

New Evidence on the Dynamics of Drug Discovery

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ABSTRACT

Some recent analysis has suggested that drug discovery efforts have been less successful lately, although it has generally focused only on approvals, the end of the lengthy development process. In this paper, we argue that understanding the impact of technological change on drug discovery over time requires estimation of the joint Markov process governing the trajectory of a new discovery through the various stages of development, and analysis of the long run total pipeline success rates implied by the observed transitions between all states. We use recent trial data to estimate that process, and find that success rates of different stages of development have changed significantly over time. In particular, success rates fell from 1996 to 2001 but have since improved. The trends for preclinical drugs are particularly encouraging, and the latest data suggest that pipeline output over the next decade may increase.

I. Introduction

In 2002, the FDA approved only 17 new molecular entities (NMEs), the nadir of a three-year decline in approvals and the lowest number approved in almost two decades. Particularly because the low number came at a time of surging R&D expenditures, many analysts were troubled. News stories labeled the pipeline “vanishing,” “dry,” “insufficient,” “diminished,” and “weak.” In a 2004 report, the FDA expressed “great concern” about the slowdown in new drug submissions.

At a time when the tools to acquire basic biomedical knowledge are more advanced than ever, a significant decline in discovery would be an important conundrum with serious policy implications. Causes of the decline would have to be identified, and, given the enormous social benefits of new discoveries, remedies proposed.

The motivation of this paper is that the existing evidence does not decisively and significantly identify a decline in the productivity of the medical research pipeline. While a simple look at the recent numbers of approvals and submissions may suggest a worrying downward trend in development, that exercise provides a very incomplete picture of the discovery process. In particular, information technology advances may significantly reduce the costs of discovering new compounds and identifying potential winners at very early stages. In this case, success rates at early stages might increase, as would the number of compounds entering the pipeline. If these occurred, the discovery future might be bright, even if recent end stage success probabilities have declined.

In this paper, we develop a Markov model of discovery that can be applied to describe the evolution of drug discovery. We then estimate the parameters of this model using clinical trial data for the U.S., and draw conclusions concerning the changing dynamics of drug

discovery throughout every stage of the discovery process. We then track the changes in success and failure probabilities throughout the discovery chain, and identify changes in success rates that have occurred and are statistically significant.

Briefly, we find that all stages of drug discovery slowed down from 1996 to 2001. The low point was 2000-2001, when the expected approval rate for all drug projects fell below 24 percent. Since then, however, drug development has picked up. Drugs in the early stages of development are now 3 to 4 times more likely to be eventually approved than they were in 2001. The trends for Preclinical drugs are particularly promising, and the expected approval rate for all drug projects is now close to 30 percent.

We proceed as follows. The next section describes the model that we apply to the discovery process, and the measures derived from the model that help identify underlying changes. Section III describes the data that we will use to estimate the model. Section IV provides a brief literature review. Section V describes our methods, Section VI discusses our results, and Section VI concludes.

II. A Markov Model of Discovery

Before a drug comes to market, it must successfully pass several phases of testing. Preclinical laboratory and animal tests are followed by Phase I, II, and III human clinical trials. If those tests are successful, the drug sponsor files a new drug application (NDA) with the FDA, asking for permission to sell the drug in U.S. markets. If the FDA approves the application, the drug clears its last hurdle and will be sold in the U.S. market.¹

¹ Center for Drug Evaluation and Research, Food and Drug Administration, FDA (1998). “CDER Handbook ,” 1998, www.fda.gov/cder/handbook/ (10 February 2006).

At every stage of the drug development process, many drugs cannot pass the test; for every drug that makes it to market, hundreds of projects fail. The FDA reports that only 1 in 1,000 compounds tested in the preclinical phase makes it to human clinical trials.² Each year, the number of NDAs approved by the FDA is approximately 15 to 30 times less than the number of applications to begin clinical trials.³

Given that drug discovery occurs at the frontier of knowledge, it is quite likely that the discovery process could evolve significantly over time. On the negative side, it could be that so many discoveries have been made that additional steps are much more difficult, a state, perhaps, that the field of physics currently finds itself in. On the positive side, breakthroughs tend to feed on one another, and information technology may make discovery easier as well.

A metric of the state of the discovery process at any moment in time could be extremely useful for policymakers, who must decide how many scarce resources to devote to medicine. To date, existing analysis tends to focus on success rates in isolation, which provides a rather incomplete perspective on the dynamic process.

Given the description of the stages of development above, it is natural to summarize drug discovery dynamics via estimation of a Markov transition matrix at each time t that summarizes the movement of prospective drugs between possible states in the development process. We consider a 10-state Markov model where the ten states are: 1) Failure; 2) No Development

² Food and Drug Administration, "FDA and the Drug Development Process: How the Agency Ensures that Drugs are Safe and Effective," FDA Publication No. FS 02-5, February 2002, www.fda.gov/opacom/factsheets/justthefacts/17drgdev.pdf (10 February 2006).

³ Center for Drug Evaluation and Research, Food and Drug Administration, "NDAs Approved in Calendar Years 1990-2004 by Therapeutic Potential and Chemical Type," 22 March 2005, www.fda.gov/cder/rdmt/default.htm (10 February 2006); Center for Drug Evaluation and Research, Food and Drug Administration, "Original INDs Received Calendar Years 1986-2004," 22 March 2005, www.fda.gov/cder/rdmt/Cyindrec.htm (10 February 2006).

Reported (NDR)⁴; 3) Phase I; 4) Phase II; 5) Phase III; 6) Preclinical; 7) Preregistered; 8) Success; 9) Suspended; 10) Unknown.

At each moment in time, there is a state vector S_t and a transition matrix A_t such that $S_{t+1}=A_t S_t$. With a large enough database, it is possible to estimate the transition probabilities in A_t , between each of these Markov states for each year. In addition, and more importantly, one can use the estimated probabilities to simulate the dynamic path implied by the estimated probabilities, compare that path to those implied by estimates of transition matrices for earlier years, and estimate the likelihood of a compound making the transition from each step in the pipeline to success given the complete 10-by-10 transition matrix. Finally, each transition matrix will have associated with it a steady-state state vector S_∞ , which reveals the proportion of compounds likely to reach the success state if that matrix were to hold for many successive years. The question of whether the pipeline is “drying up” can be formally tested by comparing the steady state success probabilities of different matrices over time, giving researchers a simple summary statistic which can be applied to summarize changes in the innovation driving process. Using data described in the next section, we will estimate the Markov matrices for each year from 1996-2004. We will then perform tests to identify changes in specific probabilities that vary from year to year, and over longer horizons as well.

III. Data

The source of the data is the R&D Insight database maintained by Adis International. The Adis database compiles publicly available information to track over 17,000 compounds in

⁴ If there has been no activity associated with a drug (no commercial information released, no recently published studies) for 18 months to 2 years, the Adis database, the source of our data, assigns the phase “no development reported.” The time frame depends on the last phase of the drug. This is the term used until a drug is confirmed as discontinued, withdrawn or suspended, or activity is resumed.

development by pharmaceutical and biotech companies around the world. This study uses the data about the phase of development for drugs developed in the U.S. between 1996 and 2004. Every indication for which a drug was being tested was tracked separately from preclinical trials to market or discontinuation, including periods when development was suspended or unreported. The number of observations ranges from 5,074 for 1996 to 17,417 observations for 2004.

While this database provides a wealth of information, its usefulness for this study is limited by the convoluted nature of drug R&D. For example, it is difficult to track development through time as drug names, disease indications, or locations of development change. New drugs that differ from existing drugs only in dosage strength or route of administration, for example, often cannot be tracked by the database.⁵ In addition, determining a drug's phase of development is not entirely objective; Adis must evaluate, for instance, whether no news from a project means that development is stalled, discontinued, or simply being kept private. The evaluation is especially difficult in the very early stages of development--does research count as a new development project or not?--and Adis has made editorial changes to the database and had "cleanups" in May-September 1998, May-July 2001, and May 2002 that primarily affected preclinical drugs.⁶ Furthermore, Adis depends on publicly available information, which could bias the analysis in favor of either more successes, as companies release information on only the most promising projects, or more failures, as companies seek to withhold information on their hot leads.

Despite these limitations, however, the Adis database remains one of the most comprehensive sources of information for a large-scale examination of drug development. Most other researchers studying the development pipeline have used information from the Adis

⁵ Correspondence with Adis, 23 June 2005.

⁶ Correspondence with Adis, 15 March 2005.

database or other similar databases⁷; those who have not used databases have relied on small samples of proprietary development information.⁸

IV. Previous Work and Existing Evidence

A. Literature Review

Previous research has examined the success rates of drug research projects using simple descriptive statistics or statistical modeling. These studies typically look at a sample of all projects in clinical trials over a long time period and calculate how many ultimately make it to market, both the unconditional probability of success and the conditional probability from each phase of development. Their estimates vary widely, with unconditional success rates ranging from less than 10 percent to over 70 percent for some types of drugs.

In a sample of 965 R&D projects by U.S. companies that started any phase of clinical trials in the 1990s, Arora et al. (2000) find a success rate of 9.5 percent. (All results are summarized in Exhibit 1.) Adams and Brantner (2003) use a sample of 3,328 drugs that entered any phase of clinical trials between 1989 and 2002 to calculate an overall success rate of 12 percent. According to their sample, a drug that makes it to Phase II trials has a 17 percent success rate, and a drug in Phase III trials has a 38 percent chance of making it to market. They warn, however, that because their sample is worldwide, including drugs that were never intended for

⁷ A. Arora et al., “The Nature and the Extent of the Market for Technology in Biopharmaceuticals,” Working Paper, European Pharmaceutical Regulation and Innovation Systems, 2000; C. Adams and V. Brantner, “New Drug Development: Estimating Entry From Human Clinical Trials,” Bureau of Economics, Federal Trade Commission, 2003; P. Danzon et al., “Productivity in Pharmaceutical-Biotechnology R&D: The Role of Experience and Alliances,” NBER Working Paper, no. 9165 (2003); R. Abrantes-Metz et al., “Pharmaceutical Development Phases: A Duration Analysis,” Working Paper No. 274, Bureau of Economics, Federal Trade Commission, 2004.

⁸ J. A. DiMasi et al., “Research and Development Costs for New Drugs by Therapeutic Category: a Study of the U.S. Pharmaceutical Industry,” *PharmacoEconomics* 7, no. 2 (1995): 152-169; J. A. DiMasi, “Risks in New Drug Development: Approval Success Rates for Investigational Drugs,” *Clinical Pharmacology & Therapeutics* 69, no. 5 (2001): 297-307; J. A. DiMasi et al., “The Price of Innovation: New Estimates of Drug Development Costs,” *Journal of Health Economics* 22, no. 2 (2003): 151-185.

the U.S. market, their results may underestimate the true success probabilities. Abrantes-Metz et al. (2004) look at a sample from the same time period and find higher success rates: 26.4 percent from Phase I, 32.7 percent from Phase II, and 56.7 percent from Phase III.

The results discussed above are only descriptive statistics, however. As such, they have a serious limitation: they must exclude right-censored data. When looking at drug projects that entered clinical trials within a specific time frame, there will inevitably be some projects that do not end a trial—either by advancement or discontinuation—within the time frame. This type of data, for which the end date is not observed in the data set, is known as right-censored and cannot be described by simple statistics. To be able to incorporate right-censored projects into their analysis, Danzon et al. (2003) make assumptions about failure rates and DiMasi et al. (1995), DiMasi (2001), DiMasi et al. (2003), and Abrantes-Metz et al. (2004) use statistical estimation procedures. Our own Markovian estimation procedure examines year-to-year transitions and incorporates the possibility of remaining in the same state, so our results are unaffected by right censoring.

Danzon et al. study 1,910 compounds that were in clinical trials between 1988 and 2000, with most observations from after 1994. They do not restrict their sample only to clinical trials investigating the compound for its primary medical indication; they include information on trials for all indications, which they note is the “most disaggregated unit of R&D output” since the FDA requires clinical trial evidence for each indication for which a drug is approved.⁹ In their sample, compounds have an average of slightly more than 3 indications each. For right-censored data, they assume eventual failure if the drug remained in the same phase for longer than a threshold equal to the maximum time observed across all trials; i.e., “if an indication entered phase 1 or 3 before 1996 and no further action is reported by 2000, we assume that it

⁹ p. 11

failed[.]...Indications that entered those phases in 1996 or later and contain no additional information are excluded from our regression analysis. We apply the same procedure to indications in phase 2 using 1995 as the threshold.”¹⁰ This assumption could be problematic if the average trial duration is changing over time, but Danzon et al. do not test the sensitivity of their results to their assumption about failures.

They estimate success probabilities for each phase by running logit regressions in which the dependent variable equals 1 if the compound successfully completes a phase for a particular indication, conditional on starting that phase, and 0 if the trial is discontinued. The independent variables are indicators for 13 therapeutic categories. Multiplying together the results from the three regressions, Danzon et al. estimate overall success rates that range from 29.6 percent for the respiratory systems category to 78.4 percent for the hormonal preparations category.

In a series of papers, DiMasi and his colleagues take a different approach that results in lower success rate estimates than the method of Danzon et al.¹¹ They predict success rates by combining two statistical estimation procedures. The first step is to model the probability of a drug “surviving” until time t using parametric survival analysis, which accounts for right-censored data. The second step is to model the probability of success given survival until time t , using qualitative choice modeling. Combining the estimated equations from these two models produces estimated success rates.

