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COMMENTARY

Success rates for new drugs entering clinical testing in the United States

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Drug development is a complex, risky, and time-consuming process. Research on new chemical entities (NCEs) that undergo clinical testing is abandoned without marketing approval in a substantial majority of cases. The extent and speed at which the development process makes new therapies available to the public are important measures of its viability. The cost of new drug development is also critically dependent on the proportion of drugs that fail in clinical testing.[1,2] In addition, reliable data on industry success rates can serve as useful benchmarks for project planning purposes. The investments required to move new drugs through development to marketing approval are substantial, and efficient use of resources requires careful consideration of expected costs and benefits.

Several studies have examined clinical success rates (i.e., the percentage of drugs tested in humans that obtain marketing approval) for various periods and with varying degrees of completeness. In a series of studies of new drug development in the United States, the Tufts Center for the Study of Drug Development (CSDD) has provided descriptive data on how cumulative success rates vary with time from investigational new drug application (IND) filing.[3-8] The Office of Technology Assessment has presented similar measures on relatively recent data, but with less time for approvals to have occurred.[9] The Office of Technology Assessment used data supplied by the Food and Drug Administration (FDA) (extending out to 54 months after IND filing) to examine success rates for new drugs and biologics with INDs filed from 1976 to 1978 and from 1984 to 1986. Tucker et al.[10] examined FDA data on the development histories of new drugs with IND applications filed from 1976 to 1978 and estimated final success rates for this group of drugs, using the success rates for drugs whose fates were known to infer success rates for compounds whose fates were unknown at the time of the study.

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. Cox[11] and Sheck et al.[12] were the first to apply a statistical methodology to the problem of estimating success rates for new drugs. As part of their

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method for estimating the research and development cost of new drug development, DiMasi et al.[1,2] used a statistical approach similar to that of Sheck et al.[12] to determine final U.S. approval success rates for NCEs first tested in humans anywhere in the world during 1970 to 1982. The studies by DiMasi et al.[1,2] also provided estimates of phase attrition rates (i.e., the rates at which compounds drop out of active testing in the clinical development phases) for these compounds.

Two studies have examined clinical success rates for biotechnology-derived drugs.[13,14] Bienz-Tadmor et al.[13] defined success as the submission of a product license application for biotechnology drugs with an IND application filed from 1980 to 1988. Submission success rates were determined through a nonstatistical mathematical technique. The limited amount of time that biotechnology drugs could have been in testing at the time of analysis and the small number of biotechnology drugs that have been approved precluded analysis of approval rates. Approval success rates for biotechnology drugs reported as under development in *Pharma projects*[15] from 1983 to 1991 have been examined by Struck.[14] The approval success rates were built on estimates of the transitional probabilities of proceeding from one phase of development to the next. However, given that 90% of the drugs were still active at the time of the study, the transitional probabilities for the later development phases are much less reliable than those for the earlier phases. In addition, implicit in the method is the assumption that success rates for biotechnology drugs that entered development in the late 1980s and early 1990s will be the same as success rates for biotechnology drugs that entered development in the mid 1980s.

Nevertheless, both studies predicted success rates that are substantially higher than those that have been reported in the past for traditional chemical compounds. The results described by Bienz-Tadmor et al.[13] also suggest that biotechnology drugs differed from chemical drugs in the pattern by which approval rates change with time from the start of clinical testing. Thus success rate analyses for chemical and biotechnology compounds should be conducted separately.

The methodologic approach used in this study to predict success rates is similar to that used by Sheck et al.[12] However, an improved technique for predicting final success rates for groups of NCEs with INDs filed in a given period is developed here. I am also able to use more recent information on the fate of compounds from the periods studied by Sheck et al.,[12] and I am able to examine later periods. In addition, unlike Sheck et al.,[12] success rates for therapeutic classes and for licensed products are examined here.

Earlier success rate studies have not considered how the size of a pharmaceutical firm may affect attrition rates or the ultimate success rate. Firms of different sizes may differ in the amount of risk they wish to assume, in their capacities to discover promising compounds, or in how effectively they manage their development efforts. A substantial number of economic studies have examined, with mixed results, various hypotheses about how firm performance is related to firm size for the pharmaceutical and other industries.[16] Studies of this type have implications for the efficiency of various market structures, a topic of particular relevance given the ramifications that a changing pharmaceutical marketplace and proposed health-care reforms may have on the structure of the U.S. pharmaceutical industry. Although a clinical success rate offers information on only one dimension of the performance of a pharmaceutical firm, it is undoubtedly an extremely important dimension.

