FINANCIAL MODEL OF THE DRUG DEVELOPMENT PROCESS

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Financial Model of the Drug Development Process
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ABSTRACT

This document is a description of a financial model of pharmaceutical research and development. The model is in the form of a large spreadsheet (approximately 2,700 pages) which is on file with Professor Stewart Myers. The model is a Monte Carlo simulation of the drug lifecycle from discovery until three years into the off-patent period. A research program is formed from a portfolio of these projects and operated for forty years. The model allows for investigations into the start-up, steady-state, and wind-down stages of a research program. Investigations, currently underway, involve the testing of new accounting rules for the pharmaceutical industry, the calculation of the cost of capital for the research and development phase of the drug lifecycle, and the cost of bringing a drug to market.

Thesis Supervisor: Professor Stewart Myers

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1 Introduction

1.1 Measures of Financial Performance
The drug development process is like looking for gold or oil. Large expenditures are made in a research and development program that experiences a high rate of project failure. Most of the drug projects never make it to the market and are canceled during the development process. Production and marketing costs for an individual drug represent a small fraction of the total revenue. It is therefore difficult to assess whether a particular company is abusing the monopoly power granted to its products through patent or represents a lucky outlier in a politically acceptable industry distribution. The losers of this process go bankrupt and are removed from the public eye.

Current accounting practice exacerbates these perception problems. In the pharmaceutical industry, investment purchases intellectual resources and proprietary technology. A reporting process based on fixed assets and production costs is systematically incorrect when applied to this technology driven industry.

Accounting is like the law. It evolves. The software industry faced similar issues. What is the intrinsic value of a software program? The answer is none, if no one wants to buy it. The value is not necessarily proportional to the degree of investment. The intellectual content is the key and that is difficult to measure before a market evaluation. However, capitalization rules were developed for this industry.

The model developed, as part of this thesis, allows the study of possible accounting rules that might be implemented. This work is an ongoing research project headed by Professor Paul Healy. This model has been used by Professor Myers to study the cost of capital appropriate for drug projects in development and a financial definition of the “true cost of a drug” using a Zero NPV at project inception as the basis.

1.2 Cost of Capital and the Opportunity Cost of Drug
The operation of a research program requires a financial commitment with expenditures, which do not vary with the macroeconomic environment. There is a discontinuity between the systematic or macroeconomic risk (i.e. beta) of the revenue stream and the investment required to bring a drug to
Financial Model of the Drug Discovery Process

market. The cash flows from the revenues and for marketing and production are variable and subject to the non-diversifiable risk of the market place. These cash flows should be discounted at a rate that reflects the non-diversifiable risk. The expenditures for bringing a successful drug to market are subject to technical risk but not beta risk. These expenditures are largely fixed relative to the market and are discounted at a lower rate. The technical risks of pharmaceutical development are significant, but these risks are fully diversified.

Discounting the expenses of bringing a drug to market at a lower rate than the revenues and operational cash results in a cost of capital curve for a drug project that is high in the early phases of development, dropping to lower levels as the project moves forward to the market. This is based on modern finance theory and does not reflect an adaptation of the discount rate to compensate for the technical risk of drug development. The shape of cost of capital curve suggests that application of discount rates obtained from the stock return of mature companies to expenditures in the development phase of a drug is inappropriate.

1.3 Simulation of a Research Program

Previous studies of the pharmaceutical industry have used models based on a single “average” drug and have focused on the costs and probabilities of bringing a successful drug to market. These methods account for the nature of the development cycle in terms of the number of canceled projects and the expense of financing these expenditures until a drug reaches the market place, but ignores start up and overhead expenses. In addition these studies do not provide any insight into methods of evaluating company performance. The reported data is for an average successful drug. The distribution of performance is not available.

A research program was selected as the basic unit of analysis. This choice allows for a more sophisticated analysis of overhead charges and program level research expenditures, not possible in the previous studies. The expenditures required to start a research program are included in this program level analysis.

Net Present Value is used as the intrinsic measure of investment performance. This Net Present Value analysis includes the variation of the cost of capital, not properly evaluated in the previous studies.

The significant technical risk and the inability to predict the outcome at each of the milestones for any specific drug lead to a wide variation of possible corporate performance. This raises questions about the ability of government or any external body to properly judge the impact of any particular company on the greater social good. The number of companies relative to the possible outcomes is small. The marketplace tends to eliminate the non-performing companies, which, of course, skews the available empirical data. It is important to assess the contribution of an industry as a whole and not focus on just a few top-performing firms that might just represent the top tail of the distribution.

1.4 Monte Carlo Analysis

Monte Carlo simulation is a method of analysis that involves the creation of a model and iteration. Each time the model is calculated input data is drawn from a predetermined distribution. After each calculation, the relevant output data are collected. The data is stored and analyzed after the experiment. A single experiment could involve as many as 10,000 iterations to properly develop the output distributions. This is a very powerful method of evaluating the effect of the variation of many simultaneously changing inputs to a complex system. The method yields not only the expected values, but also the distribution.

This method also helps establish data and model integrity. The quality of the output is still dependent on the accuracy of the input data. The amplification of an error is not eliminated using this technique, but the implications of the data are readily seen in the distribution of output. This output distribution can then be compared to the distribution of empirical data. The comparison of distributions is a more powerful check than just average values. This allows for more rigorous testing of the model and data, which improves the integrity of the completed model and the conclusions drawn from its use.

2 Model Overview

The model itself is based on a portfolio of drug candidates. The distribution of outcomes is caused by the variation in success at each of several technical milestones in the development path and the probability of competitive entry or the discovery of a new formulation when the drug is in the market.
These lotteries are all calculated the same way. A random number is generated and compared to threshold values to determine the outcome. As an example, suppose the success probability of moving past some milestone is 0.80. A random number is generated by the worksheet. If the number is less than 0.80 then the drug candidate moves to the next phase. If the number is greater than 0.80 then the project is canceled.

The variation of the model output is based on the possible events in the lifecycle of a drug. The number projects at any given time and at any stage of development will vary with each iteration of the simulation, as will the characteristics of drug candidates themselves.

The financial implications of these events are looked up in a table prepared from calculations of all the possible outcomes in a drug's lifecycle using expected value techniques. These calculations are performed before the simulation is run using input data that characterizes the performance of the program. I refer to this as the generation of the program and the simulation as the operation of the program. The data looked up are based on the outcome of the drug candidates and drugs in the portfolio are placed into a table where they can be summarized by year of program operation.

3 Research and Development

3.1 Stages of R&D

Discovery Research

This activity includes all the resources directly applied to investigations into biological systems, the identification of a target (e.g. cellular or intracellular receptor), the type of interaction required for pharmaceutical efficacy ("turn-on", "turn-off", or "block"), the development of a method of identifying or generating a compound that works, and the identification of that compound. These compounds commonly referred to as "hits" generally bind weakly to the target. The discovery strategy whether, rational design, high throughput screening of natural or combinatorial libraries, traditional recombinant technologies or a composite of several approaches, is not specified. Discovery ends with the identification of a hit.
Pre-clinical testing

In this model, the activities usually identified as "late stage research "or" lead developments are combined with the lead testing process in a single three-year phase. The hit is optimized for activity. The medicinal chemist also directs the design to generate leads with highest probability of success in the testing process. Pre-clinical testing includes:

- Bio-availability determination
- Pharmacokinetic studies
- Toxicity Testing

In addition to developing and evaluating the compound, a process for production needs to be developed and a pilot production plant must be built that conforms to the Good Manufacturing Practice (GMP) requirements of the Food and Drug Administration (FDA). An Investigational New Drug (IND) must be prepared for submission to the FDA. The FDA approval of the IND ends the pre-clinical phase of our model.

Clinical Testing

The regulatory environment defines clinical trials. We will present cursory descriptions of the phases of testing. Long-term animal testing often overlaps the clinical trial process. We took the estimates of the cost of this testing from DiMasi (1991) and allocated these expenses to phase II and phase III expenditures.

Phase I: This is a one-year study that evaluates the safety of a compound by testing in healthy humans.

Phase II: Phase II testing is conducted over a two-year period, and evaluates the safety and efficacy of a compound in a small, well-controlled human sample.

Phase III: This is the largest human study required for FDA approval. The sample is still controlled, but the compound is applied to a much more diverse sample. This phase is three years long in the model.

Filing: The results of the clinical trials, the history and methods used in the discovery, development and production are compiled into the New Drug Application (NDA). The NDA is submitted to the FDA. We have allotted three years for the FDA to approve or reject a drug. We do not allow additional testing on any compound rejected by the FDA.
3.2 R&D-Expenditure Classifications

Each of the research and development phases has three classifications for expenditures.

- Research
- Capital Expenditures
- Administration

The expenditures in the discovery phase occur each year, independent of the actual number of drug projects generated; however, in the remaining phases expenditures occur only for drugs that have not failed at a phase decision point for scientific or technical reasons.

There are also outlays for ongoing research, defined as expenditures toward finding new dosage forms and indications for patent protected drugs. The FDA can require clinical trials be continued into the marketing phase of a drug. These expenditures are considered ongoing research. In summary, ongoing research supports drugs that are already in the marketplace.

**Research**

Research expenses include the salaries and benefits for the technical staff working directly on projects. An example would be a Ph.D. researcher and the laboratory technicians reporting to that person. The supplies consumed by the group and any outside technical support required (e.g. assay support).

**Capital Expenditures**

Capital expenditures in the development phase are for laboratory instrumentation, analytical equipment, and facility modification. The development of information systems and computationally intensive activities (e.g. data mining or molecular modeling) are included. In recent years, the advances in rational design (computational chemistry, nuclear magnetic resonance, crystallography), the emergence of combinatorial chemistry, and high-throughput screening have increased the levels of capital required to support research and development. Capital expenditures are required for development and testing of each drug candidate. Depreciation of capital expenditures is tracked on a tax and book basis.

The development and construction of the GMP facility to produce a compound for trials are included in these expenditures. The construction of
the production facility to supply the market, however, is not included in this category.

There is also one initial $100 million outlay to build the facilities for the research program. This is included in the program costs, which are discussed separately.

**Administrative**

Administration includes only the administrative and management costs within each drug project. Corporate overhead is handled at the program level. Regulatory compliance is a major component of this expense classification.

**Property Plant & Equipment**

This includes all the capital expenditures required to build a GMP production facility and maintain it for the life of the drug. The expenditures are based on the market success of the drug (sales ten years after launch) with an adjustment for economies of scale. Half of the total expenditures are made in the two years prior to launch. (Further expansion of this facility is assumed unnecessary.) The remaining half of the total is allocated evenly over the first ten years of the marketing phase. The purpose of these expenditures is capital maintenance, replacing equipment, etc.

**3.3 Sources of Data**

The expenditures for R&D including both clinical and preclinical phases are based on the data in J. DiMasi et al. The data used in this study were collected on self-originated New Chemical Entities (NCE) from 12 pharmaceutical firms. The sample was restricted to NCEs tested in humans between 1970 - 1982.

The format of the data generated by the DiMasi study required transformation for use by the model. The DiMasi data was based on the concept of an average drug project. The model is constructed as a portfolio of drug projects managed within a research program. Using Monte Carlo methods and this structure allows us to look at the performance of the research program over time and yields the distribution of project outcomes in addition to the

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expected of average project result. This required the definition of project phases and classes of expenditures that were more detailed than in the DiMasi Study.

We obtained information from industry and used our best judgement to define these parameters. We adjusted them through iteration until the data conformed not only to the DiMasi data but data for the Industry as well.

**Preclinical Expenditures**

The model is formulated to imitate the traditional pharmaceutical paradigm.

1. Screening of compounds against a disease model generates “hits”

2. The hits are optimized for efficacy and safety, yielding a fewer number of “leads”

3. The leads are evaluated through preclinical testing and if promising, are advanced into Clinical Testing.

This project begins with thousands of compounds in the screening phase. The number entering Clinical Trials for will be less than four, given our level of annual R & D expenditures. The model is in the form of an Excel spreadsheet and the problem of tracking thousands of compounds is logistically impossible. We reduced the data set by having four possible projects. The cost and the probabilities are increased for the discovery and preclinical testing phases, converging in both number and level of total expenditure with the DiMasi study by the start of clinical testing.

**Demonstration of DiMasi Correspondence: Preclinical Costs**

The size of research programs varies, but research productivity can be used as a benchmark. DiMasi states that the expected cost for preclinical development is $65.5 million (1987) for each approved New Chemical Entity (NCE) with a duration of 42.6 months (3.55 years).

The model allows one year for discovery, which can occur at any point during the year (expected value: 0.5 years). The Preclinical Testing phase lasts for three years, yielding a preclinical duration for the model of 3 years (The minimum increment for model phases is one year.) The duration of the total preclinical work is the same as that in the DiMasi study.

Proving the equality of the expenditure levels per approved drug requires a calculation, which includes both the success probabilities and the level of
expenditure per drug project per year. The logic of the calculation is as follows.

The product of the success probabilities yields the expected number of approved drugs generated by the program each year of program operation.