DiMasi et al. (1995) use data from 12 pharmaceutical firms on 93 new drugs that entered clinical trials between 1970 and 1982 to find that the probability of entering the market from

¹⁰ pp. 16-17

¹¹ Danzon et al. attribute the discrepancy to the fact that they include trials for all of a drug’s medical indications, while the DiMasi papers use only the primary indication: “[I]f companies are more likely to target multiple indications for those compounds that have either already been approved or have a relatively high probability of being approved, then overall success probabilities will be higher for our measure based on all indications than for the first indication of a new compound” (17-18). Indeed, when they include number of indications in their regressions, its estimated coefficient is positive and significant.

Phase I is 23.1 percent, from Phase II is 30.7 percent, and from Phase III is 63.5 percent. DiMasi (2001) looks at 671 new drugs that started clinical testing between 1981 and 1992. Over the period 1981 to 1986, the estimated probability of success from Phase I is 24.2 percent; from Phase II, 33.0 percent, and from Phase III, 72.9 percent. For the period 1987 to 1992, the estimated success rate from Phase I declines to 22.4 percent. The probability of success from Phase II is about the same at 32.3 percent, and the Phase III success rate increases to 78.5 percent. Like the earlier study, this study also finds differences among therapeutic categories. The sample of 68 drugs in DiMasi et al. (2003) that started clinical trials between 1983 and 1994 have still lower estimated success rates: 21.5 percent from Phase I, 30.3 percent from Phase II, and 68.5 percent from Phase III.

In addition to the descriptive statistics cited above, Abrantes-Metz et al. (2004) also estimate a duration model. Unlike the analysis performed in the studies by DiMasi and his colleagues, the model estimated by Abrantes-Metz et al. includes covariates such as therapeutic category, route of administration, and company size. While this may improve the model—indeed, Abrantes-Metz et al. argue that their model is superior to those of DiMasi (2001) and DiMasi et al. (2003)—it means that estimates of general success rates, comparable to the estimates from other studies, are not available.

Based on all of these studies, it seems that the unconditional probability of approval for drugs in clinical trials is somewhere between 20 and 30 percent. For drugs that make it to Phase II, the probability increases to approximately 30 to 40 percent, and drugs that make it to Phase III have about a 60 to 80 percent chance of approval. Adams and Brantner calculate lower probabilities, and Danzon et al. calculate higher probabilities.

Some of these studies also present the transition probabilities between phases, and for the others, those probabilities can be calculated from other results. Most of these probabilities are well over 50 percent. In the DiMasi studies, the probability that a Phase II drug will advance to Phase III is always considerably lower than either the probability that a Phase I drug will advance to Phase II or the probability that a Phase III drug will be approved. In the other studies, the pattern is generally different. The probability of advancement declines as a drug moves through development.

Our Markov model will focus directly on transition probabilities. It will also add to the previous research by looking at success rates for Preclinical and Suspended drugs and by distinguishing between Phase III and Preregistered drugs. While the other studies, with the exception of DiMasi (2001), pool together data collected over a decade or more, we will evaluate year-to-year transitions in addition to pooled data. Furthermore, our study will use more recent data, look for changes over time and use dynamic simulation to draw summary conclusions.

B. FDA statistics

When analysts argue that the pipeline is declining in productivity, they usually cite the trend in NME approvals. From a high of 53 in 1996, the number of these innovative new drugs fell to 17 in 2002. The higher number of approvals in 2003 and 2004, 21 and 31 respectively, seemed promising, but 2005 saw a decline to only 20 NME approvals. The trend in NME submissions is similar.¹²

Despite the setback in 2005, however, the long-term time trend in NME approvals remains positive. In fact, with the exception of only a few years, the number of drugs approved

¹² Food and Drug Administration, "FDA's Critical Path Initiative: History, Objectives, Approach," 21 June 2005, www.fda.gov/oc/initiatives/criticalpath/presentations/bio200501_files/bio200501.html (10 February 2006).

in 2004 was the highest of any time in the past twenty-five years (Exhibit 2). And those few years are special anomalies, thanks to the Prescription Drug User Fee Act (PDUFA). According to recent research, PDUFA, which was designed to speed up approval times, is partially responsible for the anomalously high number of approvals in 1996 and the apparent drop-off in approvals in subsequent years; without it, there would have been fewer NME approvals in that time period and the trend would have been smoother.¹³

Considering new drugs more broadly does not make the pipeline look any stronger. From 1990 to 2004, the time trend in NDAs, of which NMEs are a subset, is essentially flat; since 1980, the trend is actually negative. NDA approvals have followed a pattern similar to NMEs—peaking in 1996, declining after that, and picking up recently. In 2004, NDA approvals surged to 113 from 72 in 2003, the highest total since 1997. Through November 30, 2005, however, the FDA had approved only 70 NDAs.¹⁴

The picture grows bleaker when R&D expenditures are taken into consideration. Research spending has grown exponentially, increasing by an order of magnitude over the past 20 years, but there has not been a commensurate increase in new drugs.

V. Methods (further detail in the appendix)

Using the Adis data, we constructed year-to-year transition matrices to show the probability of drugs moving from one state to another in the next year. This required matching each observation in each year to its corresponding observation in the following year. This

¹³ E. R. Berndt et al., “Industry Funding of the FDA: Effects of PDUFA on Approval Times and Withdrawal Rates,” *Nature Reviews Drug Discovery* 4, no. 7 (2005): 545-554.

¹⁴ Center for Drug Evaluation and Research, Food and Drug Administration, “NDA and BLA Approvals,” www.fda.gov/cder/rdmt/default.htm (10 February 2006).

matching process proved to be tricky. Some observations could not be matched and thus were not included in the Markov model.

For each year, there is a 10-by-1 state vector that describes the contents of the pipeline. Each cell is the count of the matchable observations in that state in that year. To focus on the development process from beginning to approval (or failure), the category “Success” includes approved drugs that are later withdrawn.

Transition matrices describe the movements of drugs between the states from year to year. Each of the 10 columns is a state in year t , and each of the 10 rows is a state in year $t+1$. Each cell shows the percentage of drugs in a particular state in year t that transitioned to a particular state in year $t+1$. Thus, each column sums to 1.

The transition matrices can be used to calculate conditional and unconditional probabilities of approval. The conditional probabilities of success are contained in the steady state matrix, if Success and Failure are absorbing states. That is, if all projects will eventually succeed or fail, the steady state matrix reveals what percentage of projects in each phase will be approved or fail, assuming that the same transition probabilities hold for a long time. In the Adis data, however, Success and Failure are not absorbing. In each year, a handful of projects categorized as successes or failures moved to other phases in the next year. This unexpected pattern of development is likely due to Adis’ database maintenance procedures. Therefore, to obtain the steady state matrices, we forced all projects in the Success and Failure states to stay in those states—i.e. the Success-Success and Failure-Failure cells in the transition matrices each equal 1—and then multiplied each transition matrix by itself 1,000 times. The unconditional probability of approval is contained in the corresponding steady state vector.

The significance of changes in these probabilities over time was tested with chi-squared tests and logistic regressions—chi-squared tests for comparing one probability in one year to the same probability in another year, and regressions for comparing all probabilities in one year to all probabilities in another year.

VI. Results

A. One-Year Transition Probabilities

The Markov transition matrices describe annual progress through the research pipeline. Pipeline output is affected by changes in the likelihood that drugs advance or fail in each phase. Declining output will require different responses depending on the point in development in which the changes occur. The Adis data reveal the following changes in the transition matrices over time (Exhibit 3):

NDR

The vast majority—well over 90 percent—of drugs categorized as NDR stay in that category in the next year. The probability of failing has ticked up since 1998, from less than 1 percent to about 3 percent.

Preclinical

For drugs in preclinical trials, the probability of failure has generally risen, from about 1 to 2 percent in the late 1990s, to 4 or 5 percent in the most recent data. At the same time, though, the probability that a preclinical drug will advance to Phase I in the next year is highest in the most recent data. In 2003, this transition probability was above 3 percent, while from 1996 to

2001, it was never more than 2.2 percent. The probability of a preclinical drug transitioning to NDR has swung dramatically from highs of 30 percent or more to lows around 4 percent.

Because the NDR classification is somewhat subjective, however, it is difficult to know whether these changes represent actual changes in the drug development process or just changes in the Adis editorial process. (Recall that Adis made editorial changes to the database three times from 1996 to 2004, and these changes primarily affected preclinical drugs.)

Phase I

The percentage of Phase I drugs moving to Phase II in the next year fell from about 13 percent in 1997 to just under 9 percent in 1998. This probability fell further in 2001, and then rose back above 9 percent in 2003, although these changes were not statistically significant. The Phase I to NDR transition probability more than doubled in 2001, then decreased by half in each of the next two years, but again, this trend cannot be definitively attributed to changes in the drug development process.

Phase II

For Phase II drugs, the trend in advancement has been falling, while the trend in failure has been rising. The one-year probability of moving from Phase II to Phase III dropped from over 9 percent in 1996 to about 6 percent in 1997 and has fallen almost in half since then. The one-year failure rate has jumped around over time, but generally increased, from around 3 percent in 1996 and 1998 to more than 6 percent in the three most recent years. The NDR transition probability had a similar pattern for Phase II drugs as it did for Phase I drugs.

Phase III

The probability of Phase III drugs advancing to Preregistration in the next year fell steadily from 1998 to 2001, declining by nearly half, but has since risen. The 2003 probability of nearly 9 percent almost matches the 1998 value. The rate at which Phase III drugs reach the market followed a similar trend. After falling below 1 percent in 2000, this transition probability was about 3 percent in 2003, the highest it has been since 1997.

Preregistration

Drugs in the Preregistration phase have been staying there longer. The percentage staying in that state in the next year has generally risen over time, although it has dropped modestly since 2000. At the same time, the percentage approved in the next year has generally fallen.

Suspended

In recent years, the percentage of suspended drugs that fail in the next year has fallen significantly, from over 23 percent in 2000 to about 3 percent in 2002. On the other hand, suspended drugs are not moving into active development either. The percentage that stay suspended in the next year has risen from about 70 percent in 2000 to above 90 percent in 2002. In the most recent data, these trends reversed slightly.

Exhibits 4-10 summarize all of these results by plotting the trends in failure and “success” rates for each phase of development. The failure rate is the probability that a drug project will fail in the next year, and the success rate is the probability that a drug’s development

will advance in the next year. For drugs in the NDR and Suspended phases, advancement means moving into active development, at any phase.

The general trend in one-year success probabilities mirrors the general trend in NME approvals: declining from 1996 to 2001 but on the rise since then. This pattern holds for drugs in Preclinical development, Phase I, Phase III, and Preregistration, but the success rates for drugs in Phase II have held steady since 2001. For both Preclinical and Phase III drugs, current success probabilities are close to their peak levels in 1996 and the improvement in one-year success rates from a few years ago to today is statistically significant.

The one-year failure probabilities also suggest an encouraging trend. All else equal, the higher costs of late-stage trials make early failure preferable to late failure, and the evidence suggests that drugs are tending to fail earlier in the development process. Failure rates in the early stages of development have risen over time, while Phase III and Preregistration failure rates have tended to fall (with the notable exception of the 2003 preregistration failure rate). The trends for Preclinical drugs look particularly good for the drug development process. The 2003-2004 success rate is the highest of the entire sample and failure rates are also rising, which suggests that researchers are becoming better able to identify promising drug projects quickly.

B. Steady State Success Probabilities

Transition matrices describe drug development one year at a time, and steady state matrices describe development over a very long time horizon. In other words, a steady state matrix for a particular year shows how many drug research projects will eventually succeed if that year's transition matrix were applied to the pipeline of drug research projects year after year for many years.

For all phases, the general time trend in steady state success probabilities was the same: declining from 1996 to 2000 or 2001, and rising since then (Exhibit 11). 1996 was the peak year for every phase except Preregistration. In most cases, success probabilities fell off in 1997 and then increased in 1998. The statistics for 2000 and 2001 were grim, with fewer than 10 percent each of NDR, Preclinical, Phase I, and Phase II expected to eventually be approved. Success rates increased from there, but only to their 1999 levels, approximately.

In 2003, the most recent year in the sample, the steady state success probabilities for the earlier phases improved from 2002. Expected success rates were 6.4 percent for Preclinical drugs, 10.3 percent for Phase I drugs, and 13.6 for Phase II drugs. The probability of success for the later phases declined relative to 2002 as 45.3 percent of Phase III drugs and 74.0 percent of Preregistration drugs were expected to eventually be approved. These figures are roughly comparable to the probabilities in Adams and Brantner (2003), but considerably lower than those in other studies. The higher probabilities from 1996 and 1997 are closer to the literature values.

In all but one year, the success rate for drugs in an unknown phase was between the rates for Phase I and Phase II drugs, or the rates for Phase II and Phase III drugs.

Steady state success probabilities are conditional probabilities that depend on a drug's phase of development, but a similar calculation produces an unconditional probability. The steady state vector describes the contents of the pipeline after the same transition matrix has been applied year after year for many years. In other words, because Success and Failure are absorbing states, the steady state vector shows how many pipeline projects will eventually be approved. The time trend in this unconditional probability of approval is similar to the trends in conditional probabilities (Exhibit 12). In 1996, 41.6 percent of all projects were expected to eventually be approved. That number dropped during the late 1990s, reached a low point of 23.5

percent in 2000, and started rising. In 2002, the probability was 29.9 percent, then in the next year, it fell to 28.1 percent, exactly the same as it was in 1999. Over the entire sample, 1996 to 2003, the unconditional probability of approval was 27.9 percent. Recall that earlier research indicated that the unconditional probability of approval from clinical trials—i.e., not including preclinical projects, as our study does—was generally between 20 and 30 percent.