METHODS

Data used for this study were obtained from a CSDD database. The CSDD database was derived from a survey of 36 U.S. pharmaceutical firms. These firms provided data on NCEs first investigated in humans anywhere in the world or for which they were the first to file a U.S. IND from 1963 to 1989. The data gathered include IND filing dates, the dates on which IND research was abandoned (as of December 31, 1989), and reasons for termination of research. A description of additional information included in this database is available elsewhere.[8] U.S. approval dates were obtained from public sources.[17,18] Current success rates for these NCEs were examined as of December 31, 1993, and statistical analysis was applied to data on past rates of research abandonment and approval to predict future success rates. Data on INDs filed in the last half of the 1980s were available but, given the length of the NCE development process, these data are too recent to use for a comprehensive statistical analysis of success rates. However, observed success rates through 1993 were determined for INDs filed during this and earlier periods.

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 biologics, certain externally used compounds (such as disinfectants, antiperspirants, and sunscreens), and nutritional compounds

(such as natural forms of vitamins and sweetening agents). This definition of an NCE differs from the FDA's definition of a new molecular entity, most notably in that the FDA's definition includes diagnostics, whereas this 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 U.S. marketing approval) was calculated for NCEs with INDs filed from 1964 to 1984. Approval dates were available through December 31, 1993, and were used in determining observed success rates. Residence times were calculated as of the end of 1989 (research termination dates were available comprehensively only through December 31, 1989). Observed and predicted cumulative approval success rates were calculated at each year from IND filing. The study period begins at 1964 because some of the 1963 INDs were for NCEs on which clinical testing had been done in the United States before 1963 (the INDs on these drugs were filed to meet the requirements of the 1962 Amendments of the Federal Food, Drug, and Cosmetic Act of 1938).

NCEs were stratified according to source (self-originated versus licensed or otherwise acquired) and therapeutic class. An NCE is self-originated if the same firm that discovered the compound also develops it. Licensed NCEs are defined as compounds that were obtained by the developing firm through licensing, purchase, barter, or other means. The data are analyzed by the period during which the IND was filed to determine whether trends in success rates exist.

Predicted success rates for IND filing periods were determined from a two-stage model of the approval process. NCEs with research still active as of December 31, 1989, constitute right-censored observations for our dataset. Survival analysis can make use of information provided by censored data.[19] 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.

Firm size. The willingness to undertake risky projects or the proficiency in bringing drug candidates to market may vary by firm size. A commonly used measure of company size is the firm's sales revenues. For some firms that develop new drugs, the revenues for pharmaceutical operations are only a small portion of total company sales. In the context of our analyses, pharmaceutical sales is a more relevant measure of firm size than is total company sales.

Company pharmaceutical sales data are available in several public sources. However, the sources are not complete for a given year and are not available for all years. Pharmaceutical sales in 1986 for each of the firms in the CSDD database were obtained from two public sources.[20,21] These data were used to group firms in the database into size classes. Approval success rate estimates were calculated for these classes for NCEs with INDs filed from 1980 to 1984.

The early to mid 1980s was a period during which the structure of the pharmaceutical industry was relatively stable; there were few mergers or acquisitions that involved separate pharmaceutical firms. By contrast, significant merger and acquisition activity occurred in the pharmaceutical industry during the early 1970s and, especially, the late 1980s. The firms in the CSDD database that filed INDs from 1980 to 1984 had not merged with or acquired other pharmaceutical firms by 1986. In addition, little, if any, of the 1986 sales revenues would have come from the sale of NCEs with INDs filed from 1980 to 1984. Thus the 1986 sales levels provide a reasonable basis for classifying firms by size for a success rate analysis of NCEs with INDs filed from 1980 to 1984.*

The 32 firms in the CSDD database (the number that existed and had filed INDs from 1980 to 1984) were divided into three groups of roughly equal number. For the analyses shown below, the 10 firms that had the highest pharmaceutical sales in 1986 were placed in the large-firm class, the 10 firms with the next highest sales levels were placed in the medium-sized-firm class, and the remaining 12 firms were placed in the small-firm class. Small, medium, and large firms earned less than $1.3 billion, between $1.3 billion and $2.1 billion, and more than $2.1 billion in pharmaceutical sales in 1986, respectively.

*Measures of the extent of a firm's research and development operations have also been examined for relationships with measures of firm performance. Data on company pharmaceutical research and development expenditures are publicly available for some firms, but I was able to obtain such data for only about half of the firms in the database. Company total research and development figures are available for all of the firms. However, using only corporate research and development expenditures or mixing pharmaceutical research and development expenditures with corporate research and development expenditures prorated, for example, on the basis of the sales distribution, would yield unreliable measures of the size of the research and development effort. Some firms have substantial nonpharmaceutical research and development efforts, and the proportion of corporate research and development devoted to drugs is probably different (larger) than the proportion of corporate sales that is obtained from drugs. The gap between these proportions is also likely to differ by firm.