1. The product of the success probability of discovery and the number of possible projects (4) yields expected number of drugs which move into the preclinical testing phase each year. Since the phase itself lasts for three years then the expected number of drug projects per year of program operation is three times the expected number entering the phase. The level of expenditures equals the product of the number of drug projects in the phase and the expenditures per project per year of program operation.

2. The input for discovery expenditures is in dollars per year of program operation. No adjustment is required.

3. The total level of preclinical expenditures per year is the sum of the discovery and preclinical testing calculations.

4. Dividing the total preclinical expenditures per year by the number of approved drugs per year yields the level of preclinical expenditures per approved drug.

5. Adjustment for inflation is also required.
FINANCIAL MODEL OF THE DRUG DISCOVERY PROCESS

I have summarized the calculations for the model in 1994 dollars in the table below.

<table>
<thead>
<tr>
<th>Description</th>
<th>Preclinical Research</th>
<th>Clinical Testing &amp; Regulatory Approval</th>
<th>Cumulative Amounts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preclinical Testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>1 year</td>
<td>3 years</td>
<td>6 years</td>
</tr>
<tr>
<td>Success Probability</td>
<td>60 %</td>
<td>90 %</td>
<td>24 %</td>
</tr>
<tr>
<td>Expected Projects (number per year)</td>
<td>Maximum of 4 projects generated per year</td>
<td>7.2</td>
<td>0.516</td>
</tr>
<tr>
<td>Expenditures per year (1994, Millions)</td>
<td>$8.73</td>
<td>$33.55</td>
<td>$42.28</td>
</tr>
</tbody>
</table>

Expenditures per Approved Drug: $81.87

Adjusting the DiMasi figure of $65.5 million 1987 dollars by the GDP deflator (1.25) yields $81.9 million per approved drug. This matches the figure given in the table above.

Clinical Expenditures and FDA Approval

The DiMasi study not only divided the clinical and regulatory period into Phase I, Phase II, Phase III, and FDA Review, as was done in the model, but also tracked long term and other animal studies which occur in parallel with Phases II and III. In addition, DiMasi did not allocate any expenditure to the FDA Review period, in contrast to the model. DiMasi reports expenditures on a per approved drug basis in 1987 dollars.
Demonstration of DiMasi Correspondence: Clinical Costs & FDA Filing

The animal trial costs were allocated to the model's Phase II and III expenditures per project per year using the expected number of drugs in each phase per approved drug as an adjustment factor. This is very similar to the treatment of the preclinical data. In addition, the expenditures for Phase III and FDA Filing were combined in the to form a number equivalent to the DiMasi data. The following numbers are all in 1994 dollars. The DiMasi data was adjusted using a GDP implicit deflator of 1.25.

The expected number of drug projects entering Phase I trials per year of program operation is 2.4 times the success probability of Preclinical testing (90%), yielding 2.16 Drugs per year in Phase I. From the previous calculation, the expected number of approved drugs per year of program operation is 0.516. I took the inputs from the model and calculated the costs on a per approved drug basis. I subtracted the allocated cost of animal testing and the result is compared to the DiMasi data in 1994 dollars.
<table>
<thead>
<tr>
<th>Description</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>FDA Filing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>75 %</td>
<td>50 %</td>
<td>85 %</td>
<td>75 %</td>
</tr>
<tr>
<td>Expected projects (number per year)</td>
<td>2.16</td>
<td>3.24</td>
<td>2.43</td>
<td>2.07</td>
</tr>
<tr>
<td>Expenditures per year (1994, Millions)</td>
<td>$ 6.0</td>
<td>$ 3.24</td>
<td>$ 14.63</td>
<td>$ 2.28</td>
</tr>
<tr>
<td>Animal Testing per Approved Drug</td>
<td>$ 3.9</td>
<td>$ 2.92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DiMasi: Expenditures per approved drug (1994, Millions)</td>
<td>$ 11.62</td>
<td>$ 16.125</td>
<td>$ 25.25</td>
<td>0</td>
</tr>
<tr>
<td>Description</td>
<td>Phase I</td>
<td>Phase II</td>
<td>Phase III</td>
<td>FDA Filing</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------</td>
<td>----------</td>
<td>-----------</td>
<td>------------</td>
</tr>
<tr>
<td>Model: Duration</td>
<td>1 year</td>
<td>2 years</td>
<td>3 years</td>
<td>3 years</td>
</tr>
<tr>
<td>DiMasi: Duration</td>
<td>1.3 years</td>
<td>2.0 years</td>
<td>3.0 years</td>
<td>2.5 years</td>
</tr>
</tbody>
</table>

| Percent of drugs entering Phase I that also enters each successive Phase. |
|----------------------|---------|----------|-----------|------------|------------|
| Description          | Phase I | Phase II | Phase III | FDA Filing | Cumulative |
| Model: Probability of entering Phase | 100 % | 75 %     | 37.5 %    | 31.9 %     | 23.9 %     |
| DiMasi: Probability of entering Phase | 100 % | 75 %     | 36.2 %    | 36.2 %     | 23 %       |

The expenditures per phase per year normalized by program size are in good agreement with the DiMasi study.

4  Marketplace

4.1 Revenue Pattern

The model uses five separate revenue profiles, one for each drug quality. The profiles are based on the revenue projection from Grabowski and Vernon (1993). The curves are based on decile data with the Breakthrough and Above Average based on the first and second decile. The Median data was used for an average drug. The Below Average and Dog curves were not directly obtained but were scaled from the Above Average Curve using the ratio of the NPV of the ninth and tenth decile to NPV of an Above Average drug. The Grabowski and Vernon data was adjusted for inflation.
4.2 Competition and New Indications

The management of competitive entry and new indications in the financial modeling of drug revenues is without precedent in the literature. The effect on the NPV of a drug is conservative with a reduction in value on average compared to the model without these influences.

The model has the capability of varying the probability of competitive entry or the discovery of a new indication with the Drug Quality, the position of the drug in its lifecycle, and the number of existing participants in the market. The maximum number of indications or competitors is limited to three. The incremental addition is based on a lottery with the success probability obtained from a data table.

The effect of the number of indications/competitors is incorporated into the revenue for an individual drug. Revenue is increased for new indications and reduced for competitors. The mathematical formulation is based on the product of the baseline revenue and two factors raised to the power of the number of new indications and competitors. The factor for new indications is greater than zero and increases the product with each new indication. The competitive factor is less than Zero, which decreases the revenue with the number of competitors.

4.3 Cost Assumptions

The manufacturing and marketing expenses are also expressed as a percent of revenue. This is our most reliable scaling method. When evaluating the level of manufacturing expenditure, keep in mind that property, plant, and equipment depreciation is handled separately.

Marketing

Marketing expense calculated as a percent of revenue. The percentage decreases over the drug lifecycle.

Manufacturing

The manufacturing cost is a percentage of revenue and does not vary over the production life of a product.

Working Capital

The working capital is calculated as a percentage of revenue.
5 R&D Management & Overhead

It is at this level where we access the costs of managing and maintaining a research program. The level of corporate involvement is included and the direct management staff required to operate a program of this size. Also included in this category are functions, which are cross-project, but cannot be allocate to any one project.

The Expenditures at this level fall into three categories:

- **Startup Expenditure:**
  Includes both an expense and capital amounts

- **General and Administrative Expenses (G&A)**

- **Ongoing Research**
  1. Supports drugs in the marketplace and
  2. Ongoing regulatory requirements,
  3. Discovery of new indications/dosage forms.
     Varies with the number of drugs in the market up to a cap.

The Program level expenditures do not vary with the number of projects (ongoing research usually equals the maximum value). The evaluation of overhead is based on these program level expenditures.
6 Accounting

6.1 Asset Treatment and Classification

Book and tax depreciation

<table>
<thead>
<tr>
<th>Description</th>
<th>Asset Category</th>
<th>Book Depreciation</th>
<th>Tax Depreciation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Capital Expenditures</td>
<td>Init Cap</td>
<td>15-year Straight-line</td>
<td>10-year Accelerated</td>
</tr>
<tr>
<td>Capital Equipment for R&amp;D</td>
<td>Res Cap</td>
<td>5-year Straight-line</td>
<td>5-year Accelerated</td>
</tr>
<tr>
<td>Property, Plant &amp; Equipment</td>
<td>PP&amp;E</td>
<td>12-year Straight-line</td>
<td>7-year Accelerated</td>
</tr>
</tbody>
</table>

Capital Equipment for use in research (Res Cap Goods)
This classification is for assets that have a short life span due to obsolescence or a limited life span. The expenditures for research equipment and computing are all included in this asset class. This category of asset has both tax and book records maintained in model. Currently the model uses a five-year straight-line schedule for book depreciation and a five-year accelerated schedule for the tax depreciation.

Property Plant and Equipment (PP&E)
This classification applies to the assets required to produce a drug, including the facility, the equipment, and any capital maintenance required by the production process. The model maintains a 12-year straight-line schedule and a seven-year accelerated table for tax purposes.

Initial Capital Investment (Init Cap)
This is the asset classification for the expenditures required to build and outfit the facility. The model maintains both a 15-year straight-line schedule for book depreciation and a ten-year accelerated schedule for tax.
Asset and Liability Accounts

Current asset and liability accounts are calculated as a percent of revenue.

6.2 Accounting Rule Experimentation

Capitalized R&D

The purpose of this asset classification is to provide a method for testing the effect of different accounting rules on the correlation of economic return and the accounting measures of performance. This classification refers to the capitalization of research expenditures. The model allows for the selection of any expense from the development process for capitalization. The book depreciation schedule can be found in the Input section of the model and is currently set to a 15-year straight-line schedule. Tax depreciation or any tax treatment at all is not included in the model.

Ongoing Research

This classification allows the model to capitalize ongoing research as part of the accounting experimental program. The model maintains a book depreciation schedule of 15-years straight-line.

7 Calculation Methods

The model of the drug program is divided into two major calculation procedures. The first is the generation of the program and the second is the simulation itself, the operation of the program. The generation of the program calculates all the financial parameters possible for a drug. The operation of the program involves the probability-weighted generation of a drug portfolio. Combined with the financial data calculated previously, the results of the drug portfolio are translated into measures of financial performance.

The model is built from four different worksheets. The most fundamental is the DInput worksheet. It is here that the user-input data is stored. Both the Program and CalcNPV use the data from this worksheet. CalcNPV generates the financial data for any drug candidate. The Program Worksheet is the program. Each calculation of the Worksheet results in the completed life of a single research program itself. The financial data calculated by CalcNPV is stored and used in this worksheet.
The memory requirements of this model are quite high. Therefore, I broke up the complete calculation of the financial data into five separate calculations. These calculations are initiated and controlled by the GenTable macro found in the PrgMacro, an XLM macro worksheet.

The generation of the program involves the calculation of all the variables for all the possible outcomes in the life of a drug and takes place in the CalcNPV worksheet. The input data required for this calculation is read from the DInput spreadsheet. These calculations include discounted cash flows in addition to state variables, such as revenue or marketing expense.

The need to know future data for the discounting process made this an interesting Worksheet problem. The data calculated from this large decision tree is tabulated and stored in the Program worksheet look-up tables. The discounting was performed on an expected value basis. After these look-up tables are generated and stored, then the CalcNPV spreadsheet can be closed. It is not required for the Monte Carlo simulation.

The operation of the program is represented by a single iteration of the Program worksheet that contains the drug portfolio. The core of this entire Worksheet is the drug portfolio table. The remainder is just the organization of data. The portfolio table includes all the events in the lifecycle of all the possible drug candidates and drugs. This is the variable part of the worksheet that is subject to statistically defined events. Four possible drug candidates are allowed each year for the first 40 years of program operation. The candidates and drugs existing at year 40 are allowed to continue, but no new candidates are generated. The program thus has three phases in its 66 year life: the start up phase when the number of possible drug candidates is increasing each year (the first 26 years); the steady state in which total possible projects and products is constant (the next 14 years); and the wind down with a decreasing number of possible projects each year. The design of the program using several phases allows the investigation into transient as well as steady-state behavior.

The data available from the industry includes pharmaceutical companies in transition. Certain biotechnology-based firms would be an example. The large pharmaceutical companies, Merck, Pfizer and Upjohn, are considered to be in steady state.

The first description will be of the generation of the program. This is the most complicated calculation in the model and will allow the reader to interpret the results of the simulation. The cash flow conventions will be presented and the treatment of working capital will be discussed. The cash
flow discussion will include the variables involved and discount rates used. The methods used to discount the cash flow will then be described in a generic way followed by a discussion of the detailed process. The operation of the portfolio will be discussed as will the methods and assumptions involved in the generation of the portfolio, in addition to the preparation of financial data. The discussion of calculation will then be expanded to policy level calculations based on the variables calculated in the CalcNPV worksheet. These calculations would include the opportunity cost of a Drug and the theoretical cost of capital for each point in the drug development process. This will conclude the discussion calculation procedure.

7.1 Cash Flow timing convention:
The conventions for the timing of cash flows are shown in Figure 1: Cash Flow Timing Convention. All cash expenditures and receipts are considered to occur on the last day of a given year. These values are then discounted at the appropriate rate to the beginning of the year.