C. Projecting Future Successes

The recent trend in pipeline output—an increasing number of NME approvals from 2002 to 2004, followed by a sharp decline in 2005—gives a mixed signal about the future strength of the pipeline. Our analysis thus far adds more detail to the picture by describing how the entire pipeline changes from year to year, but it shows transition probabilities going up and down over time. To see how those trends will play out in the future, we can use the Markov transition matrices, to conduct a dynamic simulation of future drug discovery.

We can predict the contents of the pipeline next year by multiplying the contents of this year's pipeline by a transition matrix and adding any new projects that enter the pipeline. Repeating this procedure gives the following year's pipeline, and so on. With the Adis data, the inflow into the pipeline will include projects in all phases of development, not just new preclinical projects, because Adis can add drugs to its database at any phase.

Assuming that pipeline inflow and transition probabilities stay at their 2003-2004 levels, the future looks bright. Over the next decade, the total number of drugs approved each year will rise steadily (Exhibit 13). In 2014, the number of approved drugs will be 20 percent higher than it was in 2004. A ten-year stretch of ever-increasing drug approvals is unprecedented. In

addition, the number of projects in all phases of active development increases each year, suggesting that the pipeline will continue to be strong for years to come.

This is a conservative prediction—different assumptions about future inflow and transition probabilities yield a higher expected number of approvals. For instance, using the average of the 2002-2003 and 2003-2004 transition matrices and inflow amounts, the number of drug approvals in 2014 will be 25 percent higher than it was in 2004. Calculations using the average inflow and probabilities from 1998 to 2004—i.e., the entire sample, except the unusually productive years of 1996 and 1997—yield still higher productivity. Under those conditions, the pipeline output in 2014 would be more than 40 percent higher than the 2004 output (see Appendix).

VII. Conclusions

The low number of NME approvals in recent years has some analysts concerned about the strength of the drug research pipeline. Without evaluating the changing dynamics of the drug development process, however, the number of drug approvals alone—the output of that process—gives us an incomplete picture of the pipeline. In this paper, we used a dynamic Markov model to analyze the entire path a drug takes to market and make a more complete assessment of pipeline strength.

In general, we find that progress through the pipeline became more difficult from 1996 to 2001. Research bottomed out in 2000 and 2001, when fewer than 5 percent each of NDR, Preclinical, and Phase I drugs, and fewer than 10 percent of Phase II drugs were expected to eventually be approved. In those two years, the expected approval rate for all drug projects was

just under 24 percent, the lowest of our sample. Today's low NME approval numbers may be the result of these earlier bad times at earlier stages in the pipeline.

The good news is that drug development success rates have picked up since then. The one-year success probabilities for all phases except Phase II have risen since 2001, and the current Preclinical and Phase III probabilities are close to their peak levels in 1996. These trends are reflected in the higher rates of eventual approval—NDR, Preclinical, Phase I, and Phase II drugs are now 3 to 4 times more likely to be eventually approved than they were in 2001. The expected approval rate for all drug projects is now close to 30 percent. Furthermore, these trends in success rates, combined with trends in failure rates, suggest that it is becoming easier to identify promising drug projects early in the development process.

Our dynamic simulation predicts that if current research trends stay constant over the next decade, the number of drugs approved in 2014 will be at least 20 percent higher than it was in 2004.

Exhibit 1: Literature Review, Success Probabilities

Paper	Period for beginning clinical trials	Number or type of compounds	Phase transition probabilities		Conditional probability of approval from:			Overall probability of approval from clinical trials
			I to II	II to III	Phase I	Phase II	Phase III	
<i>Descriptive Statistics</i>								
Arora et al. 2000	1990-1999	965						9.5
Adams and Brantner 2003	1989-2002	3,328	*70.6	*44.7	12.0	17.0	38.0	12.0
Abrantes-Metz et al. 2004 ¹	1989-2002	3,136	80.7	57.7	26.4	*32.7	56.7	26.4
<i>Statistical Models</i>								
DiMasi et al. 1995	1970-1982	93 ² Anti-infective Cardiovascular NSAID Neuropharmacologic	*75.0	*48.3	23.0	30.7	63.5	23.0
			*78.4	*49.9	30.2	38.5	77.2	30.2
			*63.9	*56.6	26.2	41.0	72.4	26.2
			*75.0	*41.7	22.2	29.6	70.9	22.2
			*89.8	*44.2	20.3	22.6	51.1	20.3
DiMasi 2001	1981-1986	671 ² Cardiovascular CNS Analgesic/Anesthetic Anti-infective	*73.3	*45.3	24.2	33.0	72.9	24.2
	1987-1992		*69.2	*41.2	22.6	32.7	78.5	22.6
	1981-1983							22.8
	1984-1986							25.6
	1987-1989							19.1
	1990-1992							29.7
	1981-1992							20.9
Danzon et al. 2003	1988-2000	1,910 Antithrombotic Blood Cardiovascular Antipsoriatics Urologics, Contraceptives Hormonal Antivirals Cytotoxics Anti-inflammatory Nervous system Parasitology Respiratory Carbonic anhydrase	*84.0	*79.9	44.8	*53.4	*66.8	29.6-78.4
			*84.0	*79.7	37.5	*44.6	*56.0	44.8
			*84.0	*68.6	32.7	*38.9	*56.8	37.5
			*88.7	*77.9	52.4	*59.1	*75.8	32.7
			*95.1	*90.4	71.7	*75.4	*83.4	52.4
			*92.2	*95.3	78.4	*85.1	*89.2	71.7
			*80.3	*78.2	45.0	*56.0	*71.6	78.4
			*88.8	*64.0	31.6	*35.6	*55.7	45.0
			*87.4	*81.1	53.9	*61.7	*76.0	31.6
			*84.0	*76.0	33.8	*40.3	*53.0	53.9
			*82.5	*85.4	52.0	*63.1	*73.8	33.8
			*90.8	*56.9	29.6	*32.6	*57.4	52.0
			*83.4	*76.6	64.8	*56.3	*73.4	29.6
								64.8
DiMasi et al. 2003	1983-1994	68 ²	71.0	*44.2	*21.5	*30.3	68.5	*21.5
Abrantes-Metz et al. 2004	1989-2002		~44-86	~9-37				

*Authors' calculations from results presented in the papers.

¹Abrantes-Metz et al. also report phase transition probabilities by therapeutic category.

²The DiMasi studies include only new chemical entities (NCEs), which is a classification roughly equivalent to the FDA's new molecular entities (NMEs).

Sources:

R. Abrantes-Metz et al., "Pharmaceutical Development Phases: A Duration Analysis," Working Paper No. 274, Bureau of Economics, Federal Trade Commission, 2004.

C. Adams and V. Brantner, "New Drug Development: Estimating Entry From Human Clinical Trials," Bureau of Economics, Federal Trade Commission, 2003.

A. Arora et al., "The Nature and the Extent of the Market for Technology in Biopharmaceuticals," Working Paper, European Pharmaceutical Regulation and Innovation Systems, 2000.

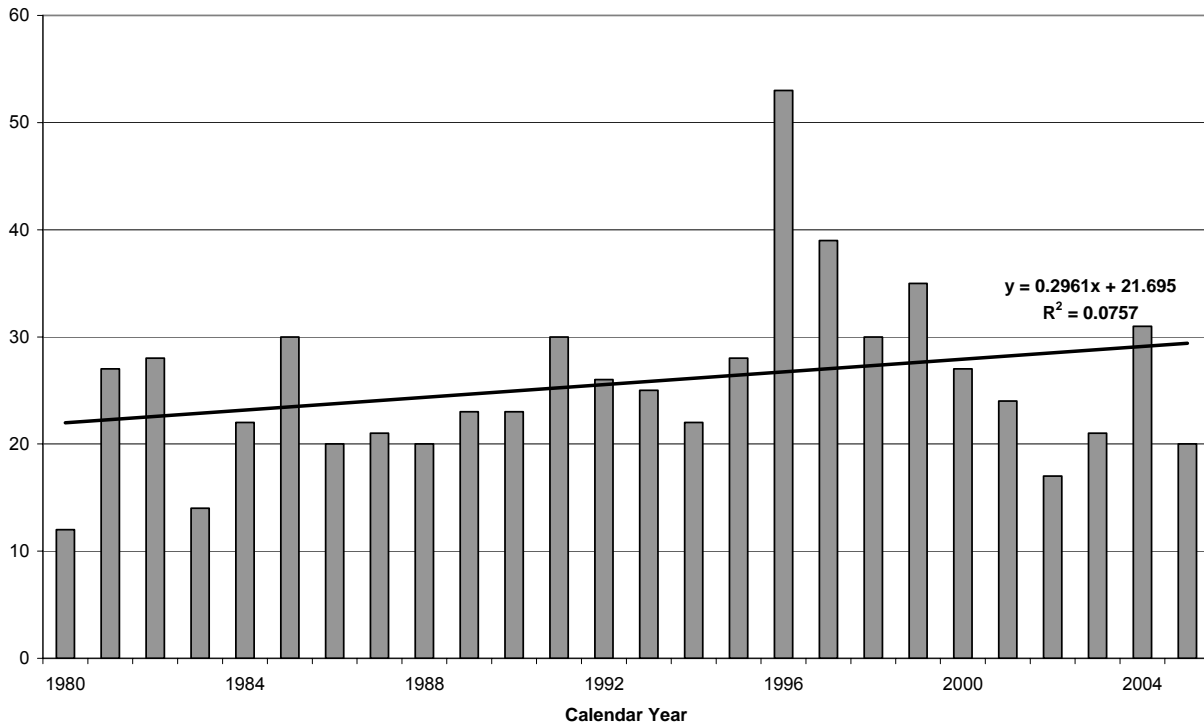
P. Danzon et al., "Productivity in Pharmaceutical-Biotechnology R&D: The Role of Experience and Alliances," NBER Working Paper, no. 9615 (2005).

J. A. DiMasi et al., "Research and Development Costs for New Drugs by Therapeutic Category: a Study of the U.S. Pharmaceutical Industry," *PharmacoEconomics* 7, no. 2 (1995): 152-169.

J. A. DiMasi, "Risks in New Drug Development: Approval Success Rates for Investigational Drugs," *Clinical Pharmacology & Therapeutics* 69, no. 5 (2001): 297-307.

J. A. DiMasi et al., "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics* 22, no. 2 (2003): 151-185.

Exhibit 2: NME Approvals 1980-2005



Sources:

- 1980-1992: Federal Drug Administration, "FDA Drug and Biologic Approvals—1992," January 8, 1993, <http://www.fda.gov/bbs/topics/ANSWERS/ANS00463.html>
- 1993-2003: Center for Drug Evaluation and Research, Federal Drug Administration, "Approval Times for Priority and Standard NMEs," <http://www.fda.gov/cder/rdmt/NMEapps93-04.htm>
- 2004: Center for Drug Evaluation and Research, Federal Drug Administration, "CDER New Molecular Entity (NME) and New Biologic Approvals in Calendar Year 2004," <http://www.fda.gov/cder/rdmt/nmecy2004.htm>
- 2005: Alex Berenson, "Drugs in '05: Much Promise Little Payoff," *New York Times*, January 11, 2006.

Exhibit 3: One-Year Transition Probabilities, by Year, Compared to Previous Year

Probabilities in bold are significantly different from probability in previous year at 95% confidence level (Chi-squared test).

Underlined probabilities are significantly less and non-underlined probabilities are significantly greater.

