, or to establish causal links between these drugs and side effects.

Finally, we did find substantial differences in clinical approval success rates by product type (large vs. small molecules). The success rate for large molecules (nearly one-third) is consistent with the findings from a study of biopharmaceutical R&D costs covering a somewhat earlier period.[6] We also found higher phase transition rates at all phases for large molecules. Although R&D costs should be much lower for large molecules given that success rates in this category are substantially higher, other factors may offset that impact. This appears to be the case for

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.