The change in working capital was not as straightforward a calculation. The expected working capital is calculated as the probability-weighted average of the possible changes. This cash flow is then assumed to occur at the end of the current year and is discounted at the mature discount rate to the beginning of the year. The present values of the future cash flows are probability weighted and discounted one year.

The CalcNPV uses the data in the Data Input Worksheet and will calculate the cash flows and the present values for every possible event which could occur in the drug lifecycle. The CalcNPV is controlled by a macro, GenTable, and is run five times to generate the look-up tables required to create a drug portfolio.

7.2 Discount Rates:
Real growth and discount rates are used in the time projections of this model. If the discount rates are changed in the data input section of the model, make sure the new rates do not include an adjustment for future inflation.

Two different discount rates are used in this model. Revenue, marketing costs, manufacturing cost, and changes in working capital are discounted at the mature drug rate. Costs and tax shields which are unaffected by the macro-economic environment are discounted at the risk free rate. These factors include administration, research and capital expenditures, in addition to the depreciation tax shields, and are referred to as Fixed Expenses.
7.3 Present Value Calculations

Development Period

The drug status code contains the current status of a drug, and for each code the probabilities of the next year's outcomes are known. This information allows the calculation of expected values for the cash flows.

In the development years the decisions are binary yielding easy methods of handling future data. The next year's data are known, as well as, the probability of moving to the new state. Figure 2, Scientific Evaluation Point, shows the scientific hurdles that a drug candidate must overcome to enter the market. At each phase the drug is challenged by a decision lottery with the success probabilities shown. If the drug passes, then it moves to the next development phase. If the drug has a negative decision, the project is canceled.

The present value calculations are made as an expectation value, but the calculation is simplified since negative decision results in a value of zero. The development phases have different duration. Within each phase the present value of cash flows are calculated using a success probability of one.

In addition to the scientific hurdles for a drug candidate, the levels of market success must be determined. The decision tree expands to five branches in the last year of Phase III, year 10 in the drug lifecycle as shown in Figure 3. It is quite possible for a drug to have great marketing potential only to fail Phase III trials or not receive FDA approval.

Marketing Period

The complexity of calculation in the Marketing Period arises from the annual determination of the entrance of new competition and the discovery of new dosage forms.

The market life of a drug is 13 years and is divided into the year of launch and four three-year periods (Post Launch I - IV). New dosage forms are allowed from the first year post launch through the last year of Post Launch III. Post Launch IV is the phase when the drug comes off patent and generic competition enters the market. New competition can enter the market from launch through the first year of post launch II. New competition is no likely to enter a market where the entrance of a generic is likely.

One approach to this problem is use the tree decision model and to follow the tree through the branches as a drug progresses. If the tree is expanded out in
this way the base of this triangle will have about sixteen thousand components. This calculation would be difficult using Worksheet methods.

8 Adaptation of the Accounting and Financial Methods to the Worksheet Environment

The probabilities change with the drug quality, the phase and the number of existing competitors and the number of dosage forms. Probability equations also change with the state of the drug candidate.

The decision tree, which is about 16,000 at the base with probability equations and the probability values which, are dependent on the status of a drug.

All the present value variables are “forward looking” in time and for a given state (i.e. same drug quality, lifecycle year, number of competitors, number of new indications) they have the same value. Therefore, the decision tree can be converted into a series of tables which are cross-referenced between the years.

The tables contain the current status of the drug and the possible states for the next year. The probability equations for each of the possible transitions are also included. The tables are calculated from the last year in the lifecycle backward in time. Calculation of present values and changes in working capital require data from sequential years. The data for each of the possible future states is retrieved from the next year and entered into the current table. The expected values for the current year can then be calculated using the probability equations and the appropriate discount rate.

8.1 Depreciation

The capital expenditures for each year of the drug lifecycle are depreciated separately using a user-defined schedule. The net assets, depreciation expense and the depreciation tax shield are summarized for each year of the drug lifecycle.

8.2 Portfolio Generation

The generation of a drug portfolio is built around a Monte Carlo simulation. The Worksheet is run iteratively with each calculation cycle, generating an independent and complete drug program. The drug program has a life of 66 total calendar years. The program can be divided into three major phases, Start-up, Steady State, and Wind Down. The start-up phase duration is 26
years. In this phase each calendar year brings more possible drug projects. When the 26th year is completed, the complete lifecycle for a drug candidate discovered in calendar year one, after this point the total number of possible projects is constant. Each new calendar year allows the addition of four possible projects and four possible projects reach the end of their lifecycles. This Steady state phase lasts through year 40. The wind down phase lasts from year 41 to 66. No new projects are allowed, and each year four possible projects reach the end of the lifecycle until projects that could have been initiated in year 40 are terminated in year 66.

9 Worksheet-Calculation

The method used to evaluate the drug program uses an operational cycle involving several steps.

1. Portfolio of drug projects is generated.
2. Data for each drug candidate is “looked up” in the tables prepared by CalcNPV.
3. Program overhead and Start-up costs are calculated and allocated.
4. Performance measures are calculated.
5. Data, which characterizes the Program, is collected and stored.

The above cycle is repeated for between 2000 and 10,000 iterations to generate statistically significant distributions of the output variables.

9.1 Portfolio Generation

The portfolio of drug candidates is generated using a fixed format table, which allows one to a maximum of four drug projects to be initiated each year. A project must undergo scientific evaluation and must be commercially evaluated as it progresses through its lifecycle. A project may be canceled in the development period or may make it to the market, perhaps as a breakthrough drug. Competitors may enter the market and the company may find new dosage forms of the drug that will increase sales. These eventualities are all possible in the model. The user inputs the probability for each event.

These decision points and commercial evaluations all use the same basic calculation method. Each consists of at least two conditional tests. The first is
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a test, which asks if the project is still ongoing. (It might have been canceled at a decision point earlier in the lifecycle.) If the project has been canceled, then no further calculation is done. For the second part of the problem, a random number is generated using Crystal Ball.

This random function includes the use of a seed number. This seed allowed us to generate several runs using the same random number sequence. Comparative experiments are possible even with variations in the lottery distributions.

These decision methods are used in four different applications in the drug development lifecycle:

- Scientific evaluation of each project as it moves from phase to phase in the Development Period,
- Determination of market success in the last year of Phase III,
- Entrance of competing products in the years from Launch to year 21 of the drug lifecycle, and
- Discovery of new dosage forms in second year of the Market Period until year twenty-three in the drug lifecycle.

A project can only be canceled in the scientific phase and, in the models current form, only for technical reasons. The scientific evaluation occurs at the end of each development phase. A random number is generated between zero and one and if it is less than the user input success probability, then the project moves to the next phase.

The determination of market success is determined using the same logic, but with a twist. The user inputs the probability of discovering each level of market success, from dog to breakthrough, five different classifications in all. The probabilities must sum to one. A random number is generated between zero and one. Instead of a single comparison as in the scientific evaluation, the Worksheet finds in which of five possible ranges the random number falls. Each range represents a drug quality determination. For example, the user could input a probability of 0.10 for all the drug qualities, except average, which is set to 0.60. If the random number is less than or equal to 0.10 then the drug is a dog. If it is greater than 0.10 but less than or equal to 0.20 then it is a below average drug. This method is used for the remaining drug quality categories.

The methods used to determine competitive entry and the discovery of new dosage forms are the same. The lottery is structured to evaluate whether a
new entrant or dosage form will be added in any given year. A competitor or
a new dosage form never leaves the market and the maximum number of
each is three. A random number is generated between zero and one. If the
number is less than the user-input probability, then one is added to the
number of competitors or dosage forms. The interesting part of this
calculation is that the probability can vary with the drug quality, year in the
lifecycle, and the number of existing competitors or dosage forms.

*Project cancellation or termination at the end of the lifecycle.*

If a drug project is canceled in the development phase, the accumulated
capitalized equipment is sold for the net asset value. This increases the cash
flow for that year, but does not have any effect on net income. The natural
termination of a drug project at the end of its lifecycle releases all the working
capital and any non-depreciated asset is again sold at the net asset price and
the proceeds contributed to the cash flow.

### 9.2 Data Reduction

Once the portfolio is generated, the financial implications can be evaluated.
The portfolio table contains the coded information required to define each
project state. The necessary financial information is then “looked up” in the
information tables generated by the CalcNPV spread sheet. Information like
Revenue, Business Cash Flow, Cash flow for Fixed Expenses, and Net Assets
are assembled in table that mirror the shape and form of portfolio table,
which contains the coded information. The data is then added up and a
number for each calendar year is calculated. These summary numbers are
available for user experimentation.

### 9.3 Program Overhead and Start-up Expenditures.

The program itself has general and administrative overhead charged each
calendar year. In addition, on-going research is allocated at the program level
to support the on-going research required by the FDA (Phase IV) and the
discovery of new dosage forms.

On-going research is phased in as drugs reach the market. The amount
increases linearly with the first five drugs entering the market. Additional
drugs entering the market do not increase the level of expenditure, but if the
number of drugs in the market falls below five then the level of spending
also decreases.
The Start-up expenditures have capital and expense components. Capital expenditures are depreciated with a user-input schedule. All of the Start-up expenditures occur at the end of year zero, equivalent to the beginning of year one.

### 9.4 Summary Variables

The evaluation of the program uses several measures of financial success or characterization. The rate of return of the program is measured in two different ways. The expected rate of return \( (R_{exp}) \) and the actual rate of return \( (R_{act}) \) are calculated from present value and cash flow data. The expected Beta is calculated using input data and the present value of the cash flows. The size of the company is determined by the Net Present Value of all the cash flows both to the portfolio of drug projects and program overhead.
10 Bibliography


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ALIFE-CYCLEFINANCIALMODEL OF PHARMACEUTICAL R&D

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A LIFE-CYCLE FINANCIAL MODEL OF PHARMACEUTICAL R&D

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This report describes a financial simulation model of pharmaceutical research and development. It illustrates the major applications of the model, including calculation of the net present value of investment in R&D, of the cost of developing a successful drug, and of the changes in the cost of capital from drug discovery to the end of the drug's commercial life. It also presents estimates of the cost of capital based on analysis of the risk characteristics of pharmaceutical and biotech stocks.

The financial model connects the tools of modern finance to a detailed description of the costs, risks and returns of pharmaceutical R&D. We offer the model as a prototype for financial analysis of R&D investment and as a way of understanding the financial structure and performance of the pharmaceutical industry.

The calculations in this report generally reflect one set of base-case assumptions. Although the assumptions do not match any particular company's situation, we believe they are representative of conditions facing major, research-intensive pharmaceutical companies in the 1980s and early 1990s. Based on these assumptions, we find that:

1. The net present value of investment in the development of a new drug is approximately zero: only +$4 million after tax. This figure does not include an allocation of the startup costs of the R&D program or of the costs of basic research or corporate general and administrative expenses. If these program-level costs are allocated, net present value is somewhat, but not significantly negative. The base-case assumptions imply no excess average profits once risk and the time value of money are properly accounted for.

2. The average cost of bringing one drug to FDA approval is $297 million after tax, but before allocation of program-level costs.

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3. The cost of capital, defined as the expected rate of return demanded by investors, depends on the risk borne by investors. For major pharmaceutical companies, we estimate the cost of capital at about 10 percent in real, that is inflation-adjusted, terms. But the cost of capital in early stages of clinical testing can be as high as 30 percent. Risk and the cost of capital decline as a drug moves through its life-cycle.

4. As finance theory predicts, the model shows that accounting rates of return are upward-biased measures of the true profitability of R&D investments.

5. Uncertainty about revenues, profits and market capitalizations is extremely high -- as expected, given the high failure rates in drug development. The range of possible outcomes is also strongly skewed to the right. This skewness means that some R&D programs will perform extremely well despite average profits for an entire cohort. It also means that after-the-fact analyses of successful (and surviving) pharmaceutical companies will find returns substantially higher than expected for the industry as a whole.

We stress that the numerical results presented in this report are not intended to describe the performance or profitability of any particular company or of the pharmaceutical industry as a whole in any particular period. These results are given to help explain how the financial simulation model works, to illustrate its implications and to clarify the financial characteristics of the pharmaceutical industry.

Outline of the report

The origins and objectives of the research project are reviewed in the next section of this report. The financial simulation model is described in detail in Section 2. Section 3 covers valuation procedures and the evidence on investors' required rates of return for the pharmaceutical and biotech industries. Section 4 illustrates the model's uses and implications and describes continuing work.

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The Research Plan

Profitability, risk and the cost of capital are particularly difficult to measure and analyze in the pharmaceutical and other R&D-intensive industries. There are at least two underlying reasons. First, risk and the cost of capital are amplified during R&D. Second, the true profitability of pharmaceutical investment is extremely difficult to estimate from standard financial data. Reported accounting rates of return are not only "noisy" but severely biased.

For these and other reasons, the tools of modern finance, which ought to apply to investment in R&D, have rarely been applied in practice.

This section expands on some of the difficulties of financial analysis of R&D and describes the research plan that led to this report.