1996-1997

		1996									
		Failure	NDR	PI	PII	PIII	Preclin	Prereg	Success	Susp	Unknown
1997	Failure	0.987	0.009	0.026	0.032	0.049	0.010	0.030	0.000	0.029	0.036
	NDR	0.003	0.953	0.031	0.016	0.003	0.123	0.000	0.000	0.000	0.024
	PI	0.006	0.000	0.759	0.004	0.000	0.020	0.000	0.000	0.000	0.006
	PII	0.000	0.000	0.146	0.829	0.011	0.014	0.000	0.000	0.014	0.137
	PIII	0.001	0.000	0.017	0.094	0.786	0.001	0.010	0.000	0.000	0.036
	Preclin	0.001	0.030	0.000	0.003	0.000	0.827	0.010	0.000	0.000	0.018
	Prereg	0.000	0.000	0.002	0.004	0.108	0.000	0.515	0.006	0.000	0.006
	Success	0.000	0.000	0.007	0.001	0.022	0.000	0.426	0.994	0.000	0.018
	Susp	0.000	0.009	0.007	0.007	0.016	0.001	0.000	0.000	0.957	0.006
	Unknown	0.001	0.000	0.005	0.007	0.005	0.003	0.010	0.000	0.000	0.714

1997-1998

		1997									
		Failure	NDR	PI	PII	PIII	Preclin	Prereg	Success	Susp	Unknown
1998	Failure	0.990	0.009	0.016	0.059	0.029	0.021	0.023	0.003	0.113	0.051
	NDR	0.000	0.966	0.034	0.020	0.004	0.296	0.000	0.000	0.021	0.074
	PI	0.001	0.002	0.781	0.011	0.007	0.018	0.000	0.000	0.000	0.041
	PII	0.000	0.000	0.131	0.819	0.048	0.008	0.000	0.000	0.000	0.065
	PIII	0.003	0.000	0.010	0.061	0.782	0.002	0.008	0.000	0.000	0.032
	Preclin	0.003	0.023	0.012	0.005	0.000	0.649	0.000	0.000	0.000	0.041
	Prereg	0.001	0.000	0.002	0.005	0.075	0.000	0.570	0.003	0.000	0.005
	Success	0.000	0.000	0.000	0.003	0.037	0.000	0.398	0.990	0.000	0.000
	Susp	0.001	0.000	0.008	0.012	0.015	0.003	0.000	0.000	0.866	0.014
	Unknown	0.001	0.000	0.006	0.003	0.002	0.002	0.000	0.003	0.000	0.677

Testing the hypothesis that the 1997-98 transition matrix is not significantly different from the 1996-97 matrix

p-value < 0.0001

1998-1999

		1998									
		Failure	NDR	PI	PII	PIII	Preclin	Prereg	Success	Susp	Unknown
1999	Failure	0.986	0.009	0.032	0.031	0.084	0.028	0.019	0.002	0.083	0.021
	NDR	0.000	0.977	0.036	0.027	0.010	0.043	0.000	0.000	0.000	0.034
	PI	0.000	0.002	0.822	0.012	0.002	0.016	0.000	0.000	0.008	0.030
	PII	0.005	0.000	0.089	0.844	0.008	0.005	0.006	0.000	0.008	0.030
	PIII	0.002	0.000	0.002	0.064	0.764	0.002	0.006	0.005	0.000	0.013
	Preclin	0.002	0.010	0.013	0.002	0.000	0.900	0.000	0.002	0.017	0.021
	Prereg	0.001	0.000	0.000	0.008	0.098	0.000	0.683	0.000	0.000	0.013
	Success	0.000	0.000	0.000	0.002	0.016	0.001	0.273	0.986	0.000	0.009
	Susp	0.001	0.001	0.005	0.008	0.014	0.004	0.012	0.000	0.883	0.000
	Unknown	0.003	0.001	0.002	0.001	0.004	0.002	0.000	0.005	0.000	0.829

Testing the hypothesis that the 1998-99 transition matrix is not significantly different from the 1997-98 matrix

p-value < 0.0001

Exhibit 3, cont'd: One-Year Transition Probabilities, by Year

1999-2000

		1999									
		Failure	NDR	PI	PII	PIII	Preclin	Prereg	Success	Susp	Unknown
2000	Failure	0.988	0.029	0.043	0.061	0.069	0.019	0.038	0.000	0.101	0.046
	NDR	0.000	0.959	0.056	0.033	0.008	0.058	0.005	0.002	0.000	0.021
	PI	0.001	0.003	0.784	0.008	0.000	0.022	0.000	0.000	0.027	0.014
	PII	0.006	0.002	0.094	0.837	0.010	0.007	0.005	0.000	0.000	0.046
	PIII	0.003	0.001	0.009	0.048	0.813	0.001	0.019	0.002	0.007	0.014
	Preclin	0.002	0.005	0.007	0.005	0.000	0.885	0.000	0.002	0.027	0.011
	Prereg	0.000	0.000	0.000	0.002	0.071	0.000	0.627	0.003	0.000	0.007
	Success	0.000	0.000	0.000	0.000	0.021	0.000	0.292	0.990	0.000	0.004
	Susp	0.000	0.000	0.006	0.004	0.008	0.003	0.005	0.000	0.839	0.004
	Unknown	0.001	0.001	0.001	0.002	0.000	0.004	0.010	0.002	0.000	0.835

Testing the hypothesis that the 1999-00 transition matrix is not significantly different from the 1998-99 matrix
 p-value 0.0028

2000-2001

		2000									
		Failure	NDR	PI	PII	PIII	Preclin	Prereg	Success	Susp	Unknown
2001	Failure	0.994	0.070	0.062	0.054	0.093	0.051	0.034	0.000	0.231	0.023
	NDR	0.001	0.916	0.055	0.051	0.026	0.156	0.010	0.000	0.019	0.046
	PI	0.001	0.001	0.776	0.006	0.000	0.016	0.005	0.000	0.013	0.023
	PII	0.001	0.001	0.090	0.833	0.033	0.006	0.000	0.000	0.013	0.037
	PIII	0.001	0.000	0.004	0.036	0.764	0.000	0.010	0.001	0.000	0.034
	Preclin	0.001	0.012	0.000	0.001	0.002	0.765	0.005	0.000	0.000	0.029
	Prereg	0.000	0.000	0.000	0.003	0.067	0.000	0.721	0.001	0.006	0.009
	Success	0.000	0.000	0.000	0.001	0.007	0.000	0.216	0.997	0.000	0.006
	Susp	0.000	0.000	0.006	0.013	0.005	0.002	0.000	0.000	0.712	0.003
	Unknown	0.000	0.001	0.006	0.002	0.003	0.003	0.000	0.000	0.006	0.791

Testing the hypothesis that the 2000-01 transition matrix is not significantly different from the 1999-00 matrix
 p-value < 0.0001

2001-2002

		2001									
		Failure	NDR	PI	PII	PIII	Preclin	Prereg	Success	Susp	Unknown
2002	Failure	0.994	0.026	0.053	0.076	0.047	0.032	0.009	0.001	0.087	0.034
	NDR	0.000	0.964	0.137	0.110	0.059	0.341	0.009	0.000	0.000	0.140
	PI	0.001	0.003	0.703	0.015	0.002	0.019	0.000	0.001	0.007	0.031
	PII	0.002	0.003	0.073	0.750	0.010	0.002	0.009	0.000	0.027	0.045
	PIII	0.000	0.000	0.009	0.032	0.802	0.001	0.027	0.002	0.020	0.025
	Preclin	0.001	0.004	0.011	0.001	0.000	0.600	0.000	0.000	0.007	0.008
	Prereg	0.000	0.000	0.000	0.000	0.052	0.000	0.718	0.000	0.007	0.008
	Success	0.000	0.000	0.000	0.001	0.020	0.000	0.205	0.995	0.000	0.011
	Susp	0.000	0.000	0.011	0.013	0.005	0.004	0.023	0.000	0.846	0.003
	Unknown	0.000	0.000	0.005	0.001	0.003	0.001	0.000	0.000	0.000	0.696

Testing the hypothesis that the 2001-02 transition matrix is not significantly different from the 2000-01 matrix
 p-value < 0.0001

Exhibit 3, cont'd: One-Year Transition Probabilities, by Year

2002-2003

		<i>2002</i>									
		Failure	NDR	PI	PII	PIII	Preclin	Prereg	Success	Susp	Unknown
2003	Failure	0.990	0.031	0.053	0.066	0.043	0.049	0.009	0.000	0.032	0.030
	NDR	0.000	0.950	0.058	0.082	0.021	0.178	0.014	0.000	0.000	0.082
	PI	0.001	0.002	0.782	0.011	0.002	0.029	0.005	0.000	0.005	0.018
	PII	0.003	0.002	0.072	0.788	0.018	0.005	0.000	0.000	0.000	0.057
	PIII	0.001	0.001	0.014	0.029	0.793	0.001	0.014	0.000	0.021	0.033
	Preclin	0.003	0.013	0.001	0.001	0.002	0.722	0.000	0.001	0.011	0.018
	Prereg	0.000	0.000	0.001	0.002	0.076	0.000	0.698	0.001	0.000	0.021
	Success	0.000	0.000	0.000	0.002	0.027	0.000	0.255	0.998	0.000	0.006
	Susp	0.001	0.001	0.018	0.019	0.018	0.015	0.005	0.000	0.931	0.000
	Unknown	0.000	0.001	0.000	0.001	0.002	0.001	0.000	0.000	0.000	0.734

Testing the hypothesis that the 2002-03 transition matrix is not significantly different from the 2001-02 matrix
 p-value < 0.0001

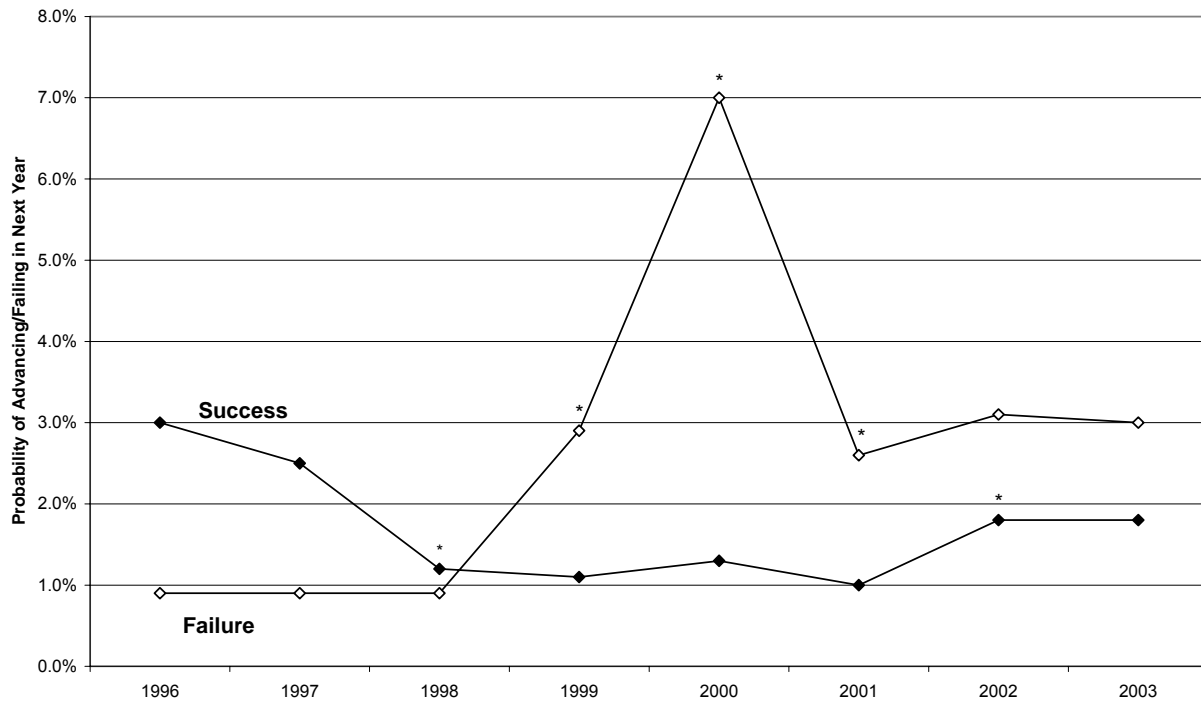
2003-2004

		<i>2003</i>									
		Failure	NDR	PI	PII	PIII	Preclin	Prereg	Success	Susp	Unknown
2004	Failure	0.993	0.030	0.044	0.062	0.052	0.040	0.050	0.001	0.052	0.051
	NDR	0.000	0.949	0.026	0.027	0.016	0.040	0.009	0.000	0.003	0.071
	PI	0.001	0.002	0.804	0.007	0.006	0.033	0.000	0.000	0.014	0.013
	PII	0.003	0.004	0.094	0.854	0.013	0.006	0.000	0.000	0.007	0.057
	PIII	0.001	0.001	0.006	0.034	0.777	0.002	0.027	0.000	0.021	0.027
	Preclin	0.002	0.010	0.009	0.002	0.000	0.871	0.005	0.000	0.014	0.013
	Prereg	0.000	0.000	0.001	0.001	0.089	0.000	0.658	0.001	0.003	0.007
	Success	0.000	0.000	0.000	0.000	0.030	0.000	0.239	0.998	0.000	0.000
	Susp	0.000	0.004	0.015	0.014	0.016	0.005	0.009	0.000	0.885	0.007
	Unknown	0.000	0.000	0.000	0.000	0.002	0.001	0.005	0.000	0.000	0.754

Testing the hypothesis that the 2003-04 transition matrix is not significantly different from the 2002-03 matrix
 p-value < 0.0001

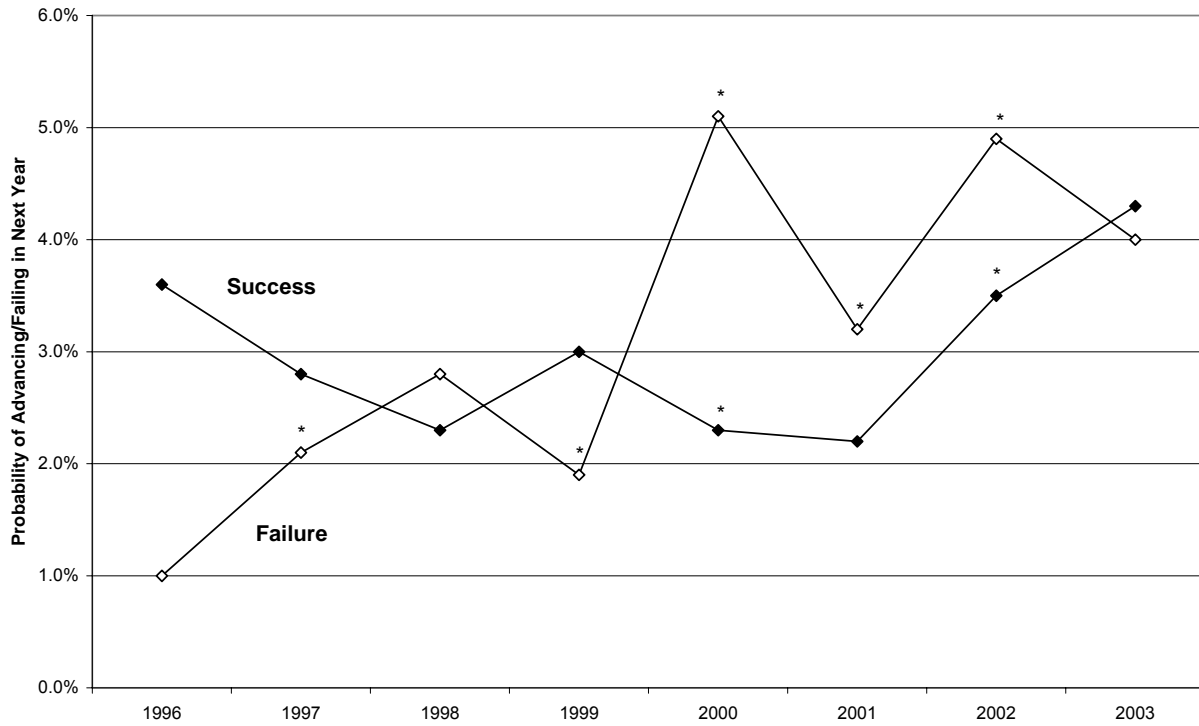
Sources: Adis International's R&D Insight drug database and authors' calculations.

