Risks in new drug development: Approval success rates for investigational drugs

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The drug development process is known to be complex, costly, and time-consuming.[1-3] The process is also risky in that most compounds that undergo clinical testing are abandoned without obtaining marketing approval. The rate at which pharmaceutical firms market new therapies in the United States is an important measure of the viability of the drug development process.[4] The cost of new drug development is also critically dependent on the proportion of drugs that fail in clinical testing.[5-7] Estimates of industry success rates can be used in benchmarking exercises for project planning purposes. Given the length and cost of the drug development process, careful consideration of all factors that have a significant impact on the process is needed to appropriately allocate research and development resources.

In a series of studies of new drug development in the United States, the Tufts Center for the Study of Drug Development (CSDD) and others have provided descriptive data on how cumulative success rates for new chemical entities (NCEs) vary with time from investigational new drug application (IND) filing.[1,8-14] Several studies have also examined clinical success rates for biotechnology-derived drugs.[15-17] Statistical modeling can be helpful in analyzing success rates for recent periods because many of the compounds will still be in active testing at the time of the analysis. Tufts CSDD has also conducted a number of studies that use this approach to predict final success rates for groups of compounds for which the ultimate fate of some of the compounds in the data set is not known.[4-7,18-20]

This study provides updated success rate analyses for NCEs. Success rate trends and variations in success rates by therapeutic class are presented. The hypothesis that pharmaceutical firms have been moving compounds through the process to either marketing approval or research abandonment more quickly is also examined. In addition, attrition rates for compounds entering clinical development phases are obtained. Finally, statistics on the reasons compounds fail in development are given.

METHODS

Data used for this study were obtained primarily from a Tufts CSDD database that contains information from ongoing surveys of pharmaceutical firms. The data provided for the most recent survey come from firms that have declined in number over the study period, as mergers have resulted in the combination of some of them. The data used for this study were obtained from the units and subsidiaries of what are now 24 parent firms. These firms provided data on NCEs first investigated in humans anywhere in the world or NCEs for which they were the first to file a US IND since 1963. The data gathered include IND filing dates, the dates on which IND research was abandoned, reasons for termination of research, the latest phase compounds were in when research was abandoned, and the date of new drug application approval. A description of additional information included in this database is available elsewhere.[1] Data were also obtained from public sources.[21,22] Current success rates for these NCEs were examined (as of December 31, 1999), and statistical analysis was applied to data on past rates of research abandonment and approval to predict future success rates. Analyses were conducted for NCEs with INDs first filed in 3- and 6-year periods from 1981 to 1992. Data on more recent INDs were available but, given the length of the NCE development

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process, they are too recent to use for a comprehensive statistical analysis of success rates.

Inclusion criteria. For purposes of this study, an NCE is defined as a new molecular compound not previously tested in humans. Excluded are new salts and esters of existing compounds, surgical and diagnostic materials, vaccines and other biologic agents, certain externally used compounds (such as disinfectants, antiperspirants, and sunscreens), and nutritional compounds (such as natural forms of vitamins and sweetening agents). Our definition of an NCE differs from the FDA's definition of a new molecular entity. The most notable difference is that the FDA's definition includes diagnostics, whereas our definition of an NCE does not.

Statistical analysis of success rates. For the statistical analyses, residence time (the length of time from IND filing to either abandonment of research without marketing approval or to new drug application approval) was calculated for NCEs with INDs first filed in successive 3-year intervals from 1981 to 1992. Approval dates were available through December 31, 1999, and were used in determining observed success rates. Residence times were also calculated as of the end of 1999. Observed and predicted cumulative approval success rates were calculated at each year from IND filing.

NCEs were stratified according to source (self-originated versus licensed-in or otherwise acquired) and therapeutic class. An NCE is defined as self-originated if it was developed entirely under the auspices of the responding firm. We define acquired NCEs to be compounds that were obtained by the developing firm through licensing, purchase, barter, or other means. To determine whether trends in success rates exist, we analyzed the data by the period during which the IND was filed.

Predicted success rates for IND filing periods were determined from a 2-stage model of the approval process. NCEs with research still active as of December 31, 1999, constitute right-censored observations for our data set. Survival analysis can make use of information provided by censored data.[23] NCEs were assumed to survive until either research was terminated without approval or marketing approval was achieved. Details of the selected models and the computational approach used to estimate final success rates are provided in the Appendix.