The risk-return staircase

Pharmaceutical R&D is risky in two senses. First, the odds of failure are high. Second, the costs of R&D amplify investors' exposure to the systematic risks that determine the cost of capital. Investors' required rates of return are highest at or just after basic research, then move down a "staircase" as (and if) research continues and commercial production approaches. This risk-return staircase is shown in concept in Figure 1. The "floor" at the bottom of the staircase is established by the risk of the mature product.

Thus there is no single cost of capital for pharmaceutical R&D. Costs of capital estimated for established pharmaceutical companies must be interpreted as weighted averages across many drugs, including some very risky ones just
emerging from basic research and some much safer ones with limited remaining economic lives. Company-average costs of capital understate the rates of return required for pharmaceutical R&D and at the same time may be too high for investment in the marketing and production of proven drugs.

Obviously the staircase slopes down, but there has been no practical way to determine the length or height of the steps. Some method of modeling the changes in risk and the cost of capital in successive stages of R&D was needed.

**Biases in reported rates of return**

Standard accounting procedures treat R&D as an expense. It is really an investment, as crucial to the value of a company as investments in tangible assets. Accountants will admit this, but since they have no objective way to value R&D, they resort to the apparently conservative “expense” rule. Unfortunately this grossly understates the values of successful pharmaceutical companies’ assets and overstates their rates of return.

In principle one can work back from reported accounting rates of return to the underlying true rates of return. However, this requires a detailed understanding of cash flows over the product life cycle, the breakdown of assets between proven products and R&D, and the distribution of R&D outlays on the various steps of the staircase.

Economists have developed ways of calculating true, economic profit rates which can be shown to work for companies on a steady-state growth path -- this implies, among other things, a steady arrival rate for new drugs -- or when product cash flows follow stable, tractable patterns. No one has systematically investigated the properties of these procedures when product cash flows follow complicated patterns, when success rates vary, and when operating cash flows respond to changes in competition, costs or other factors.

**Research Strategy**

The key to both of these problems is more detailed information about the life-cycle of pharmaceutical products. Much of that information can be captured in a probabilistic financial model.

Such a model would be extremely difficult to build for other R&D-intensive industries. In the case of pharmaceuticals, however, there are three key advantages. First, almost all new drugs must pass through several well-defined steps in order to gain FDA approval, so the R&D process is much more standardized than in, say, the computer chip industry. Second,
objective information is in the public domain. The model can incorporate historical information about R&D costs, time requirements, success rates, revenue patterns and other aspects of the industry’s economics. Third, many biotech companies are “pure plays” on pharmaceutical R&D. The risk of investment in R&D can be measured from returns on biotech stocks. (The “staircase” predicts that biotech companies should have higher risks to investors and should offer higher expected rates of return.)

The research plan therefore set out four specific tasks:

1. Build a reasonably detailed and realistic stochastic financial model of the life cycle of a new drug from the start of R&D to the end of the drug’s economic life. The model should rest on modern finance theory and should allow consistent estimates of present value, returns to investors, and the risk-adjusted cost of R&D.

2. Use this model to analyze how risk and investors’ required returns change over the life cycle of discovery, preclinical and clinical testing, FDA approval, commercial launch and production.

3. Estimate the overall cost of capital for the pharmaceutical industry, and test the model’s predictions for the risks of traded biotech and pharmaceutical stocks.

4. Use the model to analyze the errors and biases in alternative accounting measures of pharmaceutical company profitability, and to develop improved measures that could be calculated from publicly available financial data.

The most challenging part of the research was task 1, which required the construction of a detailed Monte Carlo simulation model of a drug development program. The program spans 40 years and generates hundreds of potential drugs. The model tracks the life histories of these drugs, a random number of which survive laboratory and clinical testing and receive FDA approval; these survivors are followed beyond the end of their patent lives.

Naturally the model requires a fair number of inputs, including probabilities of discovery and clinical success, costs and time requirements for clinical trials, revenue patterns, manufacturing and marketing costs, patent life, probabilities of entry of competing drugs, tax rates, expected returns required
by investors, and so on. The model’s outputs are sensitive to these and other factors.

We are not in a position to predict the success rates, costs and other parameters of pharmaceutical R&D for the late 1990s. We have drawn or adapted most of the model’s base-case inputs from historical information. Users of the model can change its inputs to fit particular cases or to test the implications of various scenarios for the future.

**The Simulation Model**

The model is a Monte Carlo simulation of a drug development program. A program starts with a multi-year commitment to development and marketing of new drugs. The commitment includes the setup costs of a R&D facility and the continuing costs of running it. Each year these outlays are, with luck, rewarded with discovery of one or more compounds with potential therapeutic value. Once discovered, these drug candidates absorb additional investment -- first for pre-clinical development, then for the several stages of clinical trials, and finally for the costs of securing FDA approval, building manufacturing capacity and investing in marketing at the drug’s commercial launch. Of course, expenses are incurred only as the drug passes scientific, regulatory and medical hurdles; if it fails at any stage, the candidate is abandoned and no further outlays are required. But if a candidate makes it to the marketplace, it begins to generate revenues and to repay the costs of developing it.

The costs of a program are thus twofold: first, the fixed costs of the R&D operation, which are incurred even if no drug candidates emerge, and, second, the costs of testing and proving the candidates -- all the candidates, not just those that turn out successfully.

So the first modeling requirement is a detailed description of the life-cycle of a single drug candidate. This includes the probability that the candidate will be discovered, and if discovered, the probabilities that it will survive at each stage of testing. If it does survive, the life-cycle description also includes the probabilities that the drug will be a “breakthrough” generating high revenues, a commercial disappointment, or three in-between possibilities.

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3 However, all costs and revenue inputs are adjusted for inflation to 1994 dollars.

4 Note that we use “R&D” generally to refer to all program and drug development costs except outlays for manufacturing capacity and marketing.
The profits of a program depend on the number of successful drugs and their performance in the marketplace. These outcomes are highly uncertain. The simulation model describes this uncertainty and its financial consequences. We believe doing so explicitly is essential, because financial analyses based just on averages are incomplete and easily misinterpreted.

The model describes uncertainty by a Monte Carlo simulation, which analyzes the scientific and financial performance of the drug development program for thousands of possible scenarios. Each scenario is generated from a unique set of random draws from probability distributions based on the odds of drug discovery, survival and commercial success. The model then compiles distributions of revenues, profitability, market values and other measures based on all the scenarios explored.

We now describe the structure of the model in more detail, beginning with overview of the life cycle of a single drug candidate.

The life cycle of a single drug

Figure 2 shows the life-cycle through FDA filing. The top bar of the figure refers to the continuing R&D program. In each year up to four candidates are discovered and enter preclinical testing; the figure follows one candidate assumed discovered at the start of year 1.

The durations, costs and success probabilities for discovery and following tests and trials are shown at the bottom of Figure 2. These are examples of the base-case input assumptions referred to above. The procedures for matching up these inputs with prior research are covered later in this section.

Figure 3 follows the life cycle from FDA approval. Commercial launch requires manufacturing capacity (which is actually constructed before launch -- see the right-hand column of Figure 2) and an initial marketing outlay, estimated as 100 percent of initial revenues.

Once the project is launched, revenues follow a sales curve, broken for convenience into four post-launch phases. The curve peaks in post-launch Phases III and IV, but ceases at the end of Phase IV, three years after the drug is assumed to go off-patent. At this point the drug drops out of the model. Any remaining off-patent revenues are assumed to be insignificantly small.5

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5 We realize that many drugs have in the past generated off-patent revenues for much longer periods. However, these revenues are far distant from the investments in R&D, and when discounted would not be financially important. Thus the simplifying assumption limiting off-patent revenues to Phase IV should not upset the model's financial implications.
The height of the sales curve depends on the drug's "quality." There are five quality levels with the following probabilities (p):

<table>
<thead>
<tr>
<th>Quality Level</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Breakthrough&quot;</td>
<td>p = .10</td>
</tr>
<tr>
<td>Above average</td>
<td>p = .10</td>
</tr>
<tr>
<td>Average</td>
<td>p = .60</td>
</tr>
<tr>
<td>Below average</td>
<td>p = .10</td>
</tr>
<tr>
<td>&quot;Dog&quot;</td>
<td>p = .10</td>
</tr>
</tbody>
</table>

Each drug is randomly assigned to one of these categories before its commercial launch. The revenue curves for each category are plotted in Figure 4.

FDA approval and determination of drug quality does not remove all uncertainty about the drug's profits. There is still a chance for good news -- expanded revenues from one or more new indications or uses, or bad news -- entry of one or more competing drugs. Whether the good or bad news arrives depends on random draws at the beginning of each post-launch phase. Suppose, for example, that an above average drug enters post-launch Phase III with no competition and no new indications. The possibilities are:

<table>
<thead>
<tr>
<th>Probabilities (per cent)</th>
<th>Peak Revenues (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Competition: None</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>60</td>
</tr>
<tr>
<td>New indications: None</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>35</td>
</tr>
</tbody>
</table>

We had no historical data on the probabilities or average effects of new indications or new competition. Thus these inputs are illustrative, not descriptive. However, the financial effects of possible competition are roughly offset by possible new indications. When both effects are "turned off," the net present value of investment in a new drug hardly changes.

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6 The random draw is actually done eight years after discovery, representing the earliest possible investment in manufacturing capacity. The investment in manufacturing depends on peak sales, and therefore must depend on drug quality. It is assumed to occur in the last two years before launch.

7 See the sensitivity analysis in Section 4.2 below.
**Base-case input assumptions**

Table 1 is a complete list of variables computed by the model for each iteration of the simulation. Appendix A shows the base-case input assumptions as they appear in the spreadsheet that is simulated.

Where possible, we have matched these assumptions to prior research, especially the historical data reported in DiMasi, et al. (1991), the "DiMasi Study," and Grabowski and Vernon (1991, 1993). This facilitates comparison of our results to theirs, and also to Chapters 2 and 3 of the OTA Report, which rest on much of the same historical data. (The "OTA Report" is a widely cited study prepared by the Office of Technology Assessment of the U.S. Congress (1993).)

However, the available historical data were not collected with a Monte Carlo financial simulation model in mind. Approximations and adaptations were necessary in several areas, including setting the length of the R&D stages, the costs and success probabilities in each phase, and the time-patterns of revenues after a drug is approved and brought to market.

Given our heavy reliance on the DiMasi Study, we emphasize that the R&D costs reported there were incurred for a sample of drugs under development in the 1980s. We have corrected for economy-wide inflation to 1994, but have not attempted to say whether inflation-adjusted R&D costs have increased. There is some evidence that they have increased.\(^8\)

We now review some of the key input assumptions in more detail.

**Stage lengths.**

The DiMasi Study reports average completion times for the various R&D stages, for example 3.5 years for discovery and preclinical testing. Tracking fractions of years would have been inconvenient in the financial simulation model, so all phases are assumed to last one, two or three years. (In this respect we follow the OTA Report.) For example, we allowed one year for discovery and three for preclinical testing, or four in total, compared to 3.5 in the DiMasi Study. But we adjusted the cost per year in each stage so that the total cost of that stage matched the figures given in the DiMasi Study. Thus total costs of drug development are not affected by the model's "rounding" of stage lengths.

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\(^8\) Research costs increased throughout the 1980s. See Henderson and Cockburn (1996), Fig. 2, p. 44, and Fig. 1, p. 113, in the DiMasi Study. A projection of that trend would give substantially higher costs for the 1990s than implied by our base-case inputs.
Success probabilities.
The probabilities that a drug candidate will succeed at the several stages of R&D are summarized in Figure 4. The following table compares these probabilities with those provided by the DiMasi Study.⁹

<table>
<thead>
<tr>
<th>Probabilities of Success</th>
<th>Discover y</th>
<th>Pre Clinica l Testing</th>
<th>Clinical Testing</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60%</td>
<td>90%</td>
<td>75%</td>
<td>50%</td>
</tr>
<tr>
<td>DiMasi Study</td>
<td>n.a.</td>
<td>n.a.</td>
<td>75%</td>
<td>48%</td>
</tr>
</tbody>
</table>

Notice that the odds of success after a drug enters clinical testing are almost identical. But the model assumes high success rates in discovery and clinical testing. For example, the odds that a potential drug will be “discovered” in a particular year is 0.60. Up to four drugs can be discovered in each year.

This is obviously a simplification: in reality the number of compounds identified as drug candidates would be much larger. But tracking a realistic number of candidates was computationally infeasible. So we restricted the potential number in each year and increased the probabilities of discovery and survival in preclinical testing. We also made offsetting increases in the costs per drug in the discovery and preclinical phases. We now turn to a brief description of how these adjustments were carried out.

Consider first a hypothetical example. Suppose that a program tests 4000 compounds per year in discovery research, and that each compound has only a 1 per cent chance of entering preclinical trials. In other words, the average number of drugs entering preclinical trials is 0.01 × 4000 = 40 per year. The cost of testing each compound is $100,000 and total expected costs are $4 million.