Exhibit 4: One-Year Success and Failure Probabilities, NDR



"Success" is moving into any phase of active development in the next year. Points marked by an asterisk are significantly different from the probability in the previous year at a 95% confidence level.
Sources: Adis International's R&D Insight drug database and authors' calculations.

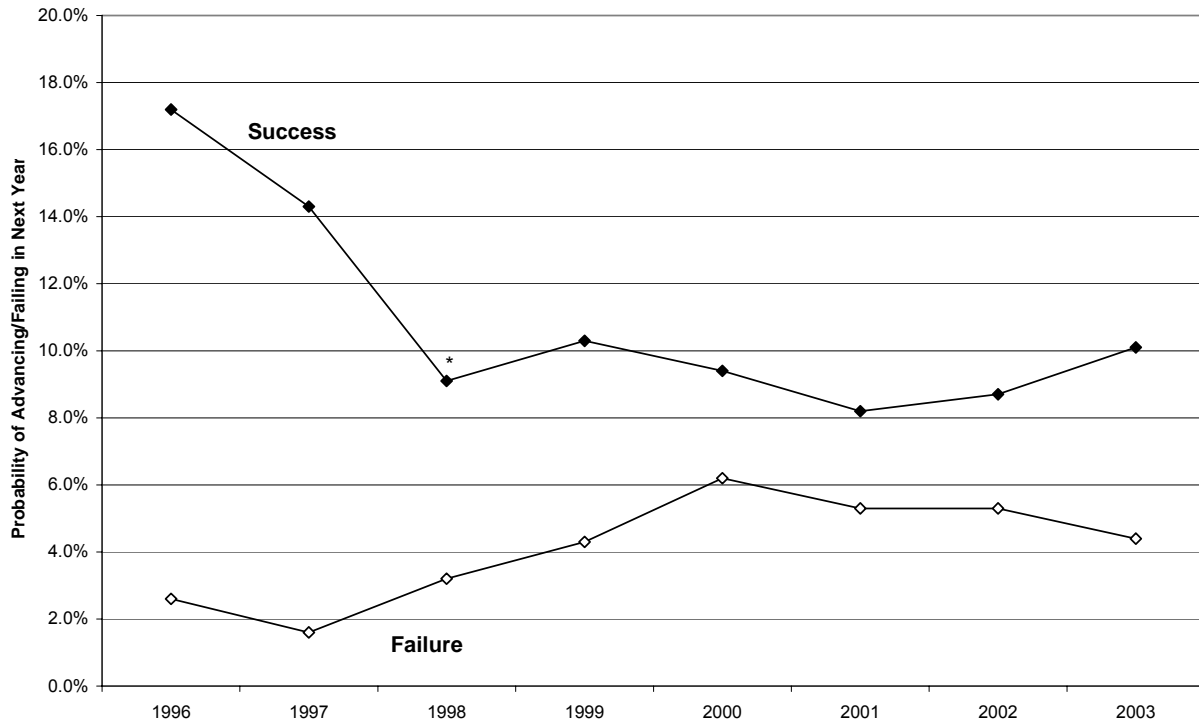
Exhibit 5: One-Year Success and Failure Probabilities, Preclinical



"Success" is advancing to a later stage of development in the next year. Points marked by an asterisk are significantly different from the probability in the previous year at a 95% confidence level.

Sources: Adis International's R&D Insight drug database and authors' calculations.

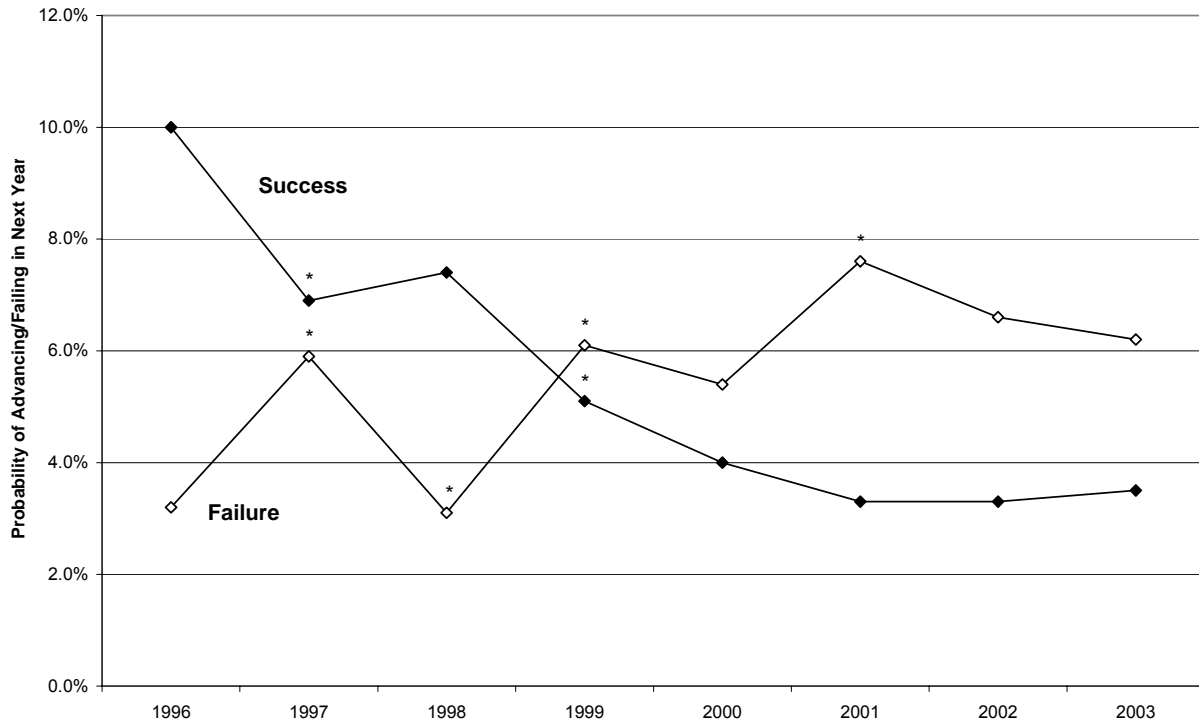
Exhibit 6: One-Year Success and Failure Probabilities, Phase I



"Success" is advancing to a later stage of development in the next year. Points marked by an asterisk are significantly different from the probability in the previous year at a 95% confidence level.

Sources: Adis International's R&D Insight drug database and authors' calculations.

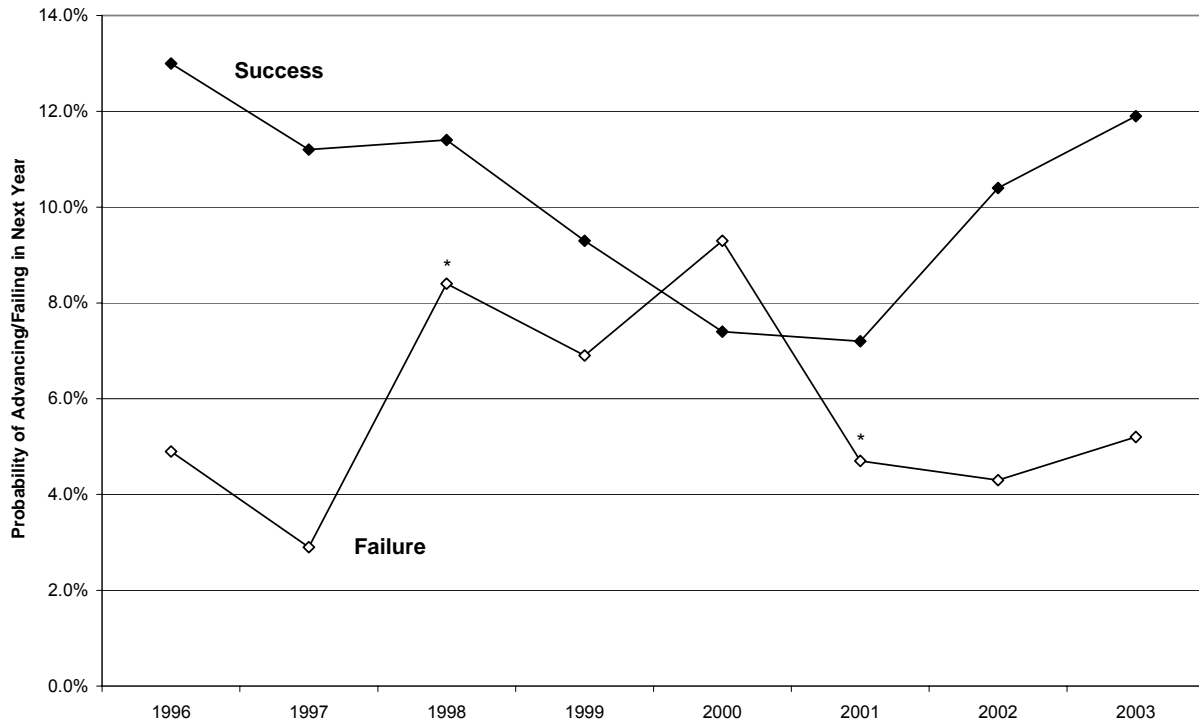
Exhibit 7: One-Year Success and Failure Probabilities, Phase II



"Success" is advancing to a later stage of development in the next year. Points marked by an asterisk are significantly different from the probability in the previous year at a 95% confidence level.

Sources: Adis International's R&D Insight drug database and authors' calculations.

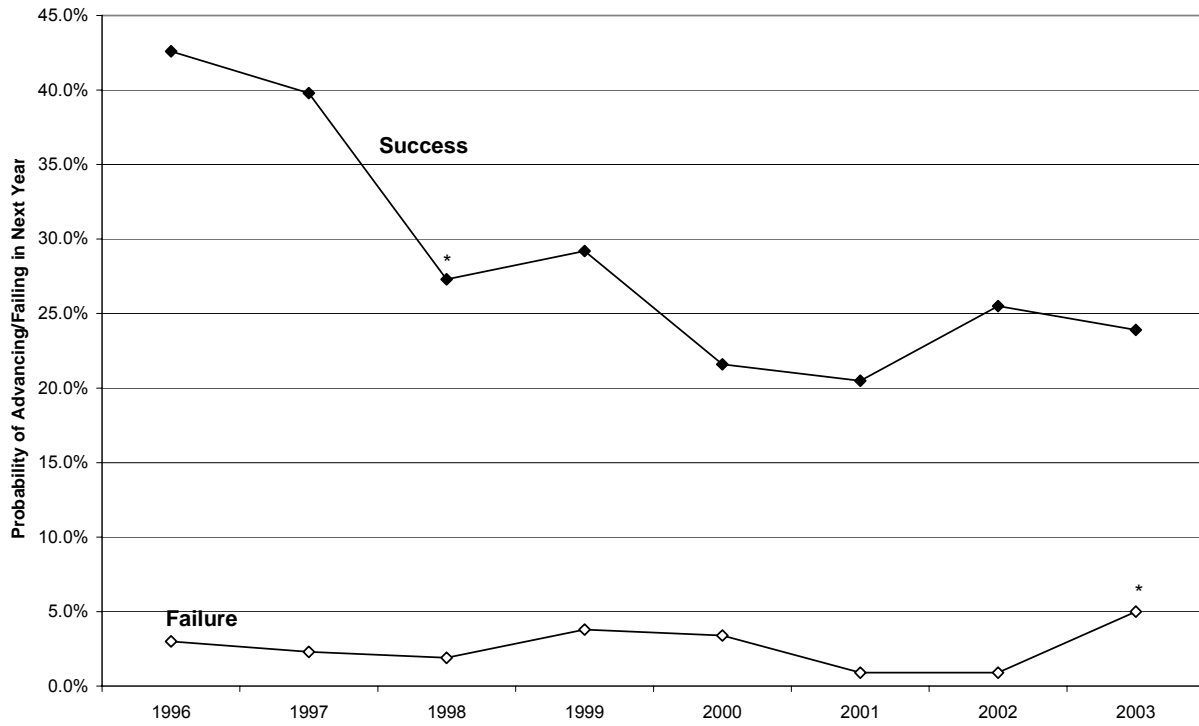
Exhibit 8: One-Year Success and Failure Probabilities, Phase III



"Success" is advancing to a later stage of development in the next year. Points marked by an asterisk are significantly different from the probability in the previous year at a 95% confidence level.