The survey data also provided information on the latest development or regulatory phase that abandoned NCEs were in at the time of termination. These data allow us to determine the distribution of research terminations by phase. In combination with predicted approval rates for IND filing intervals, they also permit us to estimate the probability of approval once a compound enters a given clinical phase and phase attrition rates (the percentage of compounds that enter a phase that are abandoned before the next phase is initiated).

RESULTS

Included in the CSDD database of investigational compounds are the development histories of 671 NCEs for which survey firms had filed a first IND from 1981 to 1992. Of these, 508 were identified as self-originated and 163 were identified as acquired. Of the 508 self-originated NCEs, 350 were initially investigated in humans in the United States. By the end of 1999, 20.9% of the NCEs with INDs filed from 1981 to 1992 had been approved for marketing in the United States. For this period, the current US approval success rates for NCEs that were acquired, self-originated, and self-originated and first tested in humans in the United States are 33.1%, 16.9%, and 8.6%, respectively. These results illustrate the significance of previous testing on measured US success rates; success rates on IND filings are higher for compounds that were licensed-in or first tested abroad.

Time to research termination. Even though some of the drugs in our database are still active, survival analysis can be used to establish the rates at which the NCEs with INDs filed during a given period will be dropped from active testing. The mean and median times to research termination for self-originated NCEs that were abandoned with INDs first filed during the periods from 1981 to 1983, 1984 to 1986, 1987 to 1989, and 1990 to 1992 are shown in Fig 1. Because NCEs in the later intervals had less time for research to be terminated, the averages for the later periods may be somewhat understated relative to the earlier periods. However, previous research and our current data suggest that the likelihood of approval, as opposed to abandonment, increases with time from IND filing. If we could add termination times for NCEs that will eventually be terminated, the impact should be much less on the median than on the mean.

Even with these qualifications, the results at least suggest that, over time, pharmaceutical firms have made quicker decisions on research failures. Mean residence time decreased 30% (1.5 years) from the 1981–1983 to the 1990–1992 IND filing intervals. Median time to research abandonment decreased 20% (0.8 years) for INDs filed in the early 1990s relative to the early 1980s.

Further evidence that the ultimate fate of investigational NCEs has tended to be resolved more rapidly

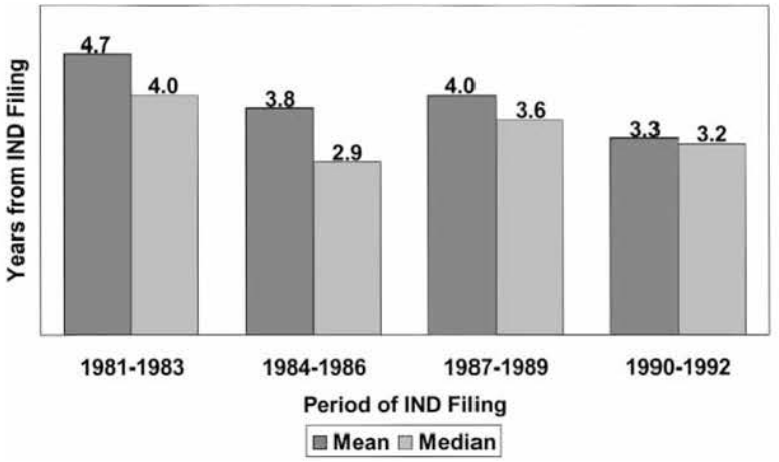

Fig 1. Mean and median time to research abandonment for self-originated new chemical entities (NCEs) with a first investigational new drug application (IND) filed during a given period.