⁹ See Table 2, p. 121, in the DiMasi Study.
Since the Monte Carlo model accommodates only four candidates, each of these must proxy for 10 compounds. Therefore the cost per drug would be scaled up from $100,000 to $1 million and the probability of success to 10 percent. Note that this scaling does not change cash flows or other financial variables; it simply offsets the artificially low number of "proxy" drugs. For financial purposes it does not matter whether one starts with 4000 actual drugs or the 40 proxies: the average discovery-phase expenditures per approved drug are identical.

Thus the success probabilities given in Figure 4 for discovery and preclinical testing are, taken out of context, too high, because each drug in these stages must proxy for a larger number in real-life research. But the model as a whole is nevertheless financially consistent, because the total costs at each stage are derived from historical data.

Appendix B describes in more detail how discovery and preclinical costs per drug are calculated given the assumed success rates shown in Figure 4.

**R&D costs stage-by-stage.**

Total R&D costs obviously depend on the number of drugs in the R&D pipeline. We needed to identify costs per drug at each stage. Then the simulation procedure can track total costs by multiplying cost per drug by the random number of drugs discovered and surviving in a particular iteration.

The DiMasi Study reports average R&D costs per approved drug. In other words, it assigns the cost of drugs which failed in R&D to the drugs that survived. Since the simulation model explicitly tracks failures as well as successes, the historical data had to be restated.

The average number of drugs in the pipeline for each approved drug can be calculated from the success probabilities given in Figure 4. For example, the 75% success rate at the last "FDA Approval" stage means that 1/.75 = 1.33 drugs must enter this phase, on average, for every approved drug. If the cost of obtaining approval is $4.4 million per approved drug, it must be 4.4/1.33 = $3.3 million per drug that survives Phase III clinical trials. This is the figure reported in the bottom-right box of Figure 2.

Appendix B gives more details on how the costs per drug per R&D phase were calculated.
Revenue Curves.

The amounts and time-patterns of revenues were based on Grabowski and Vernon (1993). They broke a sample of 67 drugs into deciles based on the present value of the drugs’ revenues. They also reported average revenue curves like those in Figure 5 for the median drug, ranked on average revenue, and for the top two deciles. We used these three curves as starting points for the “average,” “above-average” and “breakthrough” outcomes in the simulation model. The curves for “below-average” and “dog” were scaled down from “average” in proportion to the present values reported by Grabowski and Vernon for their lowest two deciles.

Note that all revenues and costs are restated in 1994 dollars.

Some other assumptions.

A glance at Appendix A reveals the large number of other inputs needed for the simulation model. Many of these are minor or routine, and do not need a detailed explanation here. For example, the model calculated all costs and revenues after-tax, but the calculation of taxes just follows current U.S. law. The marginal tax rate is the current (1996) rate of 35 per cent.

Assumptions about working capital were checked by comparing the model’s output against actual companies’ working capital ratios and adjusting the base-case ratios as necessary. For example, we first set the ratio of accounts payable to sales at 14.4 per cent. The actual ratio for a sample of large pharmaceutical companies fluctuated around 6 percent, so 6 percent was used in the base-case.

We followed Grabowski and Vernon (1993) and the OTA Report in assuming that marketing costs soak up all revenues in the first year after launch and 50 per cent of the next year’s revenues. Subsequent marketing costs are 25 per cent of revenues in the rest of post-launch Phase I and 20 per cent in Phases II, III and IV. This pattern differs from the OTA Report, but approximately

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10 These revenues include foreign sales of drugs developed in the United States. The R&D costs from the DiMasi Study do not include the costs of gaining approval for foreign sales. Therefore the base-case costs of drug development are understated, relative to revenues, to some extent.

11 The financial simulation model assumes level revenues within each launch phase, whereas Grabowski and Vernon track revenues by year. Thus the curves shown in Figure 5 cannot match the Grabowski-Vernon patterns exactly.
matches its assumed 22.5 per cent ratio of marketing to revenue over the 13-year sales period assumed in the model.\textsuperscript{12} 

Grabowski and Vernon (1993) assumed that investment in manufacturing facilities was 40 per cent of a drug’s peak revenues. We adopted this figure for “above-average” drugs, but scaled it up for breakthrough drugs and down for the other categories. The scaling formula allows for economies of scale in manufacturing.\textsuperscript{13} Half of the scaled manufacturing investment was allocated to the two years immediately before launch, and the other half was spread evenly over post-launch Phases I, II and III.

We had no direct evidence on the “overhead” and administrative costs of pharmaceutical R&D or on the costs of program startup and ongoing basic research. (These costs are not included in the DiMasi Study.) The base case assumes an initial setup cost of $150 million, including capital expenditures of $100 million, plus $11 million per year for ongoing research and $34 million per year for “Corporate G&A,” that is overhead and administration.\textsuperscript{14}

We checked the assumed G&A costs by calculating the average ratio of G&A to revenue generated by the Monte Carlo simulations and comparing to the same ratio for the sample of pharmaceutical companies. The ratios matched at about 5 per cent.

\textbf{Simplifications}

The life cycle described in Figures 2 and 3 contains three major simplifications. First, revenues and operating income are treated as if certain once drug quality and the numbers of competing drugs and new indications are set. In reality, revenues depend on many other things, including the state of the economy, foreign demand and foreign exchange rates, and changes in regulation and industry structure. Revenues and operating costs should therefore be interpreted as averages across these uncertain events. While this assumption means that our simulation model is incomplete, we believe that

\textsuperscript{12} The OTA Report assumes that marketing expenses drop to 6.5 percent of sales as soon as a drug goes off-patent. This has an odd effect: profits jump dramatically as soon as a drug’s patents expire. The life-cycle model tracks off-patent revenues for less time that the OTA Report, but maintains marketing expense at 20 percent of sales.

\textsuperscript{13} The scaling factor for breakthrough drugs is the ratio of their peak revenues to the above-average peak, raised to the power .67. We thank Prof. Dic Wang for advice on this matter.

\textsuperscript{14} For simplicity the model assumes that these program-level costs are constant from year 0 to 40. In reality they would probably increase gradually as drugs are discovered and the R&D pipeline fills.
we have captured the most important uncertainties for the industry by explicitly including scientific, medical and competitive risks. Earlier research has typically not modeled these risks explicitly.

Second, nothing in the life-cycle model decides to stop investing in a drug candidate. The model accepts failure as a random outcome. It does not distinguish failure for scientific or medical reasons from failure for business reasons. A fuller model would not hard-wire continued investment given success in prior development phases. It would at the start of each phase evaluate the option to continue, and go ahead only if the option were worth exercising.

We considered and rejected a formal options-based analysis for two reasons. First, it would have been either much less detailed or much more difficult computationally. Second, the Monte Carlo model is not necessarily inconsistent with an options approach: it simply assumes that the options to continue will be exercised if a drug candidate survives. We believe this assumption is usually true, because the odds of success in early stages of pharmaceutical R&D are very low. By the time a drug has successfully passed, say, Phase II trials, the option to continue developing it is typically so far "in the money" that it would be exercised in any case.

The third simplification takes all costs and probabilities as fixed. The simulation plays the same game over and over. In real life, some research programs have more favorable odds than others. The company does not know these odds exactly, but to the extent that it can learn, it can increase investment in the better programs and curtail the ones with relatively poor prospects, thus increasing long-run average returns and perhaps reducing uncertainty. The actual importance of this "learning effect" is unclear, since technology is advancing and the regulatory and commercial environment is changing.

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15 DiMasi (1995) reports that 23 per cent of a sample of drugs under development from 1964 to 1989 were cancelled for "economic" reasons. See Table II, pp. 8-9.

16 The failure probabilities given in Figure 4 do incorporate cancellations for business reasons. These probabilities were based on the DiMasi Study's sample, which included some drugs that failed not for clinical or scientific reasons but because the options to continue them were not exercised. Thus the life-cycle model does not ignore "business" failures. However, it does not analyze them explicitly.
The program as a cohort of drugs

We model research programs, rather than single drug candidates, for several reasons. First, firms organize internal data and make strategic R&D commitments at the program level. Second, research programs have fixed costs. Any allocation of these costs to single drugs is arbitrary. Third, the uncertainty about the performance of a program is less than for an individual drug candidate, because the successes and failures of individual drugs average out to some extent. The Monte Carlo simulation model incorporates this diversification effect. Finally, we compare some of the simulation output to real companies, which are portfolios of drugs in the market and drug candidates in various stages of development. The simulation model generates the same kind of portfolio. Note, however, that the program described by the model could be only a part of a large company's total R&D. These companies are really portfolios of programs.

The program is built up from individual drugs. Consider one iteration of the simulation. Each year up to four drugs are discovered. The discovered drugs, if any, start their life cycles. The number discovered and the drugs' subsequent successes or failures are determined by draws of random numbers and the prespecified probabilities.

The first stage of the program, from year 0 to 13, is all development. By year 13 there are, on average, about 17 drug candidates in the development pipeline. In year 14, one or more drugs may be launched and begin producing revenues. Of course these drugs must have been discovered in year 1. In year 15, drug candidates discovered in year 2 may reach the market, and so on.

A drug goes off-patent 10 years after commercial launch; its revenues cease after 13 years. Thus any drugs launched in year 14 drop out of the simulation after year 26.

By year 27, the model reaches a probabilistic steady state, in which there may be drug candidates at every stage of development and drugs in the market at every stage of the revenue curves given in Figure 5. Much of our analysis focuses on the steady-state years.

The simulated R&D program is continued until year 40. After that, no new drugs are discovered and the model gradually runs down. The fixed research costs of the program cease, although the costs of developing any drug candidates then in the pipeline continue.17 If one or more of these drugs make it to commercial launch, the model tracks them through the ends of

17 General and administrative expenses also continue.
their commercial lives. After year 54, the average number of drugs in the market declines, since nothing is discovered after year 40. Revenues from the last possible drug expire in year 66.

Figure 6 shows one actual iteration of the model. Each horizontal bar represents a drug candidate discovered in a particular year. For example, two drugs were discovered in year 30. (The blank spaces represent the drugs that could have been discovered but were not.) The length of each bar shows how long that drug survived. For those that survived through FDA approval, the unshaded part of the bar represents revenue-producing years.

This iteration was a profitable one, with revenues in year 30 of $561 million. Figure 6 shows that this revenue was achieved from relatively few drugs -- few, that is, relative to the much larger number of drugs that never made it into, or through, the development pipeline.

**Simulation procedure**

Each iteration of the program is determined by a draw of 3840 random numbers, from which a complete program history is calculated. The history includes annual after-tax cash flows, income statements, present values, and expected and actual returns to investors. Table 1 gives a list of all calculated financial variables.

We normally run about 5,000 iterations of the model to assure convergence of the frequency distributions of output variables. Each iteration solves a very large EXCEL spreadsheet. The Monte Carlo procedure uses Crystal Ball software. With a PowerMac 8500-120, 5000 iterations take about 80 hours.

The time per iteration is determined by the model's size and complexity. Much of the complexity is due to detailed accounting calculations and experiments. A stripped-down version, concentrating on cash flows and present values, runs much faster. The structure of the spreadsheet and simulation are documented in Howe (1996).

**Characteristics of the program**

Figure 7 shows the average numbers of drugs in the pipeline and in the market under the base-case assumptions. It also shows time patterns of average pre-tax R&D expenditures and revenues from year 0 to 40.

These averages show the typical scale of the simulated program under base-case assumptions. But as averages they hide most of the information produced by the simulation. Figure 8 shows frequency distributions of
several variables in year 30, a “steady state” year. In each case minimum, maximum, median and mean values are given below the distributions. The variables are:

- Number of drug candidates in development
- Number of drugs in the market
- Annual development expenses, including the fixed cost of supporting drugs in the market as well as development expenses for drugs in the pipeline
- Revenue
- NPV, defined as the total market value of the program, calculated by the discounted cash flow procedures described below
- Beta, the risk measure used in calculating the cost of capital
- Rexp, the cost of capital, that is, the expected rate of return that investors would demand at the start of year 30
- Ract, the actual rate of return that investors would have earned in year 30

The widths of the distributions for revenue, NPV, and the actual rate of return are striking. Diversification across drugs within the program does not generate safe returns.

Note also the extreme positive skewness of revenue and NPV, in contrast to the symmetrical distribution of development expenses. The best of about 5,000 runs generated a NPV in year 30 of over $11 billion, vs. a mean and median of about $3 billion. An analyst concentrating with hindsight on the most successful pharmaceutical programs would have a vastly overstated view of the true profitability of the business.  

The analyst’s problem is even more difficult because of survivorship bias. In real-life most of the poorly performing programs recorded in Figure 8 would be shut down well before year 30 and would not appear in the analyst’s sample. The simulation, however, shows the full range of possible outcomes, with one minor exception: we deleted iterations of programs with NPVs less than $500,000, because the betas and expected returns for these companies are “off the charts.” Thus even the distributions in Figure 8 include a bit of survivorship bias, and the mean and median revenues and NPVs are overstated. The overstatement is very small, however, on the order of 3 percent.
Most of the skewness in revenue and NPV comes from the uneven distribution of revenues and profits across drugs. Based on Grabowski and Vernon’s data, we set the peak sales of “breakthrough” drugs roughly 20 times higher than the peak sales of the “average,” i.e., median drug. See Figure 5.