Sources: Adis International's R&D Insight drug database and authors' calculations.

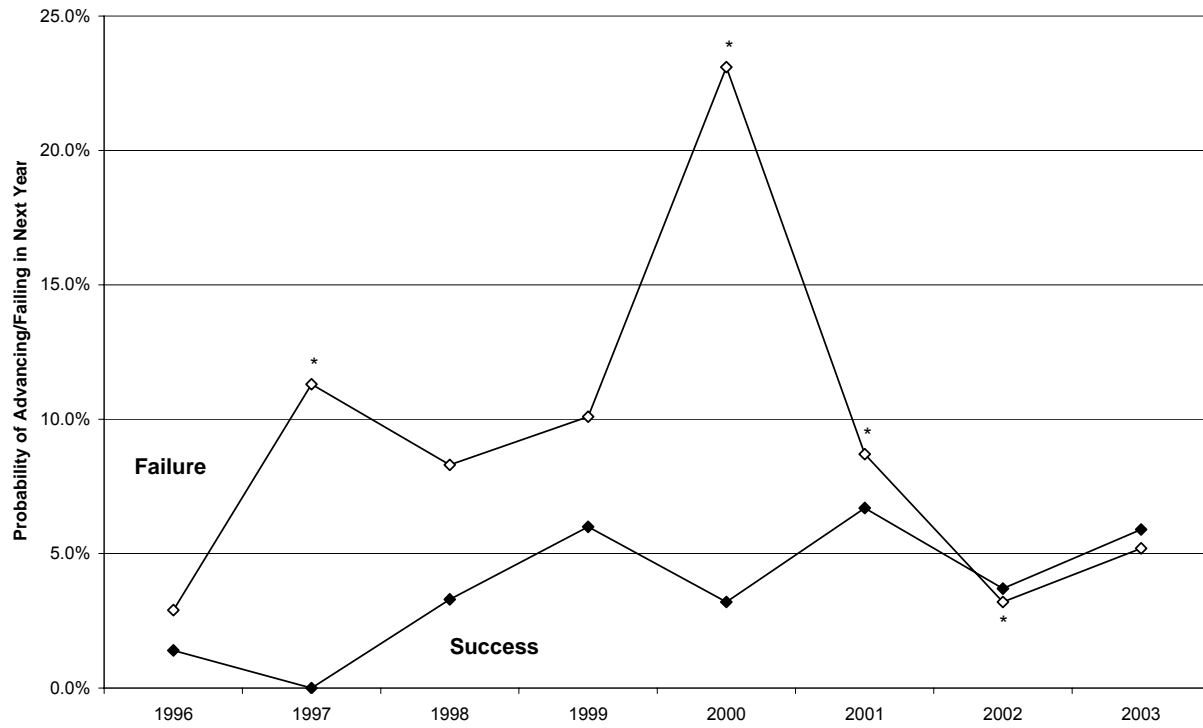
Exhibit 9: One-Year Success and Failure Probabilities, Preregistration



"Success" is advancing to a later stage of development in the next year. Points marked by an asterisk are significantly different from the probability in the previous year at a 95% confidence level.

Sources: Adis International's R&D Insight drug database and authors' calculations.

Exhibit 10: One-Year Success and Failure Probabilities, Suspended



"Success" is defined as moving into any phase of active development in the next year. Points marked by an asterisk are significantly different from the probability in the previous year at a 95% confidence level.
Sources: Adis International's R&D Insight drug database and authors' calculations.

Exhibit 11: Steady State Success Probabilities, Compared to Previous Year

Probabilities in bold are significantly different from probability in previous year at 95% confidence level (Chi-squared test).

Underlined probabilities are significantly less and non-underlined probabilities are significantly greater.

	1996	1997	1998	1999	2000	2001	2002	2003
NDR	0.151	<u>0.059</u>	0.061	<u>0.040</u>	<u>0.004</u>	0.014	0.030	0.047
Preclinical	0.199	<u>0.072</u>	0.089	<u>0.060</u>	<u>0.011</u>	0.016	0.042	0.064
Phase I	0.361	<u>0.207</u>	0.163	<u>0.101</u>	<u>0.045</u>	0.035	0.095	0.103
Phase II	0.413	<u>0.258</u>	0.274	<u>0.158</u>	<u>0.087</u>	<u>0.056</u>	0.115	0.136
Phase III	0.601	0.561	<u>0.453</u>	0.435	<u>0.268</u>	0.314	0.482	0.453
Preregistration	0.902	0.937	0.879	0.811	0.786	0.765	0.872	<u>0.740</u>
Suspended	0.138	<u>0.009</u>	0.044	0.045	0.026	0.086	0.162	0.135
Unknown	0.390	<u>0.171</u>	0.250	<u>0.155</u>	0.127	0.103	0.196	<u>0.128</u>

Testing the hypothesis that each year's steady state success rates are not significantly different from the previous year's

p-value		< 0.001	< 0.001	< 0.001	< 0.001	0.002	< 0.001	< 0.001
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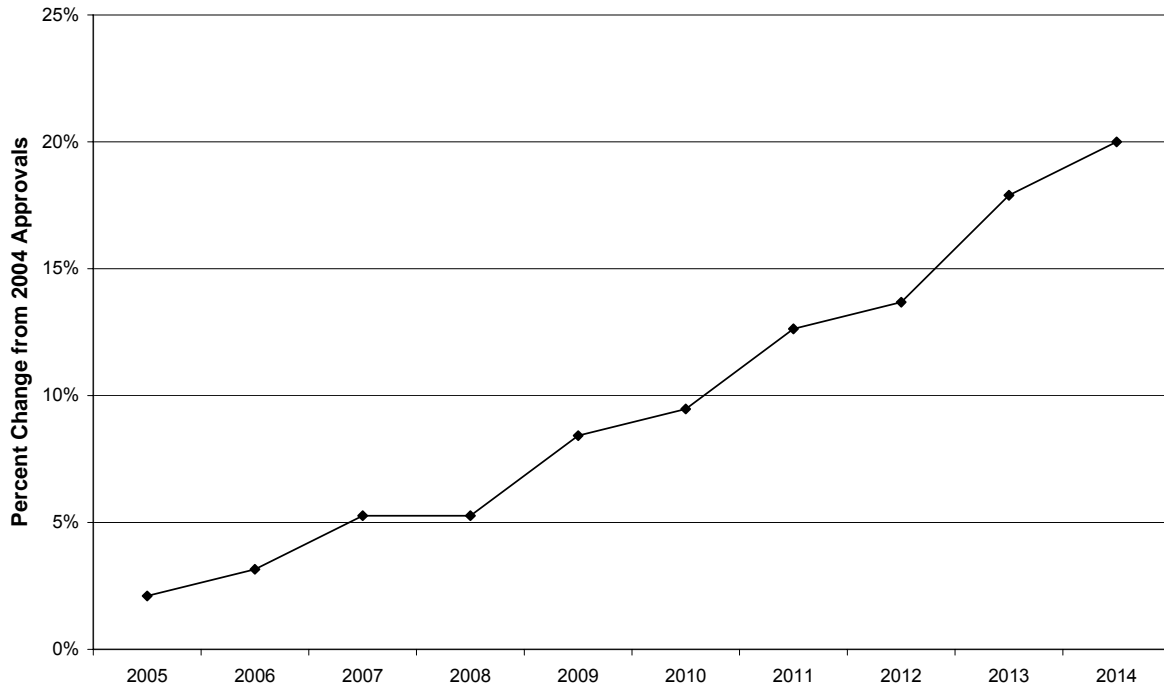
Sources: Adis International's R&D Insight drug database and authors' calculations.

Exhibit 12: Unconditional Probability of Success

1996	41.6%
1997	32.7%
1998	32.1%
1999	28.1%
2000	23.5%
2001	23.9%
2002	29.9%
2003	28.1%
All years	27.9%

Sources: Adis International's R&D Insight drug database and authors' calculations.

Exhibit 13: Predicted Drug Approvals 2005-2014, Relative to 2004 Approvals
2003-04 annual transition probabilities and annual inflow into pipeline applied to 2004 pipeline



Sources: Adis International's R&D Insight drug database and authors' calculations.

Appendix

A. Additional Methods

Matching observations

Exhibit 14 presents the number of observations in each year of the dataset. Using drug names to match projects between years does not work well because most drugs have many alternative names, because names often change as development progresses, and because one drug can be tested for many disease indications. Matching based on the number that Adis assigns each drug eliminates the problem of changing names, but not the problem of multiple indications. In other words, neither drug name nor drug number uniquely identify drug development projects.

The combination of the drug number and the disease indication also does not uniquely identify projects because approximately one percent of the observations in each year have identical numbers and indications. These “duplicate” projects typically have identical records in our dataset—same drug name, disease indication, developing company, mechanism of action, etc.—except for the phase of development. They must differ in ways not recorded in our dataset, such as route of administration or dosage.

The results of ignoring the duplicates and merging observations based on drug number and disease indication are presented in Exhibit 15 and Exhibit 17. In each year, a considerable number of development projects cannot be matched, ranging from 3.8 percent of the projects in 2002 and 2003 to 11.0 percent in 2000 (Exhibit 17). In some cases, the problem preventing matches is easy to correct, while in other cases, it is impossible. We made the following changes:

1. Over time, some disease indication names had slight spelling changes. For example, “dry eye” became “dry eyes” and “diabetic ulcers” became “diabetic ulcer.” Other disease indication names were replaced with synonyms. For example, “back ache” became “back pain,”

“septicaemia” became “sepsis,” and “insulin-dependent diabetes mellitus” became “type 1 diabetes mellitus.” We standardized all indications to their 2004 names.

2. We matched the duplicate projects through time if the phases of development allowed us to unambiguously distinguish the two projects. For example, if in year 1, a project was in Phase II and in year 2, the project was listed in both Phase I and Phase II, we matched the two Phase II projects. In other words, we did not assume that drugs moved backwards in the development pipeline. On the other hand, if in year 1, a project was in Phase I and in year 2, the project was listed in both Phase I and Phase II, the situation was ambiguous and we could not match any of the projects.

3. These two edits fixed a significant percentage of the mismatches. We then analyzed the remaining unmatched projects one by one. In some cases, the disease indication changed but was similar enough that we assumed it was the same project. For example, drugs became more specific: a drug that was being developed for cancer in one year but lung cancer the next year was counted as a match. Drugs also became more general: a drug that was being developed for Alzheimer’s disease in one year but dementia in the next year was also counted as a match.

Sometimes these specificity changes were more complicated. A drug that became more specific might have created several new projects. For example, a drug developed for bacterial infections in one year might be developed for respiratory tract infections and urinary tract infections in the next year. In that case, we matched the project in the first year to the project in the next year that came first alphabetically. The reverse situation also occurred—a drug developed for several types of infection became more general and was developed only for “bacterial infections” in the following year. In these cases, we matched the project in the second year to the project in the first year that came first alphabetically.

Exhibit 16 and Exhibit 17 show the results of these edits. While some projects still remain unmatched, it is far fewer than before the edits, ranging from 1.6 percent of observations in 2002 to 4.8 percent in 1997 (Exhibit 17). Some projects remain unmatched because development moved outside the U.S. and thus outside the scope of our study. Other projects seem to disappear, either because their disease indication changed so dramatically that we could not confidently assume it was still the same project, or for no reason that we could detect. We asked Adis about some of the disappearances we could not explain, and their explanations suggest that a lack of public information and quirks in the drug development process are the source of our matching difficulties. For example, for one drug, Adis explained, “There are 6 entries in the database under this product name. In the mid 1990’s based on the information available, we may have had a single profile that covered some of these and as more information became available, we differentiated the compounds.”¹⁵

Significance testing

The significance of changes in these probabilities over time was tested with chi-squared tests and logistic regressions—chi-squared tests for comparing one probability in one year to the same probability in another year, and regressions for comparing all probabilities in one year to all probabilities in another year. The key was to think of the probabilities as the means of indicator variables. For example, to compare the 1996-1997 and 1997-1998 Phase I to Phase II transition probabilities, all Phase I observations in 1996 were assigned a 1 if they moved to Phase II in the next year, and a 0 otherwise. The same variable was created for all Phase I observations in 1997. These two indicator variables were then compared using a chi-squared test.

To compare all transition probabilities in 1996-1997 and 1997-1998, for example, an

¹⁵ Correspondence with Adis, 24 March 2005.

indicator variable was constructed in each year to describe the transitions of all observations. This variable was the dependent variable in the logistic regression, and the independent variables were dummy variables for each phase and interactions between the phase dummies and year dummies. A joint test for the significance of the interaction variables revealed whether the transition matrices for the two years were significantly different.