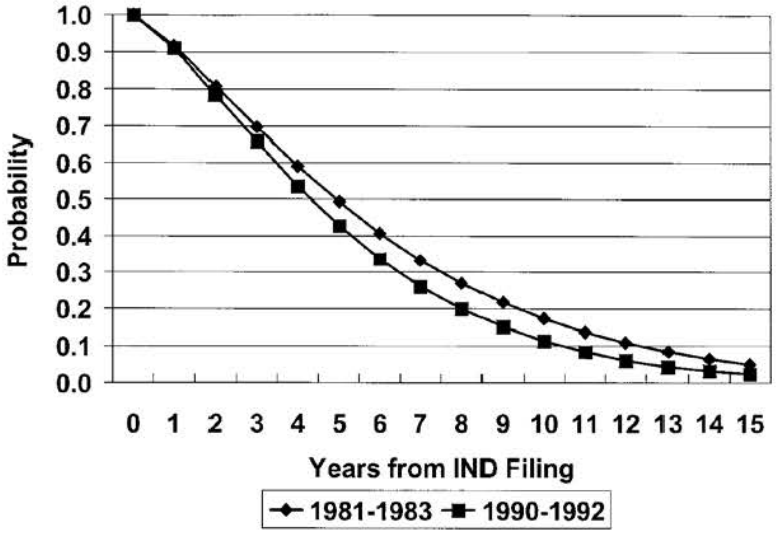

Fig 2. Estimated survival curves for self-originated NCEs with a first IND filed during a given period. The curves show the percentage of NCEs that had not been abandoned or approved for marketing in the United States (ie, still active) a given number of years from the date of IND filing. The data were fitted to Weibull distributions.

over time is shown in Fig 2. The *curves* in the figure are estimated survival curves for the 1981–1983 to 1990–1992 IND filing intervals. A *point* on the curve represents the probability that an investigational NCE will still be active a given number of years from IND filing. An NCE is inactive at a given point in time if either research has been abandoned without marketing approval or the compound has received FDA approval for marketing. It should be noted that the estimated survival curves account for censored data; that is, information regarding still active NCEs is used to estimate final survival rates.

Median survival time decreased from 4.9 years to 4.3 years (12%) for the 1981–1983 to 1990–1992 filing intervals, respectively. Faster action is also evident in the figure for different amounts of time from IND filing. The percentages of NCEs for the 1990–1992 filing period that are still active are 6 to 7 percentage points lower than those for the 1981–1983 filing period at 4 to 10 years from IND filing.

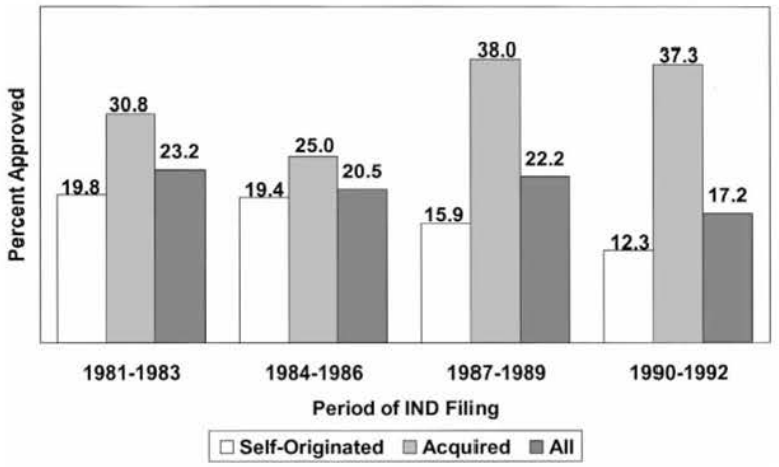

Fig 3. Current clinical approval success rates for NCEs by origin and period during which a first IND was filed.

Success rate trends. To estimate final success rates, results from the survival analyses must be combined with those from qualitative choice models of the conditional probability of approval at given residence times. The parameter estimates for both stages of the model are highly statistically significant, and goodness-of-fit measures indicate strong agreement with the data. The parameter estimates used to determine the predicted final success rates reported here and the accompanying statistical results are available upon request.

Current success rates (as of December 31, 1999) for self-originated, acquired, and all NCEs by IND filing interval are shown in Fig 3. Licensed compounds generally have undergone some testing before licensing and have been shown to be promising candidates for marketing approval. The results support the hypothesis of such a screening effect for acquired NCEs; current success rates for acquired NCEs are notably higher than those for self-originated NCEs.

A screening effect also appears to apply to self-originated compounds that have undergone some clinical testing abroad before an IND has been filed in the United States. The success rates for self-originated NCEs that were first tested in humans in the United States are much lower than the success rates for all self-originated NCEs. Current success rates by IND filing interval for self-originated NCEs first tested in the United States are 33% to 65% lower than for self-originated NCEs as a whole.

Censoring has an impact on the results for all IND filing intervals, but the effect is much greater for the more recent intervals. The proportions of NCEs that are currently active are substantially higher for these later periods. Thus the lower current success rates for self-originated NCEs in the 1987–1989 and 1990–1992 intervals may simply reflect the shorter amount of time available for the ultimate fate of those NCEs to have occurred. Trend analysis for these later periods must be aided by the application of statistical techniques to forecast approval rates for the active NCEs.