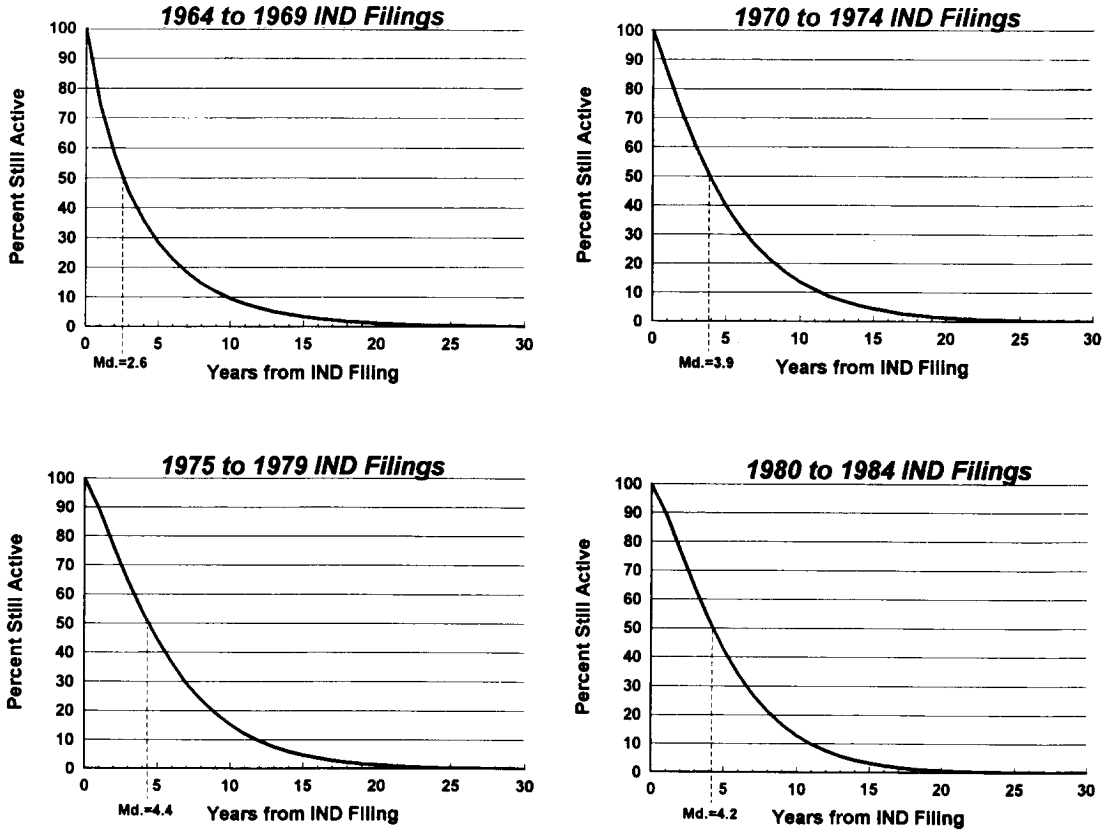

Fig. 1. Estimated survival curves for self-originated new chemical entities (NCEs) with a first investigational new drug application (IND) filed during a given period. The curves show the percentage of NCEs that had not been abandoned or approved for marketing in the United States (i.e., still active) a given number of years from the date of IND filing. Also shown are median survival times. The data were fitted to Weibull distributions.

RESULTS

The 36 pharmaceutical firms in the CSDD database of investigational NCEs filed 1943 INDs from 1964 to 1989. Of these, 1501 were identified as self-originated and 389 were identified as licensed; 53 are of unknown source. Of the 1501 self-originated NCEs, 1127 were initially investigated in humans in the United States. By the end of 1993, 17.2% of the NCEs with INDs filed from 1964 to 1989 had been approved for marketing in the United States. For this period, the current U.S. approval success rates for NCEs that were licensed, self-originated, and self-originated but first tested in humans in the United States are 29.8%, 14.6%, and 10.4%, respectively.

These results illustrate the significance of prior testing on U.S. success rates. Success rates on IND filings are higher for compounds that were licensed or first tested abroad. The impact of screening on overall success rates varied over time. For example, the proportion of self-originated NCEs that were first tested in the United States shows a marked downward trend. Whereas 79% of self-originated NCEs with IND filings from 1964 to 1984 were first tested in humans in the United States, only 61% of self-originated NCEs with INDs filed from 1985 to 1989 were first tested in the United States.