B. Additional results

One-year transition probabilities, compared to 2003-2004 (Exhibit 18)

Data for Exhibits 4-10 (Exhibits 19 and 20)

One-year success rates, compared to 2003-2004 (Exhibit 21)

One-year failure rates, compared to 2003-2004 (Exhibit 22)

Steady state success probabilities, compared to 2003-2004 (Exhibit 23)

Alternative assumptions for future projections (Exhibit 24)

Exhibit 14: Number of Observations in Adis Dataset, Before Making Transition Matrices

	1996	1997	1998	1999	2000	2001	2002	2003	2004
Failure	678	790	977	1,183	1,461	2,016	2,423	2,878	3,339
NDR	235	533	1,296	1,441	1,654	2,284	3,975	4,551	4,533
Preclinical	2,086	2,500	2,574	3,295	4,140	4,132	3,316	3,417	4,093
Phase I	436	554	644	740	814	904	903	1,026	1,215
Phase II	707	958	1,099	1,291	1,400	1,534	1,464	1,469	1,645
Phase III	387	486	507	549	605	606	647	648	647
Preregistration	103	138	164	221	213	228	219	226	231
Success	188	306	452	616	758	826	912	1,022	1,117
Suspended	75	97	120	151	161	151	191	289	342
Unknown	179	239	251	305	374	376	351	326	255
Total	5,074	6,601	8,084	9,792	11,580	13,057	14,401	15,852	17,417

Sources: Adis International R&D Insight drug database and authors' calculations.

Exhibit 15: Number of Observations in Adis Dataset, for One-Year Transition Matrices, Unedited

	1996	1997	1998	1999	2000	2001	2002	2003
Failure	648	769	955	1,121	1,376	1,984	2,380	2,837
NDR	231	515	1,265	1,341	1,547	2,268	3,915	4,518
Preclinical	1,978	2,323	2,452	3,040	3,663	3,959	3,173	3,222
Phase I	391	460	590	633	695	812	841	948
Phase II	634	830	1,013	1,130	1,247	1,459	1,390	1,394
Phase III	345	416	465	482	513	566	602	598
Preregistration	95	111	145	185	171	204	193	206
Success	165	272	404	556	651	779	859	947
Suspended	68	96	117	141	144	145	182	283
Unknown	155	203	221	258	303	346	321	289
Total	4,710	5,995	7,627	8,887	10,310	12,522	13,856	15,242

Sources: Adis International R&D Insight drug database and authors' calculations.

Exhibit 16: Number of Observations in Adis Dataset, for One-Year Transition Matrices, Edited

	1996	1997	1998	1999	2000	2001	2002	2003
Failure	667	785	972	1,175	1,446	2,009	2,413	2,867
NDR	234	528	1,286	1,420	1,637	2,280	3,955	4,528
Preclinical	2,032	2,399	2,515	3,187	4,020	4,014	3,227	3,289
Phase I	419	502	617	699	786	855	873	990
Phase II	678	880	1,066	1,226	1,364	1,495	1,436	1,444
Phase III	369	454	499	518	581	596	628	631
Preregistration	101	128	161	209	208	220	212	222
Success	181	295	435	600	746	822	911	1,015
Suspended	70	97	120	149	156	149	189	286
Unknown	168	217	234	284	350	358	331	297
Total	4,919	6,285	7,905	9,467	11,294	12,798	14,175	15,569

Sources: Adis International R&D Insight drug database and authors' calculations.

Exhibit 17: Unmatched Observations for One-Year Transition Matrices

Unedited (Exhibit 14)

	1996	1997	1998	1999	2000	2001	2002	2003
Failure	30	21	22	62	85	32	43	41
NDR	4	18	31	100	107	16	60	33
Preclinical	108	177	122	255	477	173	143	195
Phase I	45	94	54	107	119	92	62	78
Phase II	73	128	86	161	153	75	74	75
Phase III	42	70	42	67	92	40	45	50
Preregistration	8	27	19	36	42	24	26	20
Success	23	34	48	60	107	47	53	75
Suspended	7	1	3	10	17	6	9	6
Unknown	24	36	30	47	71	30	30	37
Total	364	606	457	905	1,270	535	545	610
Percent	7.2%	9.2%	5.7%	9.2%	11.0%	4.1%	3.8%	3.8%

Edited (Exhibit 15)

	1996	1997	1998	1999	2000	2001	2002	2003
Failure	11	5	5	8	15	7	10	11
NDR	1	5	10	21	17	4	20	23
Preclinical	54	101	59	108	120	118	89	128
Phase I	17	52	27	41	28	49	30	36
Phase II	29	78	33	65	36	39	28	25
Phase III	18	32	8	31	24	10	19	17
Preregistration	2	10	3	12	5	8	7	4
Success	7	11	17	16	12	4	1	7
Suspended	5	0	0	2	5	2	2	3
Unknown	11	22	17	21	24	18	20	29
Total	155	316	179	325	286	259	226	283
Percent	3.1%	4.8%	2.2%	3.3%	2.5%	2.0%	1.6%	1.8%

Sources: Adis International R&D Insight drug database and authors' calculations.

Exhibit 18: One-Year Transition Probabilities, by Year, Compared to 2003-04

Probabilities in bold are significantly different from probability in previous year at 95% confidence level (Chi-squared test).

Underlined probabilities are significantly less and non-underlined probabilities are significantly greater.

1996-1997

		1996									
		Failure	NDR	PI	PII	PIII	Preclin	Prereg	Success	Susp	Unknown
1997	Failure	0.987	0.009	0.026	<u>0.032</u>	0.049	<u>0.010</u>	0.030	0.000	0.029	0.036
	NDR	0.003	0.953	0.031	0.016	0.003	0.123	0.000	0.000	0.000	<u>0.024</u>
	PI	0.006	0.000	0.759	0.004	0.000	<u>0.020</u>	0.000	0.000	0.000	0.006
	PII	0.000	0.000	0.146	0.829	0.011	0.014	0.000	0.000	0.014	0.137
	PIII	0.001	0.000	0.017	0.094	0.786	0.001	0.010	0.000	0.000	0.036
	Preclin	0.001	0.030	<u>0.000</u>	0.003	0.000	<u>0.827</u>	0.010	0.000	0.000	0.018
	Prereg	0.000	0.000	0.002	0.004	0.108	0.000	<u>0.515</u>	0.006	0.000	0.006
	Success	0.000	0.000	0.007	0.001	0.022	0.000	0.426	0.994	0.000	0.018
	Susp	0.000	0.009	0.007	0.007	0.016	<u>0.001</u>	0.000	0.000	0.957	0.006
	Unknown	0.001	0.000	0.005	0.007	0.005	0.003	0.010	0.000	0.000	0.714

Testing the hypothesis that the 1996-97 transition matrix is not significantly different from the 2003-04 matrix

p-value < 0.0001

1997-1998

		1997									
		Failure	NDR	PI	PII	PIII	Preclin	Prereg	Success	Susp	Unknown
1998	Failure	0.990	<u>0.009</u>	<u>0.016</u>	0.059	0.029	<u>0.021</u>	0.023	0.003	0.113	0.051
	NDR	0.000	0.966	0.034	0.020	0.004	0.296	0.000	0.000	0.021	0.074
	PI	0.001	0.002	0.781	0.011	0.007	<u>0.018</u>	0.000	0.000	0.000	0.041
	PII	0.000	0.000	0.131	<u>0.819</u>	0.048	0.008	0.000	0.000	0.000	0.065
	PIII	0.003	0.000	0.010	0.061	0.782	0.002	0.008	0.000	0.000	0.032
	Preclin	0.003	0.023	0.012	0.005	0.000	<u>0.649</u>	0.000	0.000	0.000	0.041
	Prereg	0.001	0.000	0.002	0.005	0.075	0.000	0.570	0.003	0.000	0.005
	Success	0.000	0.000	0.000	0.003	0.037	0.000	0.398	<u>0.990</u>	0.000	0.000
	Susp	0.001	0.000	0.008	0.012	0.015	0.003	0.000	0.000	0.866	0.014
	Unknown	0.001	0.000	0.006	0.003	0.002	0.002	0.000	0.003	0.000	0.677

Testing the hypothesis that the 1997-98 transition matrix is not significantly different from the 2003-04 matrix

p-value < 0.0001

1998-1999

		1998									
		Failure	NDR	PI	PII	PIII	Preclin	Prereg	Success	Susp	Unknown
1999	Failure	<u>0.986</u>	<u>0.009</u>	0.032	<u>0.031</u>	0.084	<u>0.028</u>	0.019	0.002	0.083	0.021
	NDR	0.000	0.977	0.036	0.027	0.010	0.043	0.000	0.000	0.000	0.034
	PI	0.000	0.002	0.822	0.012	0.002	<u>0.016</u>	0.000	0.000	0.008	0.030
	PII	0.005	<u>0.000</u>	0.089	0.844	0.008	0.005	0.006	0.000	0.008	0.030
	PIII	0.002	0.000	0.002	0.064	0.764	0.002	0.006	0.005	0.000	0.013
	Preclin	0.002	0.010	0.013	0.002	0.000	0.900	0.000	0.002	0.017	0.021
	Prereg	0.001	0.000	0.000	0.008	0.098	0.000	0.683	0.000	0.000	0.013
	Success	0.000	0.000	0.000	0.002	0.016	0.001	0.273	<u>0.986</u>	0.000	0.009
	Susp	0.001	0.001	0.005	0.008	0.014	0.004	0.012	0.000	0.883	0.000
	Unknown	0.003	0.001	0.002	0.001	0.004	0.002	0.000	0.005	0.000	0.829

Testing the hypothesis that the 1998-99 transition matrix is not significantly different from the 2003-04 matrix

p-value < 0.0001

Exhibit 18, cont'd: One-Year Transition Probabilities, by Year, Compared to 2003-04

1999-2000

		1999									
	Failure	NDR	PI	PII	PIII	Preclin	Prereg	Success	Susp	Unknown	
2000	Failure	0.988	0.029	0.043	0.061	0.069	0.019	0.038	0.000	0.101	0.046
	NDR	0.000	0.959	0.056	0.033	0.008	0.058	0.005	0.002	0.000	0.021
	PI	0.001	0.003	0.784	0.008	0.000	0.022	0.000	0.000	0.027	0.014
	PII	0.006	0.002	0.094	0.837	0.010	0.007	0.005	0.000	0.000	0.046
	PIII	0.003	0.001	0.009	0.048	0.813	0.001	0.019	0.002	0.007	0.014
	Preclin	0.002	0.005	0.007	0.005	0.000	0.885	0.000	0.002	0.027	0.011
	Prereg	0.000	0.000	0.000	0.002	0.071	0.000	0.627	0.003	0.000	0.007
	Success	0.000	0.000	0.000	0.000	0.021	0.000	0.292	0.990	0.000	0.004
	Susp	0.000	0.000	0.006	0.004	0.008	0.003	0.005	0.000	0.839	0.004
	Unknown	0.001	0.001	0.001	0.002	0.000	0.004	0.010	0.002	0.000	0.835

Testing the hypothesis that the 1999-00 transition matrix is not significantly different from the 2003-04 matrix
p-value < 0.0001

2000-2001

		2000									
	Failure	NDR	PI	PII	PIII	Preclin	Prereg	Success	Susp	Unknown	
2001	Failure	0.994	0.070	0.062	0.054	0.093	0.051	0.034	0.000	0.231	0.023
	NDR	0.001	0.916	0.055	0.051	0.026	0.156	0.010	0.000	0.019	0.046
	PI	0.001	0.001	0.776	0.006	0.000	0.016	0.005	0.000	0.013	0.023
	PII	0.001	0.001	0.090	0.833	0.033	0.006	0.000	0.000	0.013	0.037
	PIII	0.001	0.000	0.004	0.036	0.764	0.000	0.010	0.001	0.000	0.034
	Preclin	0.001	0.012	0.000	0.001	0.002	0.765	0.005	0.000	0.000	0.029
	Prereg	0.000	0.000	0.000	0.003	0.067	0.000	0.721	0.001	0.006	0.009
	Success	0.000	0.000	0.000	0.001	0.007	0.000	0.216	0.997	0.000	0.006
	Susp	0.000	0.000	0.006	0.013	0.005	0.002	0.000	0.000	0.712	0.003
	Unknown	0.000	0.001	0.006	0.002	0.003	0.003	0.000	0.000	0.006	0.791

Testing the hypothesis that the 2000-01 transition matrix is not significantly different from the 2003-04 matrix
p-value < 0.0001

2001-2002

		2001									
	Failure	NDR	PI	PII	PIII	Preclin	Prereg	Success	Susp	Unknown	
2002	Failure	0.994	0.026	0.053	0.076	0.047	0.032	0.009	0.001	0.087	0.034
	NDR	0.000	0.964	0.137	0.110	0.059	0.341	0.009	0.000	0.000	0.140
	PI	0.001	0.003	0.703	0.015	0.002	0.019	0.000	0.001	0.007	0.031
	PII	0.002	0.003	0.073	0.750	0.010	0.002	0.009	0.000	0.027	0.045
	PIII	0.000	0.000	0.009	0.032	0.802	0.001	0.027	0.002	0.020	0.025
	Preclin	0.001	0.004	0.011	0.001	0.000	0.600	0.000	0.000	0.007	0.008
	Prereg	0.000	0.000	0.000	0.000	0.052	0.000	0.718	0.000	0.007	0.008
	Success	0.000	0.000	0.000	0.001	0.020	0.000	0.205	0.995	0.000	0.011
	Susp	0.000	0.000	0.011	0.013	0.005	0.004	0.023	0.000	0.846	0.003
	Unknown	0.000	0.000	0.005	0.001	0.003	0.001	0.000	0.000	0.000	0.696

Testing the hypothesis that the 2001-02 transition matrix is not significantly different from the 2003-04 matrix
p-value < 0.0001

Exhibit 18, cont'd: One-Year Transition Probabilities, by Year, Compared to 2003-04