Current success rates, maximum possible success rates (assuming all active NCEs are approved), and predicted final success rates for self-originated NCEs by IND filing interval are shown in Fig 4. The predicted final success rates fall between current and maximum possible success rates for all filing intervals. Although both predicted and maximum possible success rates are lower for the 1987–1989 interval relative to the intervals in the earlier 1980s, the predicted success rate for the 1990–1992 interval is 16% higher than for the interval with the next highest predicted success rate.

Comparison of predicted and actual success rates for the early time periods can validate the performance of the statistical model. For NCEs with INDs first filed from 1981 to 1983, the model predicts a cumulative success rate of 19.5% at 16 years from IND filing (the maximum amount of time available for all compounds in the group); the actual success rate for this group at 16 years from IND filing is 19.8%. Similarly, NCEs with INDs first filed from 1984 to 1986 have a predicted success rate of 18.8% at 13 years from IND filing and an actual success rate of 19.4%.

Therapeutic classes. Previous research has indicated that success rates for NCEs vary by therapeutic

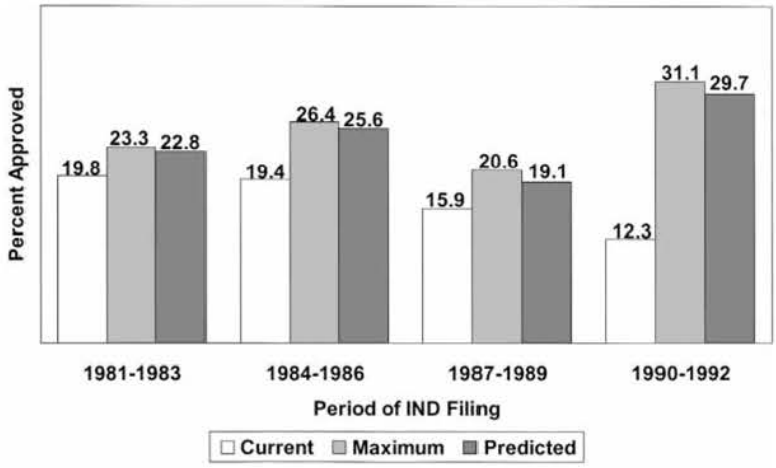

Fig 4. Current (as of December 31, 1999), maximum possible, and predicted final clinical approval success rates for self-originated NCEs by period during which a first IND was filed. Maximum possible success rates were determined under the assumption that all active compounds are eventually approved for marketing. Predicted success rates were constructed with use of estimates for a survival analysis of residence time (time from IND filing to abandonment or US marketing approval) with a Weibull distribution specification and estimates for the conditional probability of approval for a given residence time with a probit specification.

Table I. Current and maximum possible success rates by therapeutic class for self-originated NCEs with INDs first filed from 1981 to 1992*

Therapeutic class	*NCEs*	*Approved NCEs*	*Open NCEs†*	*Current success rate†*	*Maximum success rate‡*
Analgesic/anesthetic	49	10	4	20.4%	28.6%
Anti-infective	57	16	3	28.1%	33.3%
Antineoplastic	38	6	6	15.8%	31.6%
Cardiovascular	120	21	6	17.5%	22.5%
Central nervous system	110	16	14	14.5%	27.3%
Endocrine	33	6	4	18.2%	30.3%
Gastrointestinal	15	3	2	20.0%	33.3%
Immunologic	13	2	0	15.4%	15.4%
Respiratory	25	3	0	12.0%	12.0%
Miscellaneous	43	3	4	7.0%	16.3%

NCE, New chemical entity.
*Therapeutic class information is missing for five compounds.
†As of December 31, 1999.
‡Assumes that all open NCEs will eventually be approved.

class.[6,20] The current and maximum possible success rates by IND filing interval for self-originated NCEs in 9 specific therapeutic categories are shown in Table I. Because the number of compounds available for analysis is greatly reduced when the data are stratified into therapeutic categories, the entire study period (1981–1992) is used. For the immunologic and respiratory categories the fate of all of the NCEs is known so that current, maximum, and final success rates are the same.

For many of these therapeutic classes, the number of compounds with IND filings in an interval is too small for accurate statistical estimation. However, we had enough data and the fits with the statistical model described above were sufficiently good for us to estimate predicted final success rates for the analgesic/anesthetic, anti-infective, cardiovascular, and central nervous system categories. The current, maximum possible, and predicted final success rates for these 4 classes are shown in Fig 5. Relative success rate results for these

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