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 population of NCEs with INDs filed during a given period will drop out of active testing. The residence time distributions for INDs filed from 1964 to 1969, 1970 to 1974, 1975 to 1979, and 1980 to 1984 are shown in Fig. 1. The figures indicate that the median time to either research abandonment or marketing approval increased by 1.8 years from the 1960s to the late 1970s. Median residence time decreased slightly for the early 1980s to 4.2 years. Although the data are too recent to develop success rate estimates for the late 1980s IND filings, enough time has elapsed to develop a survival curve for this period. The median

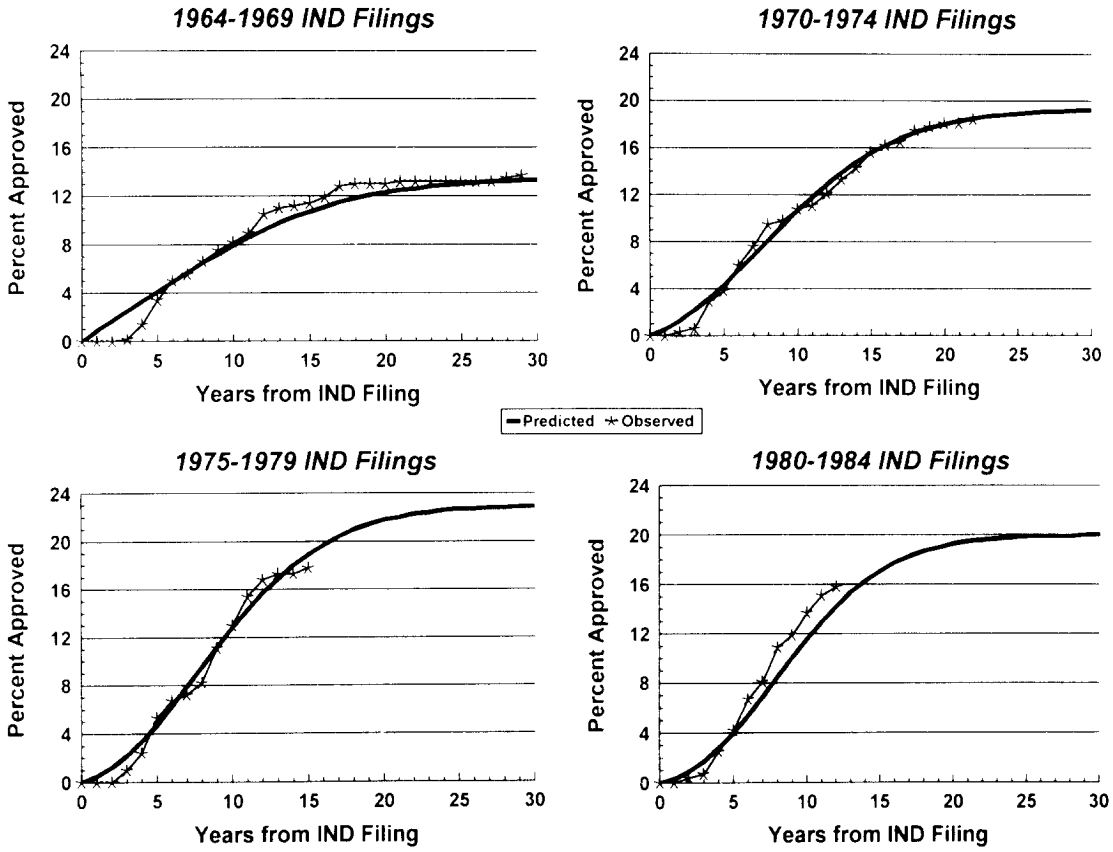

Fig. 2. Predicted and observed cumulative approval success rates for self-originated NCEs with INDs filed during various periods. For the observed success rates, note was taken of U.S. approvals through December 31, 1993. Predicted success rates were constructed by combining estimates from a survival analysis of residence time (time from IND filing to abandonment or U.S. marketing approval) with a Weibull distribution specification and estimates of the conditional probability of approval for a given residence time from a probit specification.

residence time for 1985 to 1989 filings is also 4.2 years.

Success rate trends. To estimate final success rates, results from the survival analyses are 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 on request.

The modeling process involves two separate statistical procedures. Combining them, therefore, produces two primary sources of estimation error. Nonetheless, as shown by Fig. 2, the fits of the predicted cumulative success rate curves to curves representing the actual experience of self-originated NCEs through 1993 are tight, especially for the first three intervals. The predicted curve for the early 1980s slightly underestimates the observed success rates beyond 5 years from IND filing. However, the predicted curve for the 1960s (a period for which there is now almost complete information) also underestimated observed success rates after a number of years from IND filing. The final predicted success rate, though, differs from both the observed and the maximum possible success rate for this filing interval by less than one percentage point.

Current success rates (as of December 31, 1993), maximum possible success rates (assuming all open INDs are approved), and predicted final success rates for IND filing intervals are shown in Table I. Except for the 1964 to 1969 interval, the predicted final success rates fall between current and maximum possible success rates for all groups and filing intervals. How-

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