2002-2003

		<i>2002</i>									
		Failure	NDR	PI	PII	PIII	Preclin	Prereg	Success	Susp	Unknown
2003	Failure	0.990	0.031	0.053	0.066	0.043	0.049	0.009	0.000	0.032	0.030
	NDR	0.000	0.950	0.058	0.082	0.021	0.178	0.014	0.000	0.000	0.082
	PI	0.001	0.002	0.782	0.011	0.002	0.029	0.005	0.000	0.005	0.018
	PII	0.003	0.002	0.072	0.788	0.018	0.005	0.000	0.000	0.000	0.057
	PIII	0.001	0.001	0.014	0.029	0.793	0.001	0.014	0.000	0.021	0.033
	Preclin	0.003	0.013	0.001	0.001	0.002	0.722	0.000	0.001	0.011	0.018
	Prereg	0.000	0.000	0.001	0.002	0.076	0.000	0.698	0.001	0.000	0.021
	Success	0.000	0.000	0.000	0.002	0.027	0.000	0.255	0.998	0.000	0.006
	Susp	0.001	0.001	0.018	0.019	0.018	0.015	0.005	0.000	0.931	0.000
	Unknown	0.000	0.001	0.000	0.001	0.002	0.001	0.000	0.000	0.000	0.734

Testing the hypothesis that the 2002-03 transition matrix is not significantly different from the 2003-04 matrix
 p-value < 0.0001

2003-2004

		<i>2003</i>									
		Failure	NDR	PI	PII	PIII	Preclin	Prereg	Success	Susp	Unknown
2004	Failure	0.993	0.030	0.044	0.062	0.052	0.040	0.050	0.001	0.052	0.051
	NDR	0.000	0.949	0.026	0.027	0.016	0.040	0.009	0.000	0.003	0.071
	PI	0.001	0.002	0.804	0.007	0.006	0.033	0.000	0.000	0.014	0.013
	PII	0.003	0.004	0.094	0.854	0.013	0.006	0.000	0.000	0.007	0.057
	PIII	0.001	0.001	0.006	0.034	0.777	0.002	0.027	0.000	0.021	0.027
	Preclin	0.002	0.010	0.009	0.002	0.000	0.871	0.005	0.000	0.014	0.013
	Prereg	0.000	0.000	0.001	0.001	0.089	0.000	0.658	0.001	0.003	0.007
	Success	0.000	0.000	0.000	0.000	0.030	0.000	0.239	0.998	0.000	0.000
	Susp	0.000	0.004	0.015	0.014	0.016	0.005	0.009	0.000	0.885	0.007
	Unknown	0.000	0.000	0.000	0.000	0.002	0.001	0.005	0.000	0.000	0.754

Sources: Adis International's R&D Insight drug database and authors' calculations.

Exhibit 19**Data for Exhibits 4-10, pt. 1: One-Year Success Probabilities (Probability of Advancing in Next Year)**

Probabilities in bold are significantly different from probability in previous year at 95% confidence level (Chi-squared test).

Underlined probabilities are significantly less and non-underlined probabilities are significantly greater.

	1996	1997	1998	1999	2000	2001	2002	2003
NDR*	0.030	0.025	<u>0.012</u>	0.011	0.013	0.010	0.018	0.018
Preclinical	0.036	0.028	0.023	0.030	<u>0.023</u>	0.022	0.035	0.043
Phase I	0.172	0.143	<u>0.091</u>	0.103	0.094	0.082	0.087	0.101
Phase II	0.100	<u>0.069</u>	0.074	<u>0.051</u>	0.040	0.033	0.033	0.035
Phase III	0.130	0.112	0.114	0.093	0.074	0.072	0.104	0.119
Preregistration	0.426	0.398	<u>0.273</u>	0.292	0.216	0.205	0.255	0.239
Suspended*	0.014	0.000	0.033	0.060	0.032	0.067	0.037	0.059

Testing the hypothesis that each year's success rates are not significantly different from the previous year's rates

p-value		0.109	0.017	0.089	0.073	0.677	0.007	0.460
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* For NDR and Suspended, "success" is defined as moving into any phase of active development, i.e., Preclinical, Phase I, Phase II, Phase III, Preregistration, or Success.

Sources: Adis International's R&D Insight drug database and authors' calculations.

Exhibit 20

Data for Exhibits 4-10, pt. 2: One-Year Failure Probabilities (Probability of Failing in Next Year)

Probabilities in bold are significantly different from probability in previous year at 95% confidence level (Chi-squared test).

Underlined probabilities are significantly less and non-underlined probabilities are significantly greater.

	1996	1997	1998	1999	2000	2001	2002	2003
NDR	0.009	0.009	0.009	0.029	0.070	<u>0.026</u>	0.031	0.030
Preclinical	0.010	0.021	0.028	<u>0.019</u>	0.051	<u>0.032</u>	0.049	0.040
Phase I	0.026	0.016	0.032	0.043	0.062	0.053	0.053	0.044
Phase II	0.032	0.059	<u>0.031</u>	0.061	0.054	0.076	0.066	0.062
Phase III	0.049	0.029	0.084	0.069	0.093	<u>0.047</u>	0.043	0.052
Preregistration	0.030	0.023	0.019	0.038	0.034	0.009	0.009	0.050
Suspended	0.029	0.113	0.083	0.101	0.231	<u>0.087</u>	<u>0.032</u>	0.052
Unknown	0.036	0.051	0.021	0.046	0.023	0.034	0.030	0.051

Testing the hypothesis that each year's failure rates are not significantly different from the previous year's rates

p-value		0.004	0.000	0.004	< 0.001	< 0.001	0.006	0.098
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Sources: Adis International's R&D Insight drug database and authors' calculations.

Exhibit 21: One-Year Success Probabilities, Compared to 2003-04

Probabilities in bold are significantly different from probability in previous year at 95% confidence level (Chi-squared test). Underlined probabilities are significantly less and non-underlined probabilities are significantly greater.

	1996	1997	1998	1999	2000	2001	2002	2003
NDR*	0.030	0.025	0.012	0.011	0.013	<u>0.010</u>	0.018	0.018
Preclinical	0.036	<u>0.028</u>	<u>0.023</u>	<u>0.030</u>	<u>0.023</u>	<u>0.022</u>	0.035	0.043
Phase I	0.172	0.143	0.091	0.103	0.094	0.082	0.087	0.101
Phase II	0.100	0.069	0.074	0.051	0.040	0.033	0.033	0.035
Phase III	0.130	0.112	0.114	0.093	<u>0.074</u>	<u>0.072</u>	0.104	0.119
Preregistration	0.426	0.398	0.273	0.292	0.216	0.205	0.255	0.239
Suspended*	0.014	<u>0.000</u>	0.033	0.060	0.032	0.067	0.037	0.059

Testing the hypothesis that each year's success rates are not significantly different from the 2003-04 rates

p-value < 0.001 < 0.001 < 0.001 0.025 < 0.001 < 0.001 0.460

* For NDR and Suspended, "success" is defined as moving into any phase of active development, i.e., Preclinical, Phase I, Phase II, Phase III, Preregistration, or Success.

Sources: Adis International's R&D Insight drug database and authors' calculations.

Exhibit 22: One-Year Failure Probabilities, Compared to 2003-04

Probabilities in bold are significantly different from probability in previous year at 95% confidence level (Chi-squared test). Underlined probabilities are significantly less and non-underlined probabilities are significantly greater.

	1996	1997	1998	1999	2000	2001	2002	2003
NDR	0.009	<u>0.009</u>	<u>0.009</u>	0.029	0.070	0.026	0.031	0.030
Preclinical	<u>0.010</u>	<u>0.021</u>	<u>0.028</u>	<u>0.019</u>	0.051	<u>0.032</u>	0.049	0.040
Phase I	0.026	<u>0.016</u>	0.032	0.043	0.062	0.053	0.053	0.044
Phase II	<u>0.032</u>	0.059	<u>0.031</u>	0.061	0.054	0.076	0.066	0.062
Phase III	0.049	0.029	0.084	0.069	0.093	0.047	0.043	0.052
Preregistration	0.030	0.023	0.019	0.038	0.034	<u>0.009</u>	<u>0.009</u>	0.050
Suspended	0.029	0.113	0.083	0.101	0.231	0.087	0.032	0.052
Unknown	0.036	0.051	0.021	0.046	0.023	0.034	0.030	0.051

Testing the hypothesis that each year's failure rates are not significantly different from the 2003-04 rates

p-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.033	0.098	
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Sources: Adis International's R&D Insight drug database and authors' calculations.

Exhibit 23: Steady State Success Probabilities, Compared to 2003-04

Probabilities in bold are significantly different from probability in previous year at 95% confidence level (Chi-squared test).
Underlined probabilities are significantly less and non-underlined probabilities are significantly greater.

	1996	1997	1998	1999	2000	2001	2002	2003
NDR	0.151	0.059	0.061	0.040	<u>0.004</u>	<u>0.014</u>	<u>0.030</u>	0.047
Preclinical	0.199	0.072	0.089	0.060	<u>0.011</u>	<u>0.016</u>	<u>0.042</u>	0.064
Phase I	0.361	0.207	0.163	0.101	<u>0.045</u>	<u>0.035</u>	0.095	0.103
Phase II	0.413	0.258	0.274	0.158	<u>0.087</u>	<u>0.056</u>	0.115	0.136
Phase III	0.601	0.561	0.453	0.435	<u>0.268</u>	<u>0.314</u>	0.482	0.453
Preregistration	0.902	0.937	0.879	0.811	0.786	0.765	0.872	0.740
Suspended	0.138	<u>0.009</u>	<u>0.044</u>	<u>0.045</u>	<u>0.026</u>	0.086	0.162	0.135
Unknown	0.390	0.171	0.250	0.155	0.127	0.103	0.196	0.128

Testing the hypothesis that each year's steady state success rates are not significantly different from the 2003-04 rates

p-value < 0.001 < 0.001 < 0.001 0.032 < 0.001 < 0.001 < 0.001

Sources: Adis International's R&D Insight drug database and authors' calculations.

Exhibit 24: Projected Observations in Adis Dataset, 2005-2014: Alternative Assumptions

2002-2004 average transition probabilities and 2002-2004 average inflow

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Failure	3,339	3,867	4,426	5,014	5,630	6,271	6,936	7,623	8,332	9,061	9,808
NDR	4,533	4,911	5,302	5,701	6,105	6,510	6,914	7,315	7,712	8,103	8,487
Preclin	4,093	1,340	1,450	1,545	1,628	1,700	1,764	1,821	1,872	1,917	1,958
PI	1,215	1,725	1,805	1,882	1,957	2,029	2,098	2,164	2,228	2,288	2,346
PII	1,645	655	668	683	701	720	741	763	785	807	830
PIII	647	4,317	4,503	4,659	4,790	4,904	5,002	5,088	5,165	5,234	5,297
Prereg	231	234	236	240	243	248	253	258	264	270	276
Success	1,117	1,223	1,330	1,437	1,546	1,656	1,768	1,881	1,996	2,112	2,231
Susp	342	426	509	591	672	750	826	899	971	1,040	1,107
Unknown	255	223	200	184	173	165	159	156	154	153	153
Approvals	95	106	107	107	109	110	112	113	115	116	119
% higher than 2004		11.6%	12.6%	12.6%	14.7%	15.8%	17.9%	18.9%	21.1%	22.1%	25.3%

2003-2004 transition probabilities and 1999-2004 average inflow

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Failure	3,339	3862	4423	5019	5649	6310	7001	7719	8462	9231	10021
NDR	4,533	4569	4631	4716	4820	4939	5072	5215	5368	5527	5692
Preclin	4,093	1318	1422	1522	1619	1711	1798	1880	1957	2029	2096
PI	1,215	1814	1975	2127	2272	2411	2544	2671	2792	2908	3019
PII	1,645	668	694	723	755	788	822	856	890	923	957
PIII	647	4601	5049	5443	5790	6098	6371	6614	6831	7025	7200
Prereg	231	241	250	259	268	277	287	297	308	318	328
Success	1,117	1237	1361	1488	1617	1749	1884	2022	2164	2308	2456
Susp	342	401	461	521	581	640	698	755	811	866	919
Unknown	255	257	259	261	264	266	269	271	274	276	279
Approvals	95	120	124	127	129	132	135	138	142	144	148
% higher than 2004		26.3%	30.5%	33.7%	35.8%	38.9%	42.1%	45.3%	49.5%	51.6%	55.8%

1998-2004 average transition probabilities and 1999-2004 average inflow

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Failure	3,339	3865	4421	5007	5621	6260	6924	7612	8321	9050	9800
NDR	4,533	5074	5621	6170	6716	7258	7793	8319	8835	9340	9835
Preclin	4,093	1246	1277	1308	1338	1366	1393	1419	1443	1466	1488
PI	1,215	1731	1810	1883	1950	2012	2071	2126	2178	2227	2274
PII	1,645	677	707	735	764	791	817	842	866	889	911
PIII	647	4261	4401	4519	4620	4706	4782	4849	4909	4963	5012
Prereg	231	241	252	262	272	281	290	299	308	316	324
Success	1,117	1233	1352	1473	1598	1724	1853	1985	2118	2253	2390
Susp	342	365	389	412	435	457	478	499	519	538	556
Unknown	255	276	294	309	322	334	344	354	362	370	377
Approvals	95	116	119	121	125	126	129	132	133	135	137
% higher than 2004		22.1%	25.3%	27.4%	31.6%	32.6%	35.8%	38.9%	40.0%	42.1%	44.2%

Sources: Adis International's R&D Insight drug database and authors' calculations.