The distributions of beta and expected return are also positively skewed, but the observations of these variables do not correspond to the right tails of the distributions of revenue and NPV. By year 30, the successful programs are, on average, further down the risk-return staircase shown in Figure 1. Therefore they have relatively low betas and expected returns. The poor performers remain on the upper left of the staircase, and therefore show up on the right tail of these distributions.

Figures 7 and 8 give only a taste of the simulation model’s properties and output. A fuller analysis is given in Section 4. The next section considers risk, valuation, and the cost of capital.

Valuation Procedures and the Cost of Capital

The best financial measure of value and profitability is net present value (NPV). NPV is calculated by discounting future after-tax cash flows at the cost of capital appropriate to the cash flows’ risks. This section summarizes the evidence on the cost of capital for the pharmaceutical industry and describes the discounting procedures used in the simulation model. It generally follows Myers and Shyam Sunder (1996). It does not repeat their exposition of standard financial concepts such as the Capital Asset Pricing Model (CAPM)\(^{19}\) and the weighted average cost of capital (WACC).

Myers and Shyam Sunder estimated nominal WACCs for a sample of large pharmaceutical companies in 1980, 1985 and 1990.\(^{20}\) Their estimate for 1990 was about 15 percent. The corresponding real, that is inflation adjusted, WACC was between 10 and 11 percent. (Since all cash flows in the simulation model are given in constant 1994 dollars, a real cost of capital is required.)

\(^{19}\) We do not claim that beta is a fully adequate measure of risk to investors or that the CAPM is true and complete. A deeper investigation of the cost of capital for pharmaceutical R&D might usefully explore other models and techniques.

\(^{20}\) Their report was originally prepared in 1991 for the Office of Technology assessment. At that time data were readily available only through 1990.
Tables 2 and 3 replicate the Myers-Shyam Sunder calculations for the start of 1994. Table 2 reports betas for the common stocks of major pharmaceutical companies. Beta is the most commonly used indicator of the macroeconomic risks borne by investors. The average beta is not significantly above 1.0, indicating average risk.

Given the average beta, the average expected rate of return on equity \( (r_E) \) is calculated from the CAPM. It is about 14 percent in nominal terms. Table 3 calculates the implied nominal WACC as slightly less than 14 percent. WACC and \( r_E \) are basically the same because these companies' debt ratios are close to zero.

A nominal WACC of approximately 14 percent is somewhat less than Myers and Shyam Sunder's figure for 1990. However, nominal interest rates fell between 1990 and 1994, and the expected long-run inflation rate probably fell too. An expected inflation rate of 3 to 4 percent implies a real WACC of 10 to 11 percent, for practical purposes identical to the 1990 estimate. This range is reasonable for large U.S. pharmaceutical companies, at least through the start of 1994.

Unfortunately this is not the right discount rate for the simulation model, because risk and the cost of capital change over the life cycle of a drug. We now explain the reasons why this happens.

**The risk-return staircase**

Figure 1 shows in concept how the cost of capital changes over the life-cycle of an individual drug. It can be extremely high in early stages of R&D, but declines as development continues, and levels out once the drug is established in the market and the costs of development and launch are left behind.

The cost of capital declines because risk declines. The reason risk is high early in the life cycle may not be obvious, however. When estimating the cost of capital, "risk" does not take its everyday meaning.

Most of the "risks" that trouble a pharmaceutical manager or scientist -- and all of the uncertainties explicitly simulated in the life-cycle model -- do not concern diversified investors. They have nothing to do with the macroeconomic risks that drive security returns.

"Micro" risks -- for example, the chance that a drug candidate will fail in clinical testing -- are averaged out of the returns on diversified portfolios of securities, and do not affect the discount rate. Such risks are accounted for in
the model by multiplying future cash flows by the probability of success, not by an adjustment to the cost of capital. 21

The real reason why risk is high early in the life cycle is that the costs of R&D are more or less fixed obligations, assuming the R&D continues. These fixed obligations create "R&D leverage" with effects similar to operating leverage or financial leverage: more leverage amplifies the risks borne by investors and increases their required return. 22

Myers and Shyam Sunder explain how this works and give a numerical example. An alternative explanation follows.

**R&D leverage**

Think of a "balance sheet" for a drug candidate in early development. On the left is the present value of revenues, net of manufacturing, marketing and other operating costs, from sales of the drug. Call this PV( Net Revenues ). Net revenues are multiplied, of course, by the probability that the candidate will survive to generate revenues. On the right is the present value of all future development costs, multiplied, of course, by the probabilities that the candidate will not fail and that the costs will actually have to be paid. Call this PV( Future Costs ). The other entry on the right is the candidate's NPV. NPV equals PV( Net Revenues ) minus PV( Future Costs ).

\[
\begin{array}{c|c|c}
\text{PV( Net Revenues )} & \text{PV( Future Costs )} & \text{NPV} \\
\end{array}
\]

The discount rate for PV( Net Revenues ) is determined by the risk of investment in a drug that has received FDA approval and is generating revenues. 23 Let this rate (the bottom step on the staircase in Figure 1) be \( r_{NR} \) and let \( r_{FC} \) be the discount rate for

21 This is why the discount rates used in the model are not adjusted to offset the risks of failure shown in Figure 4.

22 A call option has the same kind of leverage. The option's exercise price here corresponds to the costs of R&D. Note that the risk of a call option decreases as time passes and the option approaches maturity. An option-based model of R&D investment would also generate the pattern shown in Figure 1.

23 This risk is borne during development as well as post-launch, because PV( Net Revenues ) at launch is uncertain. This uncertainty is not modeled explicitly, but is accounted for in the model's discounting procedures.
PV(Future Costs). Note that we distinguish \( r_{NR} \) from \( r_{FC} \); there is no reason to suppose them the same. We will argue in a moment that \( r_{FC} \) is generally less than \( r_{NR} \).

The cost of capital for the overall project, \( r^* \), applies to NPV. From the balance sheet identity,\(^{24}\)

\[
    r_{NR} \ PV(\text{Net Revenues}) = r_{FC} \ PV(\text{Future Costs}) + r^* \ NPV
\]

\[
r^* = r_{NR} + (r_{NR} - r_{FC})[\frac{PV(\text{Future Costs})}{NPV}]
\] \( \quad (1) \)

If \( r_{FC} = r_{NR} \), the cost of capital \( r^* \) is fixed at \( r^* = r_{NR} \) throughout the life-cycle. But if R&D costs deserve a lower discount rate (\( r_{FC} \) less than \( r_{NR} \)), then the candidate’s cost of capital depends on the ratio of \( PV(\text{Future Costs}) \) to NPV.\(^ {25} \)

Future R&D costs are generally fixed, not variable. The company must invest in discovery, preclinical and clinical testing and in the cost of application for FDA approval in order to bring a new drug to commercial launch. It’s as if a newly discovered drug candidate came with a mortgage which had to be paid off before any revenues are received. Think of \( r_{FC} \) as the interest rate on the mortgage. Because Future Costs are a mortgage-like obligation, \( r_{FC} \) is a relatively low rate.

In the early stages of R&D, at the left side of Figure 1, the “mortgage,” i.e., \( PV(\text{Future Costs}) \), is high and NPV low, so from Eq. (1) \( r^* \) is much higher than \( r_{NR} \). But as the candidate proceeds through its life cycle, \( PV(\text{Future Costs}) \) declines as R&D outlays are made and turned into sunk costs. Other things equal, every dollar decrease in \( PV(\text{Future Costs}) \) adds a dollar to NPV, so the ratio of \( PV(\text{Future Costs}) \) to NPV declines, and so do risk to investors and the cost of capital \( r^* \).

Of course \( PV(\text{Future Costs}) \) is not a contractual obligation like a mortgage, and it is not fixed in the sense of being known for sure. The staircase shown

\(^{24}\) This equation for \( r^* \) is identical to the standard equation for adjusting the expected rate of return on equity for changes in financial leverage. In that application the ratio of \( PV(\text{Future Costs}) \) to NPV is the debt-equity ratio, \( r_{FC} \) is the rate of return on debt and \( r_{NR} \) is the opportunity cost of capital for the assets and operations of the firm.

\(^{25}\) There is also a staircase for beta (\( \beta^* \)) determined by a formula similar to Eq. (1):

\[
    \beta^* = \beta_{NR} + (\beta_{NR} - \beta_{FC})[\frac{PV(\text{Future Costs})}{NPV}]
\]
in Figure 1 requires only that R&D costs carry relatively low exposures to the macroeconomic risks that concern diversified investors, and that Future Costs would be discounted at a lower rate than Net Revenues.

The cost of capital for a candidate drug can be extremely high when it is first discovered, because NPV at that point is small and the ratio of \( PV(\text{Future Costs}) \) to NPV is high. Suppose that \( PV(\text{Net Revenues}) \) is $10 million, barely exceeding \( PV(\text{Future Costs}) \) of $9.5 million. Then NPV = $500,000:

\[
\begin{align*}
\text{PV( Net Revenues )} & = $10 \text{ million} \\
\text{PV( Future Costs )} & = $9.5 \text{ million} \\
\text{NPV} & = $500,000
\end{align*}
\]

Note that \( PV(\text{Future Costs}) / \text{NPV} = 19 \). If \( r_{\text{NR}} \), the lowest step on the cost of capital staircase, is 10 percent, and \( r_{\text{rc}} \) 6 percent, then \( r^* = 10 + (10 - 6) \times 19 = 86 \) percent. This would be the highest step on the staircase.

Now suppose the drug survives clinical testing and moves on to Phase I clinical trials. \( PV(\text{Net Revenues}) \) increases, say to $11 million, because the odds of a marketable drug have increased, and because the first potential cash inflow is closer. \( PV(\text{Future Costs}) \) generally decreases, say to $9 million, because the costs of preclinical testing are sunk.\(^{26}\) NPV is $2 million:

\[
\begin{align*}
\text{PV( Net Revenues )} & = $11 \text{ million} \\
\text{PV( Future Costs )} & = $9 \text{ million} \\
\text{NPV} & = $2 \text{ million}
\end{align*}
\]

Now the ratio of \( PV(\text{Future Costs}) \) to NPV is 4.5. Thus the cost of capital for the overall project declines to \( r^* = 10 + (10 - 6) \times 4.5 = 28 \) per cent. This is why the staircase slopes down from left to right.

\(^{26}\) \( PV(\text{Future Costs}) \) can increase when future costs are large relative to current costs. As the drug candidate moves from stage to stage, the future costs are discounted for fewer periods. The resulting increase in their value can more than offset the disappearance of costs that become sunk. \( PV(\text{Future Costs}) \) always decreases as a fraction of \( PV(\text{Net Revenues}) \), however, when a drug candidate successfully moves on to the next stage of development.
Notice that this reasoning has nothing to do with the risk that the drug candidate will fail for scientific or medical reasons. The probabilities of failure are of course tracked in the simulation model. The higher the odds of failure, the lower PV(Net Revenues), PV(Future Costs) and NPV. However, the risk of failure is not correlated with the macroeconomic risks that concern investors and determine the cost of capital. These odds of failure do not affect \( r_{NR} \) or \( r_f \); they affect the staircase for \( r^* \) only by reducing the expected cash flows underlying PV(Net Revenue) and PV(Future Costs) and by changing the ratio PV(Future Costs)/NPV.

A more detailed numerical example of R&D leverage and the risk-return staircase is given in Appendix C.

**Tests for R&D leverage in pharmaceutical and biotech stock returns**

The effects of R&D leverage follow directly from basic finance theory. These effects can also be seen in the higher risks of biotech stocks compared to mature pharmaceutical companies. Most biotech stocks are nearly pure plays on R&D, having gone public before any of their candidate drugs received FDA approval. Their common stock returns reflect the risks of drugs in development. Because of R&D leverage, their betas should be higher than the betas for large pharmaceuticals reported in Table 3. Thus, by observing the actual risk of biotech stocks, we can test, and roughly calibrate, the risk-return staircase.

Lakshmi Shyam Sunder compared biotech and pharmaceutical betas for this research project. As predicted the biotech betas have been consistently higher than betas for mature pharmaceutical companies. Table 4 summarizes her results.\(^{27}\)

Shyam Sunder estimated year-by-year equity betas\(^{28}\) from weekly returns for a sample of large pharmaceuticals (essentially the same sample as in Tables 2 and 3) and for several biotech samples. The first (line 2 of Table 4) consisted of all biotech stocks for which returns were available on the CRSP and NASDAQ data bases. The second consisted of a group of biotech firms followed by Recombinant Capital (line 3). The average betas reported in Table 4 for these two samples were higher than for the large pharmaceuticals in all

\(^{27}\) A more complete statement of her tests and results will be given in a separate paper.

\(^{28}\) Strictly speaking equity betas should be corrected for differences in financial leverage, but only a handful of the pharmaceutical and biotech companies had significant amounts of debt.
years save 1990, where the betas were about the same, and in 1989, where the biotech betas were less.

Line 4 shows alternative estimates for the Recombinant Data sample, using a Scholes-Williams correction for possible biases in the beta estimates due to thin trading. In this case the biotech betas are systematically higher in all years except 1989.

The number of biotech companies in these samples increased fivefold between 1983 and 1992, and doubled between 1989 and 1992. The composition of the samples was far from stable. Therefore Shyam Sunder tracked the companies that were continuously traded since 1986. The betas for these subsamples are reported in lines 5 and 6 of Table 4. They are consistently larger than the large pharmaceuticals' betas, again with the exception of 1989.

Of course not all biotech companies are on the same step of the risk-return staircase. Some have one or more products already in the market or close to it. These companies' betas should be lower than betas for fledgling biotechs. Shyam Sunder checked this using a classification developed by Recombinant Capital. The classification sorted the Recombinant Capital sample in three "tiers:"

Tier 1: "Mature" biotech firms with at least one approved drug
Tier 2: Firms with drug candidates in advanced stages of clinical testing
Tier 3: Firms without drug candidates in advanced stages of clinical testing

Tier 1 firms should have less R&D leverage that Tiers 2 and 3, and therefore lower betas. This is confirmed by the estimated biotech betas. The mean betas for 1992 were 1.38 for Tier 1, 2.39 for Tier 2 and 2.17 for Tier 3. The difference between the Tier 1 beta and the betas for Tiers 2 and 3 was highly significant, although there was no significant difference between Tiers 2 and 3.

These results, plus the betas reported in Table 4, confirm the importance of R&D leverage for the risks facing investors. As predicted, biotech companies have significantly higher betas. We emphasize that these higher betas estimates have nothing to do with the scientific or clinical successes or failures of the biotech companies. Beta is an indicator of macroeconomic risk; it captures only the volatility in stock returns that is correlated with the stock market as a whole.

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29 A smaller sample of biotech firms traded since 1983 gave consistent results.
Valuation in the simulation model

Discounting in the simulation model could be complicated, because the cost of capital $r^*$ changes each year for each drug. There is a simple alternative procedure, however. Note that $r^*$ changes only because $\text{PV( Net Revenues )}$ changes relative to $\text{PV( Future Costs )}$ and NPV. Therefore NPV can be calculated by

1. Discounting Net Revenues, and all cash flows that vary proportionally with revenues, at the "variable" rate $r_{\text{NR}}$.
2. Discounting all Future Costs that do not vary with revenues at a "fixed" rate $r_{\text{FC}}$.
3. Subtracting to obtain NPV.

The overall cost of capital $r^*$ can then be calculated directly from Eq. (1). Note, however, that the cost of capital $r^*$ is not needed to calculate NPV. It is derived from NPV and PV( Future Costs ). Strictly speaking, it is an output, not an input, of the valuation analysis.

NPV is calculated separately for each drug that is "alive" in each year. The program NPV is calculated by the same three steps after aggregating across drugs and adding the present value of the costs of the program to PV( Future Costs ). The cost of capital for the program ( denoted as $R_{\text{exp}}$ in Figure 7 ) is also calculated from Eq. (1) in each year of each iteration of the simulation.

The base-case discount rates used in this report are $r_{\text{NR}} = 9$ percent and $r_{\text{FC}} = 6$ percent. We believe these rates are reasonable given the purposes of the model and the other base-case assumptions. The rate for Net Revenues is less than the 10 to 11 percent real cost of capital implied by Table 3. This makes sense because Table 3 is derived from data for mature companies which are portfolios of drugs in the market and drug candidates at various stages of the development pipeline. These companies' costs of capital are averages across the staircase and overstate the appropriate discount rate for calculating PV( Net Revenues ).

We do not assume the "fixed" costs are literally risk-free. A real discount rate of $r_{\text{FC}} = 6$ percent implies a nominal rate of 9 to 10 percent, roughly 3 percentage points above long-term Treasury yields in early 1994.
The combination of $r_{NR} = 9$ percent and $r_{FC} = 6$ percent can generate very high costs of capital for freshly discovered drugs. But the simulation model does not track one drug only, but a program generating a portfolio of drugs at various stages of the R&D program and the commercial life cycle. Simulated betas or costs of capital are averages across the risk-return staircase.

We chose $r_{NR}$ and $r_{f}$ so that these simulated averages approximate observed betas and costs of capital for mature pharmaceutical companies. For example, the simulated cost of capital for the successful iterations of the model (the left side of the distribution of $R_{exp}$ in Figure 7) is approximately equal to the 10 to 11 percent real cost of capital estimated for large pharmaceutical companies.

The choice of $r_{NR}$ and $r_{f}$ is nevertheless partly judgment. Therefore we show below how our main numerical results would change using different pairs of discount rates.

**Some Implication of the Life-Cycle Model**

We showed one implication of the life-cycle model in Figure 8: the extreme uncertainty and strong positive skewness of program revenues, profits, cash flows and market values. The model demonstrates the great uncertainty about payoffs from investment in pharmaceutical R&D.

We do not claim that the variances of the distributions in Figure 8 match those of actual companies. There are various differences. For example, the simulations do not incorporate all sources of uncertainty, because the revenue patterns (shown in Figure 5) are fixed. On the other hand, large pharmaceutical companies achieve more diversification than in the simulated program. They have portfolios of programs. (Biotech companies are generally less diversified than the simulated programs, however.)

Our Monte Carlo simulation model may not be wholly "realistic," but it does describe the financial structure of pharmaceutical R&D, and its base-case inputs are mostly based on historical data. Thus it's instructive to consider the model's implications for the profitability of pharmaceutical R&D, for the cost of bringing a new drug to market, for the cost of capital, and for the accuracy of accounting rates of return.

**Profitability of investment in pharmaceutical R&D**

The true average profitability of investment in pharmaceutical R&D is not revealed by ordinary financial data. Standard accounting rates of return, as
reported, say, by "Fortune"\textsuperscript{30} can be severely biased. Attempts to adjust or correct standard accounting data require strong simplifying assumptions\textsuperscript{31} and are often inconclusive. Moreover, successes are noticed more than failures. In real life, poorly performing programs are shut down or folded into other research activities. Such programs are not observed after the fact. Those that survive and are observed will have less variance and higher average profits than the original cohort.\textsuperscript{32} Companies sampled with hindsight as "large pharmaceuticals" will have more than their share of research programs that turned out well. Studies focused on such companies will overstate the profitability of investment in pharmaceutical R&D.

These problems can be avoided by measuring economic profitability before the fact, that is by calculating the NPV of R&D investment at year 0 when a drug candidate is discovered. This is impossible to document in real life but not difficult in the life-cycle model.

NPV is the standard financial measure of expected profitability relative to the cost of capital. NPV is based on cash flows, and so is immune to accounting noise or bias. NPV adjusts for risk to investors and the time value of money. In a competitive industry, the NPV of new investment tends towards zero, as true economic rates of return tend toward competitive levels.

The NPV of an about-to-be-discovered drug depends on the Net Revenues it may generate and the Future Costs of developing it:

$$NPV = PV(\text{Net Revenues}) - PV(\text{Future Costs})$$

\textsuperscript{30} "Fortune"'s profitability rankings are biased in at least two ways. First, the profitability of pharmaceutical and other R&D-intensive industries is generally overstated because the value of R&D is not included in book assets or equity. Second, "Fortune" calculates return on assets as the ratio of net income after interest to book assets. This biases the ranking against companies with high interest expense, and makes companies with low debt ratios -- such as pharmaceuticals -- appear relatively more profitable. "Fortune" should add after-tax interest charges back to net income before calculating the ratio of income to assets. See the annual "Fortune 500" issue, for example, May 15, 1995.

\textsuperscript{31} See, for example, Baber and Kang (1991).

\textsuperscript{32} There is no reason to shut down poorly performing programs in the simulation, because the odds of future success are fixed regardless of the number or characteristics of drugs already discovered.
Financial Model of the Drug Discovery Process

Here PV(Net Revenues) is the value of net cash flows from sale of the drug, and PV(Future Costs) is the value of all development costs and required capital expenditures. All future costs and cash flows are multiplied by the probabilities they will actually occur, and all are after-tax.\textsuperscript{33} Note that any given drug candidate has only a 60 percent chance of discovery, so all PVs are multiplied by .6.

Under the model's base case assumptions,

\[
NPV = 17.10 - 13.04 = 4.06, \text{ about } $4 \text{ million}
\]

This does not include any costs of the program itself. We therefore subtract one-fourth of the equivalent annual cost of the program.\textsuperscript{34}

\[
NPV(\text{net of program costs}) = 4.06 - 7.45 = -3.39, \text{ about } -$3.4 \text{ million}
\]

In other words, our base-case assumptions imply expected returns exceeding the cost of capital if only the direct costs of developing a specific drug are considered. However, these "excess" returns are necessary to cover the general costs of the development program. When these costs are allocated to a particular drug, its NPV is negative, indicating expected returns less than the cost of capital. However, do not conclude from this that returns to investment in pharmaceutical R&D have been inferior. The correct reading is normal profitability. In other words, the NPV of investment in pharmaceutical R&D, with proper accounting, for failure rates in drug development and the risks born by investors, is approximately zero.

We say "approximately" because actual expected costs and revenues cannot be pinned down precisely. Program level costs are especially difficult to identify and allocate, and could be overstated in our base-case assumptions. Different discount rates would also shift the NPVs. For example, suppose that the rates for Net Revenues (r_{NR}) and Future Costs (r_{FC}) are changed to 10 and 5 percent or 10 and 7 percent:

\textsuperscript{33} Capital expenditures generate depreciation tax shields. These shields are netted against Future Costs.

\textsuperscript{34} We first calculated the total present value of program-level costs over the program's 40 year life, then converted the present value to an equivalent annual cost. Since four drugs can be discovered in each program year, one-fourth of the equivalent annual cost is allocated to each drug.
<table>
<thead>
<tr>
<th>Discount Rates</th>
<th>NPV, millions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Direct</td>
</tr>
<tr>
<td></td>
<td>Investment Only</td>
</tr>
<tr>
<td>$r_{NR}$ (Net revenue)</td>
<td>$r_{FC}$ (Future costs)</td>
</tr>
<tr>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>10%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Our finding of approximately normal profitability -- and no indication of significant excess profitability -- matches the findings of Grabowski and Vernon (1993).\[^{35}\] The OTA Report's references to "excess profits" in the pharmaceutical industry are discussed below.

**Cost of drug development**

It is now customary to speak of the "cost of developing a newly approved drug." The OTA Report, for example, estimated this cost at $194 million after tax at commercial launch.\[^{36}\] Such costs are supposed to include all the costs of drug development, scaled up to reflect the odds of failure in development. The costs are compounded forward at the cost of capital to the date of commercial launch.

We cannot follow exactly that procedure, because there is no single, fixed cost of capital in the life cycle model. The correct procedure is:

\[^{35}\] Grabowski and Vernon estimated a NPV of $22 million at launch -- not at the start of R&D -- by comparing cost at launch to the present value of subsequent net revenues. They did not characterize this difference as significant "excess" profits. They calculated an internal rate of return over the entire life cycle of 11.1 per cent, less than one percentage point above their assumed cost of capital of 10.5 per cent. Grabowski and Vernon did not attempt to incorporate the changes in the cost of capital during R&D, e.g. by the procedure given in Section 4.2 below.

FINANCIAL MODEL OF THE DRUG DISCOVERY PROCESS

**Step 1** Calculate PV(Future Costs), the present value of future R&D costs, at the time of drug discovery, using \( r_{FC} \), the discount rate for Future Costs. Since the object in this case is to calculate cost at launch, this present value should include Future Costs only from discovery through launch. This value applies to a single drug candidate, and reflects the odds that the candidate will fail one of the R&D stages. (If it does fail, R&D costs of course cease.)

**Step 2** Compound PV(Future Costs) forward to the commercial launch date using \( r_{NR} \), the discount rate for Net Revenues. Compounding forward at \( r_{NR} \) is required to offset the risks to investors who will ultimately receive the Net Revenues if the drug succeeds.\(^{37}\)

**Step 3** Scale up the compounded value to offset the failure rate of newly discovered drugs. In other words, multiply the compounded value from Step 2 by the number of drug candidates required on average to generate one FDA-approved drug.

The base-case PV(Future Costs) was reported above as $13.04 million, but this figure includes some Future Costs post-launch, for example the cost of ongoing research. If these post-launch costs are excluded, PV(Future Costs) drops to $12.49 million. This corresponds to Step 1. In Step 2, we compound forward at \( r_{NR} = .09 \) for the 13 years between discovery and launch:

\[
12.49(1.09)^{13} = $38.3 \text{ million.}
\]

The base-case probabilities summarized in Figure 3 imply a cumulative failure rate of 87.1 percent, and a success rate of 12.9 percent. The number of candidates per successful drug is therefore \( 1/ .129 = 7.75 \). Step 3 then multiples by 38.3 by 7.75, the average number of candidates needed for one commercial launch: 38.3 x 7.75 = $296.8 million.

A numerical example tracing this three-step calculation of the cost of drug development is included in Appendix C.

Under base-case assumptions, the cost of bringing a single drug to successful launch is $296.8 million. This figure is after-tax. It covers all development costs, including the risk that the drug will not be discovered or will fail in development, plus the cost of building manufacturing capacity. It does not cover manufacturing or marketing costs.

\(^{37}\) "Risk" here refers to the macroeconomic risks embodied in PV(Net Revenues) during the R&D phase of a drug's life cycle. The risk that a drug will fail during R&D affects expected Net Revenues but not \( r_{NR} \).
This cost is the value at launch which gives NPV = 0 for the drug candidate at year 0. In other words, “cost at launch” is the answer to the following question: “How much does a drug have to be worth at launch in order to compensate investors for the costs and risks of drug development?”

If investors are to be fairly compensated, their payoff must equal their accumulated risk-adjusted cost.

This cost at launch of about $297 million includes only the direct costs of developing the drug. It does not include any share of program costs, that is, the setup cost of of a drug development program, the cost of basic research and of research overhead or administration. Including these costs adds $7.5 million to PV(Future Costs) at Step 1, $23 million in Step 2, and $178 million in Step 3. Thus the base-case cost of launch, with program costs allocated, is $297 plus $178, or $475 million.

We believe program costs are material, but in this respect our base-case assumptions are harder to check. A company using the life-cycle model for internal purposes would probably enter different assumptions. For example, if a company decided to ignore the setup costs of a research program, cost at launch would drop to $433 million with program costs allocated.

Of course all these calculations depend on many other input assumptions. For example, the effects of varying the costs of capital are:

<table>
<thead>
<tr>
<th>$r_{NR}$</th>
<th>$r_{FC}$</th>
<th>Cost at launch</th>
<th>Cost with Program Costs Allocated</th>
</tr>
</thead>
<tbody>
<tr>
<td>9%</td>
<td>6%</td>
<td>$297</td>
<td>$475</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>357</td>
<td>561</td>
</tr>
<tr>
<td>10</td>
<td>7</td>
<td>315</td>
<td>514</td>
</tr>
</tbody>
</table>

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38 Given the complexity of the financial simulation model, it proved convenient to calculate cost at launch by varying the revenue curves given in Figure 5 until NPV = 0, and then calculating PV(Net Revenues). This value of PV(Net Revenues) is identical to cost at launch as calculated by the three-step procedure given above.

39 This is one fourth of the equivalent annual cost corresponding to program-level expenses.

40 We did confirm from the model's output that average ratios of G&A costs to sales and net profits to sales were, on average, about the same as the respective ratios for a sample of large pharmaceutical companies. This gives some assurance that the base-case assumptions about program-level costs are reasonable.
All the costs at launch reported above are after-tax. The pre-tax, base-case cost at launch is $429 million, and $697 million with pre-tax program costs allocated.

**Comparison to the OTA Report.**

The OTA Report estimated cost at launch at $194 million in 1990 dollars, after-tax and not including program-level costs. Adjusting for inflation from 1990 to 1994 would bring this figure to $218 million, still substantially less than our base-case estimate of $297 million. The main reasons for this difference are as follows.

First, the OTA used a higher 46 per cent tax rate. Reducing the tax rate to our base-case value of 35 percent would increase the OTA’s cost at launch to $262 million in 1994 dollars. Second, the life-cycle model includes the cost of manufacturing capacity constructed prior to launch in the cost at launch; this cost is not included in the OTA’s figure. Third, the OTA’s method for calculating cost at launch did not properly incorporate changes in the cost of capital during drug development.\(^{41}\)

It is possible to make too much of these differences. The OTA’s approach to calculating the cost at launch is broadly similar to the life-cycle model’s, and both approaches give answers above $250 million (before any recognition of program-level costs) if a post-1986 tax rate is used. We do disagree with the OTA’s use of a 46 per cent tax rate for costs and a much lower rate (32 per cent) for revenues. Use of a single, consistent tax rate better shows the underlying economics of pharmaceutical investment.

The OTA Report’s cost at launch is $36 million less than its estimate of the present value at launch of subsequent revenues. The Report interpreted this as “excess profitability” (p. 22). However, this “excess” is solely due to the use of a lower tax rate for revenues than costs. Any such excess had nothing to do with the profitability of investment in pharmaceutical R&D compared to investment in other industries.\(^{42}\) It is true that marginal corporate tax rates

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\(^{41}\) The OTA Report compounds each year’s R&D cost forward to launch at a different rate. The earliest costs are compounded at a rate 4 percentage points higher than the 9.8 per cent cost of capital used to discount revenues. Later costs are compounded forward at successively lower rates until the “floor” of 9.8 per cent is reached. This is not equivalent to the three-step procedure given above. It also misinterprets the staircase, which plots the one-period rates of return demanded by investors on all previous costs.

\(^{42}\) Even if the excess profitability seen in the OTA Report is true it is not significant. The “OTA estimated that excess returns over R&D costs would be eliminated if the annual revenue per
dropped during the period studied by the OTA, but the benefits of the lower rates went to all United States corporations.

Grabowski and Vernon (1994, p. 388) estimate cost at launch at $188 million in 1990 dollars, or $211 million in 1994 dollars. This estimate, like the OTA Report's, covers only the direct R&D costs of drug development.

**Sensitivity analyses.**

Table 5 shows how NPV and cost at launch vary under several further variations on the base case. Line 1 repeats the base-case numbers given above (without allocation of program costs). Line 2 assumes that overall success rates are increased by five percentage points. This nearly doubles NPV at year 0 and reduces cost at launch by about $40 million.

The figures in line 3 assume that the fraction of breakthrough drugs is reduced from one in ten to one in 20, with an offsetting increase in the frequency of "average" drugs. This cuts NPV almost to zero before allocation of program costs. It also reduces cost at launch slightly, since the costs of manufacturing capacity incurred before launch are higher for the breakthrough drugs than for the other categories.

The figures in line 4 assume that the revenue curves for all drug categories are cut by 10 per cent in all years. Notice that this has much less of an effect on NPV than the cutback in breakthroughs shown on line 3. Of course shifts in revenue curves have no effect on cost at launch.

Finally, line 5 shows the effects of turning off any change of new indications or competing drugs. NPV increases slightly, showing that the upside from new indications slightly outweighs the downside from possible competition. The net effect is not great, however. Again, cost at launch is not affected.

**The risk-return staircase**

Figure 9 shows how the cost of capital $r^*$ declines from year 1 of a drug's lifecycle through launch, assuming success of course, and also assuming that the drug's initial NPV = 0. (Because $r^*$ depends on the relative sizes of

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compound was reduced by 4.3 percent over the product's life." (OTA Report, p. 22). An "excess" of 4.3 percent is not significant considering the inevitable problems in estimating inputs and the normal fluctuations of profits in risky, competitive industries.
PV(Net Revenues) and PV(Future Costs), it also depends on NPV. The most natural reference point is NPV = 0.)

Figure 9 is the numerical realization of the risk-return staircase shown in concept in Figure 1. It confirms that R&D leverage can dramatically increase risk and the cost of capital. Given the structure and base-case inputs of the life-cycle simulation model, the cost of capital in year 1 of a drug's life cycle is double the cost of capital for a mature drug.

The simulated distribution of \( r^* \) for the program as a whole is labeled Rexp in Figure 8. Rexp is the average cost of capital for a portfolio of drugs at various steps of the staircase. Successful programs with several mature, successful drugs will show up in Figure 8 with low costs of capital. Programs with few or no marketable drugs, and only drugs in the R&D pipeline, will show high values for Rexp.

The following hypothetical example illustrates the relationship between success in drug development and the cost of capital. Consider two iterations of the model, A and B. In A, 15 drugs, including two breakthroughs, are successfully brought to market by, say, year 30. This is far better than average performance, so iteration A has a very high NPV. Most of the NPV is due to the present value of the net revenues generated by its successful drugs, and PV(Future Costs) is a small fraction of NPV. The cost of capital (Rexp) for iteration A will therefore be only slightly higher than \( r_{fc} \), the cost of capital (and discount rate for) an approved drug.

Iteration B, on the other hand, is an unlucky one, with only five successful drugs and no breakthroughs. For B, the ratio of PV(Future Costs) to NPV remains high, even in year 30, and Rexp will therefore be far above \( r_{fc} \).

Thus in Figure 8 the lucky iterations like A have low costs of capital.
Unlucky iterations like B have high costs of capital. The lowest possible cost of capital is \( r^* = r_{NR} \), the highest well over 100 percent. Thus the distribution of Rexp is skewed strongly to the right.

Figure 8 plots Rexp for year 30 for each of 4999 iterations of the simulation. All the iterations are 30 years old, and all have an equal chances of developing successful drugs. A similar plot for, say, year 10 would show systematically higher costs of capital because all drugs would still be in the R&D pipeline -- the first possible launch date is year 14. At year 10 the simulated programs are, like most biotech companies, pure plays on R&D.
Accounting rates of return

The potential biases in accounting rates of return are well-known, though not always paid sufficient attention. The bias in R&D-intensive industries is upward, because generally accepted accounting principles (GAAP) expense R&D investments. The value of these investments does not appear on the balance sheet, so assets are understated. Therefore accounting rates of return, which are ratios of income to assets, are overstated.

These biases have been demonstrated with models -- examples, usually -- that usually assume certainty and steady-state growth. In this context it is not difficult to develop capitalization rules for R&D which eliminate the upward bias. But would capitalizing R&D "work" in the face of uncertainty, and for companies that are always in transition, never in a steady state?

The life cycle model allows an analysis of how uncertainty and accounting interact. We simulate actual and accounting rates of return, and experiment with alternative accounting procedures. The experiments are not yet complete, but early results are interesting.

Figure 10 compares the distribution of rates of return on assets under two accounting procedures. The first follows GAAP, the second capitalizes drug development expenses, but only from Phase III on. The capitalized expenses are amortized linearly over 15 years. The two returns, labeled ROAgap and ROAcr respectively, are calculated in each year of each iteration of the simulation. The distributions shown are for year 30.

The first page of Figure 10 shows two striking differences. First, capitalizing development expenses reduces the mean return by 13 percent (from 26 to 13 percent) and the median return by 23 percent. Second, the variance of ROAgap is clearly greater than ROAcr. It appears that capitalizing R&D not only offsets some of the upward bias in accounting returns, but also takes out some of the "noise."

But these distributions could be misleading because they mix iterations over a wide range of success rates, NPVs and costs of capital. Therefore the second page of Figure 10 reports the difference between each iteration's ROA and the cost of capital at year 30 for that iteration. The cost of capital is a measure of the true rate of return period by period.

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44 This takes the true return as an average or expectation. We have also compared ROAs to the actual one-year rates of return to investors. However, accounting procedures are not
On average ROAgap is 16 percent above the cost of capital. This is not surprising given the upward bias of accounting rates of return. Capitalizing some drug development costs reduces this bias by 13 percentage points. Notice also that ROAgap - Rexp has a very wide range and is skewed left. The distribution of ROAcr - Rexp is more symmetric and less noisy (Note the reduced scale of the x-axis.) -- that is, it eliminates some of the variance of ROAgap - Rexp.

Figure 11 plots ratios of net income to NPV. These are earnings-intrinsic value ratios. Again, the top plot uses GAAP, the bottom plot capitalizes development expenses from Discovery. Here the differences are difficult to see, because NPV unlike book value, represents the true, forward-looking value of the program.

Paul Healy and the authors are conducting extensive accounting experiments with the life cycle model. These will be described in a forthcoming paper.

Conclusions

The life cycle model described in this report differs from prior analyses in two important respects. First, we model uncertainty explicitly, using Monte Carlo simulation of drug development programs. Most prior work deals only with average costs, success rates and net revenues of individual drugs. Second, our discounting and valuation procedures are consistent with modern finance and explicitly track changes in risk and the cost of capital across the pharmaceutical life cycle.

We believe this life-cycle model provides a more complete and informative description of investment in pharmaceutical R&D. For example, analyses based on averages cannot show the variance and skewness of NPV and the cost of capital in a cross-section of pharmaceutical investments. Analyses of average biases in accounting rates of return cannot show the noise in these returns or the reduction of noise, as well as bias, when part of R&D outlays are capitalized.

We have also calculated the ex ante NPV of drug development, a measure of average profitability relative to the cost of capital, and the average cost of bringing one drug to market. Of course, these calculations reflect our base-case input assumptions, and sensitivity analyses can show substantially different
designed to measure true returns over short intervals. Presumably they try to measure longer-run, average returns. The development of standards for judging the performance of accounting returns under uncertainty needs further thought.
results. Yet we believe these base-case assumptions are reasonable and representative, although not definitively "realistic."

The main task of this research project was construction of the Monte Carlo financial simulation model. This report describes the structure, assumptions and general implications of this model. constructed for this research project. Several more focused research papers will follow. These include a more technical description of the model itself, an analysis of accounting profitability measures, and an updated analysis of costs of capital for the pharmaceutical and biotech industries.